Canadian College of Neuropsychopharmacology
COLLÈGE CANADIEN DE NEUROPSYCHOPHARMACOLOGIE

CCNP – 47th Annual Meeting

Program Overview

Thomson House, McGill University

Montreal, Quebec

September 17 – 19, 2025

Canadian College of Neuropsychopharmacology
COLLÈGE CANADIEN DE NEUROPSYCHOPHARMACOLOGIE

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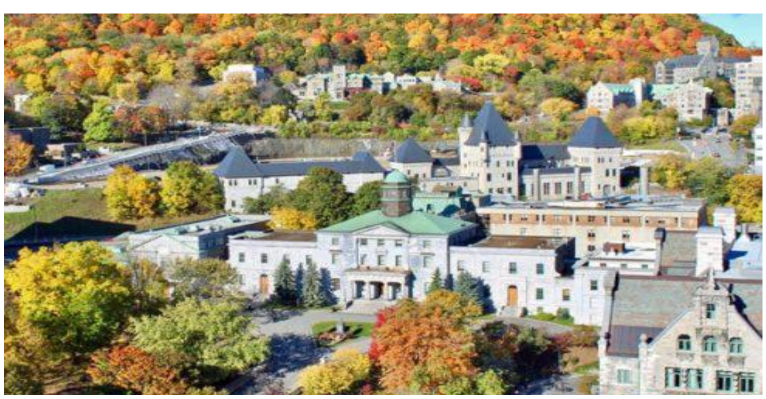
A sincere thank you to our LOC for your hard work, dedication and patience in the organization of our 47th Annual Meeting!



Journal of **Psychiatry and Neuroscience**

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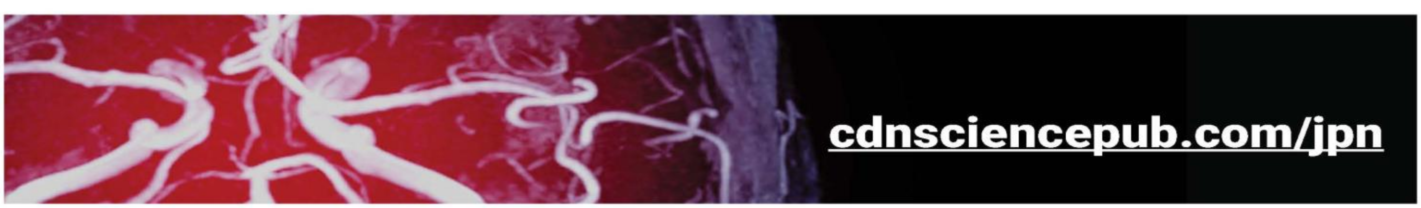

OUR KEYNOTE SPEAKERS

Dr. Diego Pizzagalli

Dr. Pizzagalli is the Founding Director of the Noel Drury M.D. Institute for Translational Depression Discoveries, University of California at Irvine.

He is a Distinguished Professor in the Department of Psychiatry and Human Behavior and the Department of Neurobiology and Behavior.

The title of his keynote presentation is:

"Translational and Cross-Species Approaches to Anhedonia: Implications for Treatment Development and Stratification"

Dr. Rosemary Bagot

Dr. Bagot is an Associate Professor of Behavioural Neuroscience at McGill University.

She is a Tier II Canada Research Chair in Behavioural Neuro-genomics.

The title of her keynote presentation is:

"Neural Circuit Mechanisms of Affective Processing"

OUR MAJOR AWARDS WINNERS

Dr. James Kennedy

CCNP Medal

Dr. James (Jim) Kennedy has training in three major areas: neuroscience, clinical psychiatry, and molecular genetics. His main research interest over the past 30 years has been investigating the role of genetics in the causes and treatment of neuropsychiatric disorders. His discoveries include: 1) the remarkable variation in the DRD4 gene (with Dr van Tol) and its role in ADHD, one of the most consistently replicated findings in all of behavioral genetics; 2) defining the roles of the DRD3 (issued patent) and VMAT2 genes in Tardive Dyskinesia (VMAT2 drug valbenazine FDA approved for TD in 2017); and 3) the creation of a six gene panel for prediction of antipsychotic-induced weight gain (Tiwari et al, 2016 issued US patent). Dr. Kennedy has one of the most comprehensive collections of DNAs (N = 35,000) for any one PI in the world in terms of range of psychiatric disorders (N=18) and sub-phenotypes (N=50+). In his role as head of the Tanenbaum Centre for Pharmacogenetics, he is leading a pharmacogenomics research program (N=12,000 patients tested), and randomized controlled trials (N=500) involving patients with schizophrenia and depression. He has trained over 40 graduate students and 55 research fellows, several of whom are now Full Professors. He currently supervises 12 Principal Investigator level scientists in his role as Director of the Molecular Brain Science Department at CAMH.

Dr. Krista L. Lanctôt

Heinz Lehmann Award - For Outstanding Contributions to Neuropsychopharmacology

Dr. Krista L. Lanctôt has a PhD in Clinical Pharmacology from the University of Toronto, and holds the Bernick Chair in Geriatric Psychopharmacology. She is a Senior Scientist in Geriatric Psychiatry and in the Hurvitz Brain Sciences Program at Sunnybrook Research Institute, Research Co-Director in the Department of Psychiatry at Sunnybrook Health Sciences Centre and Heads the Geriatric Psychopharmacology Research Group. At the University of Toronto, she is a Professor of Psychiatry and of Pharmacology/Toxicology, and the Vice Chair of Basic and Clinical Sciences in the Department of Psychiatry.

Dr. Lanctôt is an active researcher 400+ published papers. Her group's research has focused on optimizing the treatment of cognition and neuropsychiatric symptoms associated with dementia and in predementia states. She was part of the International Psychogeriatric Association consensus clinical and research definition of agitation group in 2014 and 2024, and the 2021 IPA agitation treatment algorithm. She was group co-lead and corresponding author for the 2023 ISCTM diagnostic criteria for apathy. She currently holds grants as a Principal Investigator from the Alzheimer's Drug Discovery Foundation, Alzheimer Society of Canada, Alzheimer's Association US, Weston Brain Institute and Canadian Institutes of Health Research. She is a full member of the School of Graduate Studies in the Temerty Faculty of Medicine, University of Toronto, previous winner of the Faculty of Medicine Graduate Education Award, and has trained more than 40 graduate students.

Dr. Alexander McGirr

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

Dr. McGirr is a clinician scientist and psychiatrist based out of the University of Calgary and Hotchkiss Brain Institute. His primary research interests involve understanding intrinsic brain function in psychiatric disorders in order to augment and improve interventions. In particular, his group is are interested in non-invasive neurostimulation treatments to target specific circuits involved in illness with tools such as Transcranial Magnetic Stimulation, and how to use psychopharmacological innovations to fully harness the clinical benefits for patients. In parallel, they seek to further this understanding in animal models of chronic stress using advanced, in vivo, genetically encoded neuronal activity sensors in conjunction with optogenetic techniques to inform human treatments. The overarching goals, therefore, constitute an iterative bedside-to-bench-to-bedside feed forward loop, advancing long-term goals of improving outcomes in psychiatric disorders.

Dr. Benoit Labonté

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

Dr. Labonté is Associate Professor at Université Laval and Research Chair in partnership with Sentinel North – Molecular Neurobiology of Mood Disorders. Dr. Benoit Labonté's research aims to understand the biological basis of depression and other mood disorders, with a specific focus on sex differences. Although depression is twice as common in women, most preclinical studies have been conducted primarily in males. Dr. Labonté's research has recently shown that genes expressed in the brains of model animals and humans with depression are very different in the two sexes.

Dr. Labonté's research focuses on mouse models of mood disorders, but his results have been confirmed by the analysis of human samples from brain banks and blood tests. These studies have identified genes and proteins that are specifically activated or repressed in depressed males or females. These genes constitute therapeutic targets that could be used to treat this disease in a personalized fashion.

Finally, studies in the Labonté laboratory also aim to understand the neural circuits involved in the regulation of mood. By combining multiple cellular and molecular approaches, his team can understand the contribution that certain neuronal populations make to the expression of depressive behaviors.

It is therefore in the context of developing better, more targeted therapeutic approaches to treat men and women that Dr. Labonté's team aims to improve our understanding of the molecular mechanisms underlying mood disorders.

SYMPOSIA SESSIONS

Thursday, September 18 – Thomson House

Symposium 1

Chair: Dr. Daniel Mueller (University of Toronto)

"Converging pathways in bipolar disorder: from genetics, cellular energetics, and brain to clinical trajectories"

Dr. James Kennedy (University of Toronto) – *"Polygenic and pharmacogenomic insights into bipolar disorder: toward personalized care"*

Dr. Ana Paula Mendes-Silva (University of Saskatchewan) – *"Mitochondrial mechanisms in bipolar disorder"*

Dr. Sara Afjeh (Centre for Addiction and Mental Health) – *"Transcriptomics and gene co-expression networks and age of onset in bipolar disorder"*

Dr. Martin Alda (Dalhousie University) – *"Phenotypic complexity, mediation response, and longitudinal outcomes in bipolar disorder"*

Symposium 2

Chair: Dr. Yuliya Knyahnysta (Queen's University)

"Beyond the pill: novel neuropsychiatric interventions for treatment-resistant depression"

Dr. Yuliya Knyahnysta (Queen's University) – *"Ketamine therapy in psychiatry: state of evidence and unanswered questions"*

Dr. Stefan Kloiber (University of Toronto) – *"Cannabinoids for treatment of depression?"*

Dr. Jennifer Swainson (University of Alberta) – *"Ketamine for depression: exploring treatment models to improve access"*

Dr. Claudio Soares (Queen's University) – *"The state of science on the use of psychedelics as therapeutic agents in the medical setting"*

SYMPOSIA SESSIONS

Friday, September 19 – Thomson House

Symposium 3

Chair: Dr. Paul Albert (University of Ottawa)

“Early and rapid changes in brain plasticity in mental illness and its treatment”

Dr. Cecilia Flores (McGill University) – *“Making dopamine connections in adolescence”*

Dr. Belen Blasco (McGill University) – *“Synaptic density in early psychosis and clinical high risk”*

Dr. Caroline Ménard (Université Laval) – *“Astrocyte plasticity in resilience versus vulnerability to chronic stress”*

Dr. Paul Albert (University of Ottawa) – *“Restoration of serotonin and norepinephrine connections for antidepressant action”*

Symposium 4

Chairs: Ms. Serena Wu (McGill University) and Dr. Veronica Chelu (McGill University)

“Psychedelics and psychiatry”

Dr. Olesia Bilash (Cornell University) – *“Psilocybin differentially engages GABAergic microcircuits in the cortex”*

Dr. Gabriella Gobbi (McGill University) – *“Effects of LSD and psilocybin on behavior and serotonin neuronal activity”*

Dr. Jessie Muir (Princeton) – *“Isolation of psychedelic responsive neurons underlying anxiolytic behavioral states”*

Dr. Kyle Greenway (McGill University) – *“Taking ‘set and setting’ seriously as researchers”*

Symposium 5

Chair: Dr. Venkat Bhat (University of Toronto)

“AI and psychiatry”

Dr. Tristan Glatard (University of Toronto) – *“Designing and evaluating reliable models for psychiatry with the brain health data platform”*

Dr. Simon Ducharme (McGill University) – *"AI for precision psychiatry"*

Dr. David Benrimoh (McGill University) – *"Development, evaluation, and implementation and regulatory authorization of an AI-powered clinical decision support system for major depression"*

Dr. Venkat Bhat (University of Toronto) – *"Generative AI and psychiatry"*

CCNP NEXT GENERATION SYMPOSIUM

Thursday, September 18 – Thomson House

(Abstracts chosen for Oral Presentations)

Chair: Dr. Nicole Palacio Prada (McGill University)

1. The dysregulation of the glymphatic system in patients with psychosis spectrum disorders

Vittal Korann, M.Tech, Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada. Kristoffer J. Panganiban, HBSc, Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada. Nicolette Stogios, PhD, Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, ON, Canada. Gary Remington, MD, PhD, FRCPC, Department of Psychiatry, University of Toronto, Toronto, ON, Canada. Ariel Graff-Guerrero, MD, PhD, FRCPC, Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, ON, Canada. Araba Chintoh, MBBS, PhD, FRCPC, Department of Psychiatry, University of Toronto, Toronto, ON, Canada. Margaret K. Hahn, MD, PhD, FRCPC, Department of Psychiatry, University of Toronto, Toronto, ON, Canada. Sri Mahavir Agarwal, MD, PhD, Department of Psychiatry, University of Toronto, Toronto, ON, Canada.

Introduction: The pathophysiological mechanisms influencing psychosis spectrum disorders (PSDs) are largely unknown. The glymphatic system (GS), which is a brain waste clearance pathway, has recently been implicated in its pathophysiology and has also been shown to be disrupted in various neurodegenerative and vascular diseases. Initial studies examining the glymphatic system in PSDs have reported disruptions, but the findings have been confounded by medication effects as they included antipsychotic (AP)-treated patients. In this study, we used diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) as a technique to measure the functionality of the GS in a sample of AP-minimally exposed patients with PSDs and healthy controls (HCs).
Methods: The study included 13 AP-minimally exposed (= 2 weeks AP exposure in the past 3 months/lifetime) patients with PSDs and 114 HCs. We quantified water diffusion metrics along the x-, y-, and z-axis in both projection and association fibers to derive the DTI-ALPS index, a proxy for glymphatic activity. Between-group differences were analyzed using two-way ANCOVA controlling for age and sex. Partial correlations were used to assess the association between the ALPS index and clinical variables.

Results: Analyses revealed that AP-minimally exposed PSD patients had a lower DTI-ALPS index value than HCs in both hemispheres and the whole brain (all $p < 0.005$). Significant differences were also observed between the x and y projections/associations between patients and HCs ($p < 0.001$). Furthermore, we did not find any significant correlations (all $p > 0.05$) between the DTI-ALPS index with age, BMI, symptomatology, and metabolic parameters.

Conclusion: This study shows that the GS is dysregulated in AP-minimally exposed patients with PSDs. Understanding the mechanisms that influence the GS may help to understand the pathophysiology of PSDs as proper waste clearance is needed for normal brain functioning.

2. **Investigating Psilocybin's Acute and Persistent Effects on Neuronal Activity in the Prefrontal Cortex**

Serena Wu, Integrated Program in Neuroscience, McGill University, Montreal QC, Canada Rosemary C. Bagot, PhD Department of Psychology, McGill University , Montreal, Quebec; Ludmer Center for Neuroinformatics and Mental Health , Montreal, Quebec

Introduction: Psilocybin, a psychedelic drug and selective serotonin receptor agonist, has recently experienced a resurgence in scientific research due to its therapeutic potential for several psychiatric disorders. Few preclinical studies grounded in biological mechanisms have been conducted, and the long-term circuit-level consequences of psilocybin remain poorly understood. Psilocybin binds to all serotonin receptor subtypes, both excitatory and inhibitory. The engagement of these diverse receptors likely induces complex heterogeneous downstream effects that together contribute to the long-term behavioral changes observed following psilocybin administration. Specifically, in the prefrontal cortex (PFC), a region of interest in mediating psilocybin's therapeutic effects because of its high serotonin receptor density and implications in the etiology of psychiatric disorders, previous work has found that psilocybin rapidly and persistently increases dendritic spine growth. However, the long-term circuit-level consequences of such plasticity remain poorly understood. I hypothesize that psilocybin will heterogeneously affect individual neurons with long lasting, time-varying impacts.

Methods: I am performing single-photon calcium imaging using a miniaturized microscope to acquire longitudinal, single-cell resolution recordings of PFC neuronal activity in the homecage during and after acute psilocybin administration and in the days following, allowing me to investigate psilocybin's acute and chronic effects on PFC neuronal activity.

Results: Acute psilocybin does not significantly alter average calcium event rates across the entire population of PFC neurons. However, using spectral clustering, I identified distinct neuronal subgroups with unique responses to psilocybin. Specifically, we identified clusters of cells that preferentially fire across the post-injection period, either in the early, middle or late parts of the session. Early clusters exhibit elevated activity immediately following psilocybin administration, while late clusters show increased firing later in the session. **Conclusions**: These findings suggest that psilocybin exerts temporally dynamic and cluster-specific effects on neuronal activity during the acute phase.

4. Dopamine D2/3 Receptor Availability During the Transition to Addiction: Repeat PET Studies in High-Risk Volunteers

M. Nikolic, BSc, Integrated Program in Neuroscience, McGill University, Montreal, Canada; M. Iqbal, MSc, Department of Psychology, McGill University; N. Palacio, BSc, Integrated Program in Neuroscience, McGill University; C. Caswell, BSc, Integrated Program in Neuroscience, McGill University; S.M.L. Cox, PhD, Department of Psychiatry, McGill University; N. Jaworska, PhD, Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Canada; J.R. Séguin, PhD, Azrieli Research Center, CHU Ste-Justine; Department of Psychiatry and Addictology, Université de Montréal; G. Masserweh, PhD, Department of Neurology and Neurosurgery, McGill University; F. Vitaro, PhD, School of Psychoeducation, Université de Montréal; Azrieli Research Center, CHU Ste-Justine; M. Brendgen, PhD, Department of Psychology, Université de Québec à Montréal; Azrieli Research Center, CHU Ste-Justine; S. Parent, PhD, School of Psychoeducation, Université de Montréal; M. Boivin, PhD, Department of Psychology, Université Laval; S. Côté, PhD, Azrieli Research Center, CHU Ste-Justine; Department of Social & Preventative Medicine, Université de Montréal; R.E. Tremblay, PhD, School of Psychoeducation, Université de Montréal; N. Castellanos-Ryan, PhD, School of Psychoeducation, Université de Montréal; M. Leyton, PhD, Integrated Program in Neuroscience; Department of Psychology; Department of Psychiatry; Department of Neurology & Neurosurgery, Montreal Neurological Institute, McGill University.

Introduction: People with substance use disorders (SUDs) have low dopamine D2/3 receptor availability. It remains controversial, however, whether this is a pre-existing vulnerability trait or an effect of heavy drug use. **Methods**: [^{18}F]Fallypride positron emission tomography scans were conducted in longitudinally followed youth at ages 18 (Wave-1, n=58) and 25 (Wave-2, n=47). Binding potential (BPND) values were derived for 12 striatal and extrastriatal regions of interest (ROIs). A linear mixed-effects model examined effects of Group (Emerging SUD vs Control), Time, and ROI, including all two- and three-way interactions. Post hoc comparisons and correlations were controlled for using Bonferroni and Benjamini–Hochberg corrections, respectively.

Results: At Wave-1, BPND values were higher in the Emerging SUD than Control group in the ventral (VS; $p = .007$), associative (AS; $p = .013$), and sensorimotor striatum (SMS; $p < .001$). At Wave-2, BPND values were lower in the Emerging SUD than Control group in the AS ($p = .004$) and SMS ($p < .001$). Both groups exhibited decreases in BPND values during the intervening seven years, but the magnitude of these decreases was greater in those who had developed an SUD, particularly in the AS ($p<.001$), SMS ($p<.001$), and VS ($p=0.003$). Individual differences in Wave-2 AS and SMS BPND values correlated negatively with lifetime alcohol use occasions (AS: $r = –.363$, $p = .017$; SMS: $r = –.332$, $p = .030$). None of these effects were influenced by sex or driven by stressful life events (all $p > 0.221$).

Conclusion: This study provides the first longitudinal evidence in humans that striatal D2/3 receptor availability is elevated in high-risk participants prior to the onset of an SUD and then declines in those who develop an SUD, plausibly reflecting compensatory responses to repeated drug-induced dopamine surges.

5. Memory Impairments Predict Social Functioning Through Anhedonia: Evidence from a Transdiagnostic UK Biobank Sample

Isabella Di Matteo, BSc [1,2]; Katie M. Lavigne, PhD [2,3]; Delphine Raucher-Chéné, MD, PhD [2,3]
Affiliations: [1]. Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada [2]. Douglas Research Centre, McGill University, Montreal, QC, Canada [3]. Department of Psychiatry, McGill University, Montreal, QC, Canada

Introduction: Cognitive dysfunction, particularly verbal memory deficits, is common across psychiatric disorders and linked to negative symptoms and impaired social functioning. This study examined whether anhedonia, a transdiagnostic symptom of diminished motivation and pleasure, mediates the relationship between verbal memory and social functioning. We hypothesized that mediation effects would vary by sex and symptom spectra defined by the Hierarchical Taxonomy of Psychopathology (HiTOP).

Methods: Using UK Biobank data, we analyzed 4,290 individuals with lifetime ICD-10 psychiatric diagnoses and 4,290 matched controls, excluding those with organic disorders, intellectual disability, neurological conditions, or age over 65. Key measures included verbal memory (paired-associate learning), self-reported anhedonia, and frequency of social visits as a proxy for social functioning. Patients were categorized into internalizing, externalizing, and psychotic HiTOP spectra based on symptoms. Linear regressions tested associations among memory, anhedonia, and social visits, adjusting for age, sex, socioeconomic deprivation, and HiTOP spectra. Moderated mediation analyses examined indirect effects and moderation by diagnosis, sex, and symptom spectra.

Results: Patients showed poorer memory (ß = –0.20, $p < .001$), higher anhedonia (ß = 0.25, $p < .001$), and slightly more social visits than controls (ß = 0.07, $p < .001$). Verbal memory was negatively associated with anhedonia (ß = –0.01, $p < .001$), which predicted fewer social visits (ß = –0.18, $p < .001$). Mediation confirmed anhedonia significantly mediated the memory-to-social visits relationship (indirect effect = 0.0023, $p < 0.001$). In contrast, the direct effect was not significant (ß = 0.0066, $p = .19$). Moderation analyses revealed stronger mediation among patients, males, and those with internalizing symptoms.

Conclusion: These findings suggest that, in a broad transdiagnostic sample, verbal memory impairments contribute to social dysfunction through anhedonia. This highlights a shared mechanism linking cognitive deficits and social difficulties across disorders, supporting dimensional models like HiTOP and identifying anhedonia as a promising transdiagnostic target.

6. Small RNA isomiR profiling in clinical depression

Alice Morgunova[1], [2], Ghalia Rehawi[3],[4],[5], Susann Sauer[3], Monika Rex-Haffner[3], Elisabeth Binder[3], Janine Knauer-Arloth[3],[4], Cecilia Flores[1],[2] [1]. McGill University, Department of Psychiatry [2]. Douglas Mental Health Research Institute [3]. Max Planck Institute of Psychiatry, 8080[4] Munich, Germany [4]. Institute of Computational Biology, Helmholtz Zentrum München, 8[5]76[4] Neuherberg, Germany [5]. Data Science in Systems Biology, TUM School of Life Sciences, Technical University of Munich, 8[5354] Freising, Germany

Introduction: Depression is the leading cause of disability worldwide, yet biological tools for early detection remain limited. Circulating microRNAs (miRNAs), small non-coding RNAs that regulate gene networks, represent a compelling molecular target. Variants of miRNAs, known as isomiRs, arise from post-transcriptional modifications and may offer additional biological insight but are largely understudied. This project aimed to perform deep profiling of isomiR expression and diversity in a deeply-phenotyped clinical cohort to identify novel epigenetic candidates.

Methods: We analyzed plasma samples from 140 participants (71 depression cases, average age 33 years, 62% female) with detailed clinical, physiological, and omics characterization. Small RNAs were extracted from 200 µL of plasma and sequenced at high depth (~20M reads/sample) using the Nova X platform. After quality control, differential expression was assessed using limma with voom transformation, controlling for age, body mass index, and technical variables (FDR < 0.05). IsomiR associations with cortisol were assessed using linear models, while their relationships with mRNA transcripts were identified via lasso regression and validated through sequence-matching and pathway enrichment analyses.

Results: We identified 17 dysregulated isomiRs across five miRNA families, with 18 of 19 isomiRs downregulated (p adj <0.05) in depression. Six isomiRs showed negative associations with cortisol levels, independent of psychiatric diagnosis. Several isomiRs also demonstrated regulatory relationships with mRNA targets implicated in axon guidance, Wnt signal transduction pathway and neurosynaptic localization. IsomiRs alone demonstrated diagnostic power with an AUC of 0.89, which increased to 0.95 when combined with case-specific mRNA targets.

Conclusions: By characterizing isomiRs, this study identifies novel signatures associated with depression, advancing efforts to uncover clinically relevant small RNA markers. These blood-detectable isomiRs highlight molecular pathways for early detection and accelerate the progress of precision medicine in psychiatry.

POSTER PRESENTATIONS

Thursday / Friday, September 18 / 19 – Thomson House

(listed alphabetically by presenters' names and in bold)

Congratulations to the following who are recipients of the W. G. Dewhurst Travel Award: Abdullah Abdullah, Oriel Feldman, Bertina Jebanesan, Yejin Kang, Yinqi Laetitia Wang, Qiya Xu!

Congratulations to Mathilde Argote for being the recipient of this year's Jock Cleghorn Prize for Best Poster!!!

Sex-specific impairments in auditory processing at both the inferior colliculus and auditory cortex of a mouse model of Fragile X Syndrome and autism

Abdullah Abdullah, B.Pharm [1] , Xiuping Liu, PhD [2] , Kartikeya Murari, PhD [3],[4],[5], Jun Yan, PhD [2],[3] , Ning Cheng, PhD [3],6,7,8 .[1]Cumming School of Medicine, University of Calgary, Calgary, T[2]N [1]N[4], Canada; [2]Department of Physiology and Pharmacology, University of Calgary, Calgary, T[2]N [1]N[4], Canada; [3]Hotchkiss Brain Institute, University of Calgary, Calgary, T[2]N [1]N[4], Canada; [4]Department of Biomedical Engineering, Schulich School of Engineering, University of Calgary, Calgary, T[2]N [1]N[4], Canada; [5]Electrical and Software Engineering, University of Calgary, Calgary, T[2]N [1]N[4], Canada; 6Faculty of Veterinary Medicine, University of Calgary, Calgary, T[2]N [1]N[4], Canada; 7Alberta Children's Hospital Research Institute, University of Calgary, Calgary, T[2]N [1]N[4], Canada; 8Owerko Centre, University of Calgary, Calgary, T[2]N [1]N[4], Canada.

Introduction: Auditory hypersensitivity is a debilitating phenotype in Fragile X Syndrome (FXS), the leading monogenic cause of autism, affecting both females and males, with no effective supportive approaches. Despite growing interest in sensory dysfunction in FXS and autism, auditory hypersensitivity in females remains understudied. Furthermore, adaptation, a process by which sensory inputs are filtered by reducing neuronal responses to repeating stimuli, may contribute to auditory hypersensitivity but has been rarely examined in FXS. It is an important neural mechanism that allows us to suppress unnecessary inputs while remaining responsive to novel stimulus from our surroundings. Here, we hypothesized that deficits in adaptation could contribute to auditory processing impairments, in both female and male FMR1-knockout (KO) mice, a well-established preclinical mouse model of FXS and autism.
Methods: We first investigated auditory processing in response to a simple auditory stimulus paradigm at both the inferior colliculus (IC) and auditory cortex (AC) of female and male FMR1-KO mice compared with wildtype (WT) controls. Further, adaptation was assessed using two auditory paradigms, namely oddball and two-tone suppression.
Results: In-vivo electrophysiology recordings from IC and AC neurons of FMR1-KO mice demonstrated robustly increased neuronal response to auditory stimuli compared to WT mice. We also observed pronounced impairments in adaptation in KO mice. Interestingly, analyzing females and males separately revealed that sex differences existed in multiple parameters in FMR1-KO mice but not WT controls.

Conclusion: Robust auditory processing deficits was observed in both female and male FMR1-KO mice, with notable differences between the sexes, highlighting the importance of including female subjects in future studies. Additionally, the observed impairments in adaptation suggest a potential mechanism underlying auditory hypersensitivity in FXS, possibly due to altered inhibitory function at both the IC and AC.

Prenatal Cannabis and Tobacco Co-exposure and its Association with Childhood Cognitive Development: Evidence from the ABCD Study

Mathilde Argote, PhD [1,2,], Anaïs Rubsamen, BA [1], Rachel A. Rabin, PhD [2,3] [1], McGill University, Montreal, QC, Canada [2], The Douglas Mental Health University Institute, Verdun, QC, Canada [3], Department of Psychiatry, McGill University, Montreal, QC, Canada.

Introduction: Cannabis legalization has increased prenatal use, and among pregnant users, about 45% also use tobacco. While the individual effects of prenatal cannabis and tobacco exposure on cognition are known, their combined impact is overlooked. We aimed to compare cognitive performance in children with prenatal co-exposure to those with single-substance exposure or no exposure.
Methods: Data from 9-11 year-old children (N=9873) were derived from the Adolescent Brain Cognitive Development (ABCD) study and parsed into four groups: 1) children with prenatal co-exposure (CT, n=243), 2) cannabis-only (CO, n=199); 3) tobacco-only (TO, n=828); and 4) no exposure (CTL, n=7683). Cognitive outcomes included fluid intelligence, reflecting reasoning, and crystallized intelligence, representing acquired knowledge. Fluid and crystallized scores were measured via the NIH Toolbox cognition battery. Linear mixed models were used to evaluate group differences in cognitive outcomes while employing the relevant covariates.
Results: CT had lower fluid scores than CO (b =1.93, p=0.04), CTL (b =1.72, p=0.01), and TO (b =1.54, p=0.04). Crystallized scores did not differ between CT and other groups (CO: b=0.60, p=0.33; CTL: b=0.22, p=0.61; TO: b=0.14, p=0.77). The interaction between cannabis and tobacco was associated with lower fluid scores at trend level (b =-1.96, p = 0.06).
Conclusion: Overall, results suggest a synergistic effect of prenatal cannabis and tobacco exposure on fluid intelligence. In contrast, crystallized intelligence showed no significant difference between groups. Future research should investigate the mechanisms underlying the association between prenatal co-exposure and fluid cognition given that these deficits may result in long-term consequences on child education and development.

Protocadherin-alphaC2 is required for fluoxetine-induced serotonin re-innervation and behavioral recovery after stroke

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Introduction: Post-stroke depression (PSD) commonly occurs within 3 months after a stroke in 30–50% of stroke survivors. It impairs cognition and anxiety regulation, increases long-term mortality and risk of recurrent stroke. Current treatments with selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (FLX), yield

incomplete remission. To model PSD, we administered unilateral microinjection of endothelin-1 (ET-1) into the medial prefrontal cortex (mPFC) of mice to induce ischemia. After 5–6 weeks of FLX treatment, behavioral phenotypes improved, and 5-HT axonal circuitry was restored. Since protocadherin-aC2 (PcdhaC2), essential for serotonergic circuit organization during development, we hypothesized that it is required during adulthood for FLX-induced axonal recovery and its antidepressant effects.
Methodology: Pcdha genes were knocked-out in adult 5-HT neurons in tamoxifen-inducible TPH2-ACON mice. Then mice were given stroke and treated with FLX or vehicle for three weeks and during behavioral and cognitive assessments. Brains were collected and immunostained for FosB and SERT to evaluate brain-wide activity and serotonergic axon density and varicosities.
Results: In wild-type mice, FLX induced behavioral and cognitive recovery, increased PcdhaC2 expression in 5-HT neurons, restored serotonergic innervation, and increased FosB and GAD67 expression in mPFC. In contrast, in Pcdha-cKO mice FLX did not improve behavior/cognition and regrowing serotonergic axons became tangled with reductions in SERT axonal volume and varicosities in hippocampus and mPFC stroke site. Anterograde transsynaptic tracing will be done to map the synaptic connectivity of 5-HT axons following stroke and FLX treatment.
Conclusion: Thus, PcdhaC2 is critical for FLX-induced serotonergic neuroplasticity and recovery from PSD.

Cross-Paradigm Effects of Social Defeat and Learned Helplessness Stress: A Role for BDNF-ERK and Noradrenergic Signaling

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Introduction: Individual variability in resilience to stress-related disorders, such as depression and PTSD, is shaped by both molecular and neural circuit adaptations. In this study, we investigate cross-resilience to chronic social defeat stress (CSDS) and learned helplessness (LH), with a focus on the involvement of the BDNF-ERK signaling pathway and the noradrenergic system.
Methods: Male and female C57BL/6J mice were subjected to 10 days of CSDS, resulting in the emergence of resilient (RES) or susceptible (SUSC) phenotypes. These were followed by a 30-day LH protocol using inescapable foot shocks. Key brain regions (ventral tegmental area, amygdala and nucleus accumbens) were analyzed for BDNF and ERK1/2 signaling. To assess the role of norepinephrine (NE), female NE-deficient mice (VMAT2loxDBHcre KO) were included, as KO males consistently exhibit a SUSC phenotype in CSDS and are thus unsuitable for assessing cross-resilience.
Results: Our findings indicate that RES and SUSC phenotypes emerge distinctly in both CSDS and LH models, with marked sex-specific differences. Males that were SUSC for both CSDS and LH had lower BDNF protein level in the NAc and AMY and reduced phospho-ERK1/2 in the VTA. SUSC females showed elevated BDNF and region-specific changes in ERK1/2. In NE KO females, resilience to CSDS persisted despite LH exposure. However, in wild-type (WT) males, resilience was completely reversed, and in WT females, it was partially reversed, suggesting that NE depletion preserves resilience under additional stress. **Conclusion**: Our findings reveal sex-specific behavioral and molecular mechanisms underlying cross-resilience to social and

physical stressors, implicating the BDNF-ERK signaling cascade and noradrenergic pathways as potential contributors to cross-resilience mechanisms.

Understanding the impact of social stress on sociability and drug reward sensitivity in adolescence

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Introduction Social adversity in adolescence increases vulnerability to substance use disorders later in life, however, whether this risk is linked to stress-induced social impairment soon after exposure is unknown. Here we assessed the short-term effects of social stress in adolescence on sensitivity to the rewarding effects of amphetamine in male mice.
Methods Mice were exposed to the (Accelerated Social Defeat) AcSD paradigm whereby adolescent C57/BL6 male mice were introduced (10 min) twice a day to a different CD-1 mice from postnatal day (PD) 25-28. CD-1 mice aggressive behavior was primed by introducing an adult mouse for 30 sec prior to the adolescent mouse. 24h after the last session, a standard social interaction test was used to measure sociability and to segregate defeated mice into susceptible (social avoidant) or resilient (non-social avoidant) groups. From PD30-35, the rewarding properties of amphetamine (4 mg/kg) were assessed using the conditioned place preference paradigm.
Results Defeated mice show social avoidance (Susceptible) compared to control mice ($p<0.0001$ 95% CI [0.8331, 2.224]), however a proportion shows similar interaction as controls (Resilient) ($p<0.0970$ 95% CI [-1.184 to 0.07580]). On the contrary, differences in sociability did not translate into differences in amphetamine reward sensitivity - AMPH induced CPP in all groups ($F(1, 17) = 6.054$ $p=0.024$) but there was no interaction between drug and stress factors ($F(2, 17) = 0.1468$, $p=0.864$). No correlations were found either between social interaction ratios or time in the corners with CPP preferences scores.
Conclusion Social stress in adolescence does not seem to impact sensitivity to AMPH-induced reward soon after defeat exposure. We are assessing if adolescent social adversity influences drug-induced reward in the long term, similar to its enduring impact on impulse control.

Neurostructural Correlates of Polygenic Risk for Anxiety Disorders among Youth with and without Bipolar Disorder

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Introduction: Anxiety disorders (ADs) are common among youth with bipolar disorder (BD). We recently found that ADs are associated with significantly more adverse clinical characteristics in youth with vs. without BD. The current study seeks to advance understanding of mechanisms underlying these clinical findings. We therefore examined neurostructural correlates of polygenic risk scores for ADs (AD-PRS) in relation to youth BD.
Methods: T1-weighted MRI was obtained from 111 youth ages 13-20 (n=67 BD, n=44 healthy controls [HC]). AD-PRS were generated using PRS-CS-auto, based on adult genome-wide association study summary statistics. Analyses examined the association of AD-PRS with cortical surface area (SA), volume, and thickness in the whole sample, and within BD and HC. Region of interest (ROI; amygdala, ventromedial prefrontal cortex [vmPFC], anterior cingulate cortex) and vertex-wise analyses were undertaken.
Results: In ROI analyses, higher AD-PRS was associated with lower vmPFC thickness (ß=-0.26 p=0.010) in the overall sample and was associated with larger amygdala volume in BD (ß=0.21 p=0.034) but not HC (ß=-0.21 p=0.072). In vertex-wise analyses, higher AD-PRS was associated with lower right superior frontal gyrus volume, lower left rostral middle frontal gyrus thickness, and lower middle temporal gyrus thickness in the overall sample.
Conclusion: We found that AD-PRS is associated with structural alterations in frontal and temporal brain regions implicated in emotion regulation and cognitive control. While replication is warranted, present findings suggest that the association of AD-PRS with amygdalar volume may contribute in part to the particularly adverse clinical correlates of ADs in youth with BD.

Fishing for Complements: Emerging Associations Between the Complement System and Schizophrenia

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Introduction: The complement system is a key effector of innate immunity, mediating elimination of pathogens and cellular debris via phagocytosis and cell lysis and inducing inflammatory responses. Intriguingly, recent studies suggest that functions of the complement system extend beyond immune surveillance, being essential for vital brain homeostatic processes such as synaptic plasticity. The objective of this study was to compare protein and mRNA expression of a panel of complement components and regulators in postmortem brain tissue from schizophrenia (SCZ) and control subjects.
Methods: Postmortem brain samples comprising frontal cortical regions were obtained from 35 individuals with SCZ and 35 controls, courtesy of the Stanley Medical Research Institute. Protein and/or mRNA expression of complement components (C1q, C3, C4, C7, C9, C5b-9) and complement regulators (C1-inhibitor, FB, FH, FI, Sez6, CSMD1, CD55, CD59) was quantified by immunoblotting and/or quantitative PCR. Data was compared between diagnostic groups using ANCOVA.
Results: C4A mRNA expression was increased in SCZ, although C4 protein levels did not differ between

groups. Levels of C7, C9 and C5b-9 protein were significantly higher in SCZ compared to controls. In terms of regulators, expression of Sez6 mRNA was lower in SCZ relative to controls, while C1-inhibitor protein levels were higher. Alterations in complement mRNA expression or protein levels in SCZ were typically driven by male subjects.
Conclusion: Overall, this study provides evidence that both early and late components of the complement system are increased in SCZ, and that modulation by complement regulators may be disturbed in this disorder.

Neuronal Activation During an Acute Food Deprivation-Induced Heroin Seeking Test, After Punishment-Imposed Abstinence, in Male Rats.

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Introduction: The biggest challenge in the treatment of drug addiction is preventing relapse. Abstinence is often self-imposed: addicts choose to abstain from drug use due to the associated negative consequences. Using a punishment-imposed abstinence model, we aim to identify the brain regions involved in food deprivation stress-induced relapse to heroin.
Methods: Rats (male Long Evans, N=30) underwent heroin self-administration training (0.1 mg/kg/infusion) for 2 weeks using the seek-take chain procedure. After self-administration, rats went through 4 days of punishment-imposed abstinence, with a probabilistic footshock (30%, 0.5 s, 0.2-0.4 mA) instead of access to the take lever. Rats were exposed to a 24 h food deprivation or a sated period before the heroin test. To assess Fos activation, brains were collected during punishment (N=4), food deprivation/sated day (FD: N=3/Sated: N=3) and food-deprivation-induced heroin seeking test or sated test (FD test: N=7, Sated test: N=7).
Results: Acute food deprivation significantly increased heroin relapse after punishment-imposed abstinence and Fos expression in the IL compared to the sated test group. During food deprivation heroin test, the NAcShell activation was positively correlated with heroin seeking, and the following brain areas showed significant correlations: CeA-BLA (r = 0.887), PrL-IL (r = 0.986), PrL-Cg1 (r = 0.851), NAcCore-NAcShell (r = 0.915), BNST-NAcCore (r = 0.923) and Cg1-NAcCore (r = 0.932). On the sated tests, the aPVT was negatively correlated with heroin seeking, and the two significant correlations were the BNST-NAcShell (r = 0.980) and NAcShell with IL (r = 0.988).
Conclusion: These results suggest an involvement of the IL and NAcShell in acute food deprivation-induced heroin seeking, after punishment-imposed abstinence.

Effect of individual and combined cytochrome P450 activity scores on symptom improvement and side effects in youth treated with sertraline

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Introduction: Sertraline is commonly used to treat mental health conditions in children and adolescents. However, its tolerability and efficacy vary between individuals, partly due to interindividual differences in drug metabolism. This study assessed the individual and combined impact of genetic variation in cytochrome P450 drug-metabolizing enzymes on patient-reported side effects and symptom improvement in youth.
Methods: 347 youth, aged 6-24, receiving sertraline treatment were included. Participants reported sertraline dose, duration, adherence, concomitant medications, side effects, and symptom improvement. DNA was extracted from saliva samples and genotyped for CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Individual activity scores and a weighted combinatorial CYP450 activity score was created. Binomial logistic regression models were used to assess the impact individual and combined CYP450 activity scores had on patient-reported side effects and symptom improvement, both with and without correction for phenoconversion.
Results: After adjusting for phenoconversion, other CYP450 activity scores, and covariates, higher activity scores for CYP2D6 (OR = 0.66, 95% CI = 0.45–0.97) and CYP3A4 (OR = 0.047, 95% CI = 0.004–0.612) were associated with reduced odds of symptom improvement. A higher combined CYP450 activity score was also associated with reduced odds of symptom improvement. No significant associations were observed for side effects (OR = 0.078, 95% CI = 0.007–0.895).
Conclusion: These findings confirm the complexity of sertraline metabolism and suggest that a combined CYP450 activity score may be associated with symptom improvement in youth. If replicated, these results may inform updates to pharmacogenetic prescribing guidelines for sertraline and support more personalized sertraline use in children and adolescents.

Combined in vivo fiber photometry and intravenous self-administration reveals activation of ventral hippocampus neurons by drug-taking and drug-seeking

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Introduction: Substance use disorder (SUD) remains a persistent public health crisis, with relapse posing a major barrier to long-term recovery. Environmental contexts previously associated with drug use frequently trigger relapse, but the neural mechanisms underlying this association remain unclear. This study aimed to characterize how drug-related experiences reshape ventral hippocampus (vHPC) activity, a brain region implicated in linking contextual cues to reward and previously suggested to promote drug-seeking behaviour.
Methods: Intravenous self-administration (IVSA) in male mice, combined with fiber photometry calcium imaging, was used to monitor vHPC activity during drug-taking and drug-seeking. Mice received stereotaxic surgery to implant GCaMP8s into the vHPC and insert an optical fiber, and jugular vein catheterization to enable intravenous drug delivery. Following recovery, mice self-administered heroin (0.05mg/kg/inf) or cocaine (0.5mg/kg/inf) via lever pressing under a fixed-ratio 1 schedule. Mice then underwent forced abstinence and were tested for drug-seeking behaviour, measured as lever pressing in the absence of drug reinforcement, at 24 hours and 30 days after the final IVSA session. vHPC neural activity was recorded during day 8 of IVSA,

and in 24h drug-seeking and 30d drug-seeking. Neural activity was aligned to lever presses to assess event-related neural dynamics.
Results: Both heroin and cocaine IVSA elicited robust vHPC activation during drug intake. Heroin-seeking induced a significant increase in vHPC activity at 24 hours post-abstinence, with even greater activation at 30 days ($p < 0.05$). Effects with cocaine were less robust, potentially reflecting a drug-specific role for the vHPC in contextual neural encoding.
Conclusions: These findings indicate that the vHPC is dynamically engaged during both drug-taking and drug-seeking, particularly in heroin relapse. This highlights a potential mechanism by which contextual cues drive relapse and underscores the vHPC as a candidate target for interventions aimed at reducing relapse risk in SUD.

Alterations in morphine reward through acquisition of a positive- or negative-feature interoceptive morphine occasion setter in male and female rats

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Introduction: Occasion setters can be used to disambiguate associations of exteroceptive conditioned stimuli (CS) and appetitive unconditioned stimuli under both feature positive (FP) and feature negative (FN) conditions. We hypothesized that the incentive value of the occasion setter is altered following training in a valence-specific direction. To investigate the impact of FP and FN training history, we assessed an interoceptive morphine stimulus occasion setter on subsequent morphine reward.
Methods: Male and female rats were assigned to FP, FN, or control (FX) groups. All groups received daily, intermixed injections of morphine or saline prior to training sessions. On morphine sessions, FP rats were presented with a light CS followed by sucrose access; sucrose was withheld on saline sessions. FN rats were trained on the opposite contingency. Control groups received sucrose on half of morphine and half of saline sessions. Immediately following training, rats entered place conditioning wherein morphine was paired with a distinct context of a two-sided chamber, and saline with the other. During preference testing, rats had access to both sides of the chamber.
Results: Rats acquired FP and FN discrimination. FX showed high sucrose-seeking on both morphine and saline sessions. FX rats subsequently expressed the highest morphine place preference score. There was no effect of sex and a notable effect of training history across all groups. Contrary to the original hypothesis, rats trained under the FN contingency demonstrated a higher place preference than FP.
Conclusions: FX groups demonstrated the most robust morphine place preference. The attenuated morphine preference in FP relative to FN groups may be due to the loss of additive rewarding effects of morphine and sucrose learned during discrimination training. FN groups never experienced morphine in the presence of sucrose, which may have allowed morphine to retain its original incentive value.

Synaptic Density in Youth with Cannabis Use: Preliminary Cross-sectional Findings From [18F]SynVesT-1 PET Imaging in the Toronto Adolescent and Youth (TAY) Cohort & Healthy Controls

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Introduction: Adolescence is a key period for neurodevelopment, marked by synaptic pruning. While chronic cannabis use has been linked with lower synaptic density in adults, it remains unclear whether this finding extends to youth. Here, we investigate if near-daily cannabis exposure in youth is related to lower synaptic density in the brain, leveraging PET imaging with [18F]SynVesT-1.
Methods: A preliminary sample of individuals from the ongoing Toronto Adolescent and Youth (TAY) cohort study, as well as an ongoing control study were recruited to complete a PET scan with the radiopharmaceutical [18F]SynVesT-1. MRI of each participant was used to delineate six corticolimbic regions of interest (ROIs). Time-activity curves were fitted using a simplified reference tissue model (SRTM-2) with the centrum semiovale (CS) as the reference region. Non-displaceable binding potential (BPnd) were compared between individuals. Timeline Followback for the last 90 days (TLFB-90) was used to delineate near daily use of cannabis (+5 days a week in the last 90 days).
Results: Fifty individuals from the TAY study (17M, 33F; 20.8 years), and thirteen individuals from a control study (7M, 6F, 20.8 years) completed imaging scans. In total, sixteen reported near daily use of cannabis (68 days of the last 90 days V.S. 8 days in non-daily users). Overall, there was there was marginally lower binding in the hippocampus (-9.2%, p=0.07) when controlling for differences in childhood trauma (CTQ).
Conclusion: These preliminary findings in youth are consistent with adult studies showing lower synaptic density associated with heavy cannabis use, suggesting that cannabis may impact the brain during a sensitive period of neurodevelopment. Future work will continue to assess differences in synaptic density in youth with cannabis use tracked longitudinally, and explored in relation to emerging psychopathology.

Striatal Heterogeneity: Functional & Organizational Roles of Newly Defined D1 Neuron Subpopulations

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Introduction: The striatum is a well-conserved brain structure implicated in motor, reward, and cognition in addition to psychiatric disease. Medium spiny neurons (MSNs) make up the bulk of the striatum and have been classically divided based on dopamine receptor expression into D1- and D2-MSNs. Although this division has been useful in explaining function, it largely ignores the significance of striatal heterogeneity, such as the varied organization of MSNs, i.e. their compartmentalization into patches and matrix, or their diverse molecular structure outside of the D1/D2 binary. Using mice, we aim to clarify the significance of this heterogeneity by functionally exploring newly defined D1-MSN subtypes which deviate from the D1/D2 binary. AIM 1 explores the D1-NKB-MSN, heterogeneous in both its co-expression of Tac2 and its organization into subpopulations in the nucleus accumbens and lateral stripe of the striatum.

Methods: Using in-situ hybridization, viral tracing, and cell-specific knockouts in transgenic mice, we will assess D1-NKB-MSN's projections, effects on behavior, and D1's role in this functioning. AIM 2 focuses on the D1-D2-MSN, heterogeneous in its co-expression of both D1 and D2. Preliminary results reveal disrupting this MSN may alter the patch/matrix organization. Using mice with D1 knocked out in D1-D2-MSNs, conditional viral apoptotic injections, and immunohistochemistry for patch/matrix indicators (mu-opioid and calbindin), we will examine the D1-D2-MSN's role in striatal patterning and the influence of D1 on this role.
Preliminary results: Although sample size is not yet high enough for statistical analysis, patches are greatly reduced/diminished (in both number and intensity) in the dorsal striatum of mice with disrupted D1-D2-MSNs as compared to controls.
Conclusion: Our study will refine our understanding of striatal functioning by incorporating molecular and organizational heterogeneity into binary models of striatal dopaminergic functioning. This will advance fundamental neurobiology and expose research targets for striatal-related psychiatric diseases.

Investigating Fatty Acid Amide Hydrolase in Occupational Trauma Exposed Healthy Controls and Posttraumatic Stress Disorder; a PET Study of [11C]CURB

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Introduction: Exposure to traumatic events is common but only some individuals develop posttraumatic stress disorder (PTSD). Those in high-risk occupations, such as military personnel and first responders face higher risk due to repeated or chronic trauma exposure. In preclinical models, elevated levels of fatty acid amide hydrolase (FAAH)—the enzyme responsible for breaking down the endocannabinoid anandamide (AEA)—have been consistently associated with PTSD-like behaviors. However, the role of FAAH in human PTSD remains unclear. This study used positron emission tomography (PET) to test the hypothesis that FAAH levels are elevated in individuals with occupational PTSD.
Methods: 25 participants with occupational trauma exposure (OTE; n= 10 healthy controls) completed PET imaging with the FAAH probe [11C]CURB. All participants were genotyped for the FAAH C385A polymorphism. A repeated measures ANCOVA (ROI (7) x group (2)) controlling for FAAH was run to investigate group differences in corticolimbic FAAH levels. Differences in clinical symptoms were also assessed.

Results: There were no significant group differences in age, sex, genotype or cannabis/alcohol history. The PTSD group exhibited moderate symptom severity (PSS= 26.7±7.6) and reported significantly higher levels of anxiety (GAD-7; p=.001), and depression (PHQ-9; p=.001) compared to healthy controls. [11C]CURB binding was ~12.0%-16.3% lower in the PTSD group (p=.041) with notably lower values in the temporal cortex (-

16.3%, p=.020) and insula (-14.8%, p=.025). [11C]CURB binding did not significantly correlate with symptom severity.
Conclusion: Relative to OTE controls, individuals with occupational PTSD have lower levels of FAAH and increased symptoms of anxiety, depression, and trauma. This pattern contrasts with preclinical models, where elevated FAAH has been associated with stress responses. These discrepancies highlight the need for further clinical research to understand the mechanisms underlying lower FAAH in PTSD, including the potential influence of treatment and chronicity.

Adult rat ultrasonic vocalizations as potential markers of aversion in nicotine withdrawal

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Introduction: The standard rat model of nicotine withdrawal employs drug administration via constant-rate subcutaneous minipump, and produces peripheral signs of opioid-like withdrawal. In adult rats, withdrawal from certain other addictive drugs, when combined with aversive stimuli, promotes the emission of 22-kHz ("alarm/distress") ultrasonic vocalizations (USVs). The heterogeneous 50-kHz USV family has been little studied during drug withdrawal, but has been linked to positive/negative emotion. Therefore, we used oral nicotine exposure to more closely approximate diurnal nicotine exposure in smokers, and we analyzed USV recordings.
Methods: Male Long-Evans rats received nicotine in their drinking water (0, 0.02, or 0.05 mg/ml) for 3 weeks. USVs were recorded at the end of chronic exposure, and at 1 and 2 days after discontinuation. During the once-daily recording sessions, an aversive air puff stimulus was applied intermittently.
Results: Contrary to expectations, 22-kHz calls were virtually absent in all test sessions. Spontaneous nicotine withdrawal did not affect the rate of 50-kHz call emission, but altered the relative prevalence of 50-kHz call subtypes in the higher-dose nicotine group. Specifically, "flat" calls became more prevalent at the expense of "trill" calls; the same kind of shift has been seen in some other aversive drug states, whereas acute psychostimulants and morphine produce the opposite shift. No group differences were detected prior to nicotine discontinuation. Opioid-like somatic withdrawal signs were absent.
Conclusions: Our chronic oral nicotine regimen, combined with ultrasonic vocalization analysis, appears able to capture a negative emotional state associated with early nicotine withdrawal. Unlike in the standard minipump-based rat model, peripheral opioid-like withdrawal signs did not occur. Hence, our procedure may be useful in modelling negative emotion during nicotine withdrawal, which represents a major – but potentially tractable – obstacle to quitting smoking. Funding: NSERC and CIHR.

Up in Smoke: Tracking Changes in Cigarette Use During 28 Days of Cannabis Abstinence

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Introduction: Cannabis and tobacco are commonly used together, and tobacco co-use has been linked to higher rates of cannabis initiation and greater addiction severity of both substances, suggesting a complementary relationship. If such a relationship exists, abstaining from one substance might lead to reduced use of the other. To test this hypothesis, we examined whether cigarette use decreased during 28 days of cannabis abstinence among individuals who co-use both substances.
Method: Thirty-four non-treatment seeking individuals reporting past month cigarette use and meeting diagnostic criteria for a cannabis use disorder and/or using cannabis = 4 per week were selected from a larger dataset. Of these, 28 participants were assigned to an abstinent arm (CAN-) and six participants to a cannabis as usual arm (CAN+). Participants in the CAN- arm, underwent 28 days of cannabis abstinence supported by contingency management and weekly behavioural support sessions. In both groups, the average number of cigarettes smoked per day the prior week was assessed at baseline and then weekly (days 0, 7, 14, 21, and 28) using the Timeline Followback. Cannabis abstinence was verified biochemically with twice-weekly urine analysis.
Results: Nine participants in the CAN- group relapsed and were excluded from the analyses. The CAN- (n=19) and the CAN+ (n=6) groups were similar on demographic and substance use variables. A repeated measures ANOVA revealed no significant main effect of time on cigarette use, $F(3, 54) = 0.96$, $p = .40$, and no significant time x group interaction, $F(2.23, 59.51) = 0.38$, $p = .71$.
Conclusion: Our findings suggest that despite a complimentary relationship between cannabis and tobacco, among people who co-use, cigarette use remains stable during 28 days of cannabis abstinence. These results highlight the need for separate, targeted interventions for each substance. Future research should explore whether a similar pattern is observed during tobacco abstinence.

Pain Predicts Treatment Response to Nabilone for Agitation in Alzheimer's Disease

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Introduction: Agitation in Alzheimer's disease (AD) is a common and challenging symptom that can be exacerbated by underlying pain. Understanding patient factors that influence treatment response is critical for personalized care. This study examined baseline pain as a potential moderator of treatment efficacy of nabilone for agitation.
Methods: We analyzed data from 39 AD patients who participated in a phase II crossover trial evaluating the safety and efficacy of nabilone for agitation in AD. There were no detectable order or carryover effects at the end of the washout period; we treated phase-specific baselines as independent datapoints. We categorized responders as those with changes = -8 points on the Cohen-Mansfield Agitation Inventory (CMAI). The predicted response was modeled using logistic regression. Predictors included treatment group, baseline pain

severity measured by the Pain Assessment in Advanced Dementia (PAINAD) scale, baseline CMAI scores, concomitant analgesics, and the interaction between treatment and pain.
Results: Treatment phases showed no difference in baseline CMAI and pain scores ($t = 0.43$, $p = 0.66$; $W = 651$, $p = 0.81$). The interaction between pain and treatment was significant ($OR = 3.28$, $p = 0.04$), indicating that higher baseline pain levels were associated with a greater response to nabilone. Higher baseline pain severity showed a trend of lower placebo response ($OR = 0.41$, $p = 0.06$). In addition, a higher baseline CMAI score predicted greater odds of response ($OR = 1.06$, $p < 0.01$). Concomitant analgesics did not affect treatment response rates ($OR = 0.58$, $p = 0.40$).
Conclusion: The data presented in this study suggest that baseline pain severity moderates the efficacy of nabilone in treating agitation in AD. This finding is consistent with the purported analgesic effects of cannabinoids and highlights the importance of including pain evaluations in persons with AD to optimize agitation management.

Actions of chronic restraint stress, zinc, and vortioxetine on behavior, brain activity and serotonin projections

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Introduction: Major depressive disorder leads to neurochemical changes that alter brain structure and function. Selective Serotonin (5-HT) Reuptake Inhibitors (SSRIs) are the first-line treatment; however, only 50% of patients remit with a 6-8-week latency. To address the role of 5-HT innervation, we previously used 6-week unpredictable mild stress (UCMS) to model depression. This reduced brain activity and 5-HT projections, and restoration of 5-HT innervation in hippocampus via stimulation of 5-HT neurons correlated with behavioral improvement. To further investigate, we used a 3-week chronic restraint stress (CRS) in male C57BL6 mice subjected to different Zinc (Zn) diets and treated with multimodal antidepressant Vortioxetine.
Methods: FosB was used as a marker of chronically active cells. 5-HT innervation was quantified by staining for 5-HT transporter; 5-HT synapses and triads were identified as synaptophysin-stained sites within 5-HT axons in apposition to gephyrin- or PSD95-stained spines.
Results: The CRS protocol induced weight loss, cognitive decline and anxiety/depression-like phenotypes, as seen in EPM and NSF tests. After CRS, widespread reductions in FosB+ cells were seen, including in nucleus accumbens, lateral septum, hippocampus, and dorsal raphe but no changes in 5-HT innervation. Vortioxetine reversed behavioural effect, but did not alter FosB in most regions, but increased 5-HT axonal volume in the hippocampal CA1 area.
Conclusion: Similar to UCMS, CRS induced depression/anxiety-like phenotypes regardless of Zn diet and reduced brain-wide activity, but did not affect 5-HT innervation. However, Vortioxetine+Zinc increased 5-HT innervation in the hippocampus, suggesting its role in mediating antidepressant response.

Neural Predictors of Depression Outcomes in Depressed Adolescents: A Multimodal Neuroimaging Study

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Introduction: Depression treatment outcomes vary widely among patients, with substantial individual differences in symptom improvement that neuroimaging biomarkers could help predict. This study evaluated whether baseline functional and structural neuroimaging measures can predict 1-year depression severity outcomes in depressed adolescents.
Methods: Clinical participants completed baseline neuroimaging assessments including task-based fMRI (Cyberball social exclusion, N=46; Go/No-Go inhibitory control, N=43) and structural MRI (cortical surface area, N=49). Depression severity was assessed at 1-year follow-up using the Beck Depression Inventory (BDI). Linear regression models predicted 1-year BDI scores controlling for baseline depression severity, age, and sex. False discovery rate correction addressed multiple comparisons across brain regions.
Results: Cognitive control fMRI showed the strongest predictive associations. The largest effect was right cingulate activation during Go/No-Go (ß=3.70, 95% CI: 0.01-7.39), suggesting each unit increase in cingulate engagement was associated with a 3.7-point increase in depression severity. Additional cognitive control regions showed modest associations: left precentral (ß=-2.97, 95% CI: -8.03-2.09) and right fusiform (ß=-1.78, 95% CI: -4.97-1.41). Structural measures showed intermediate predictive value: left middle temporal (ß=-3.12, 95% CI: -7.47-1.23), left superior temporal (ß=2.72, 95% CI: -1.23-6.68) and left insula (ß=2.52, 95% CI: -1.33-6.36). Social exclusion showed weakest associations: right inferior frontal (ß=1.64, 95% CI: -1.56-4.84).
Conclusion: While no brain regions reached statistical significance, cognitive control fMRI showed strongest predictive associations, followed by structural measures and social exclusion activation. These findings suggest task-specific neural responses, particularly during cognitive control, may provide informative biomarkers for predicting depression trajectories, though larger samples are needed for definitive conclusions.

Differential and Dose-Dependent Effects of Heroin on Memory Consolidation

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Introduction: It has been proposed that reinforcing drugs promote the development of addiction through the enhancement of consolidation of memories formed during drug use. From a cognitive-behavioural perspective, such hypothesis would predict drug-induced modulation of consolidation on functions of different memory systems involved in addiction. Our laboratory has demonstrated consistent evidence of memory consolidation facilitation by heroin for episodic memories. In the current studies, we explored the effects of post-training heroin in male Sprague-Dawley rats on stimulus-affect learning, as well as consolidation of spatial learning.

Method: Experiment 1 employed place conditioning by 1 mg/kg heroin (n=48) or 20 mg/kg cocaine (n=30) and tested the effects of post-conditioning injections of vehicle, 1 mg/kg heroin, or 1 mg/kg heroin + 3 mg/kg naloxone. Animals were tested after 1 pairing (test 1) and 4 pairings (test 2). Experiment 2 tested the effects of heroin on consolidation of spatial learning using a version of the Barnes maze task assessing the acquisition of a consistent escape location. Rats (n=60) were trained to find a fixed escape box on 10 sessions and received either vehicle, 1 or 2 mg/kg heroin post-training. At the end of training, animals were tested on a probe trial during which the escape hole was relocated.

Result: In Experiment 1, post-training heroin negatively impacted the development of a place preference, and this heroin-induced impairment of consolidation was prevented by naloxone. In Experiment 2, it was found that 1 mg/kg increased escape latency, training target investigation, and training quadrant locomotion during the probe trial, suggesting enhanced perseveration of the trained response. In contrast, 2 mg/kg heroin decreased target hole exploration on probe, likely reflecting impaired spatial learning.

Conclusion: These studies using the opiate heroin suggest that drug reinforcers do not have equivalent effects on consolidation of traces mediated by different memory systems.

Does Puberty Interact with Drugs of Abuse to Organize Dopamine and Cognitive Development in Male Mice?

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Introduction Stimulant drugs of abuse in adolescence increase psychiatric risk, with marked differences in susceptibility between males and females and between recreational and therapeutic drug use. Amphetamine in adolescence disrupts dopamine development via the Netrin-1/DCC system, inducing impulse control deficits in adulthood in male mice, whereas females are completely protected, suggesting a role of pubertal gonadal hormones in the sex-specific sensitivity.
Methods Male mice underwent orchidectomy (ORX) or Sham surgery at weaning to prevent puberty. Two days later, mice were administered amphetamine using a recreational (4 mg/kg; AMPH) or a therapeutic (Adderall)-like dose (0.5 mg/kg, ALD) regimen, or saline. Rewarding effects were assessed during treatment using conditioned place preference (CPP). In adulthood, mice were trained for discrimination learning and reaction time before the Go/No-Go task. In a separate cohort, dopamine transporter–positive neurons were

isolated using antibody-based magnetic sorting to measure Netrin-1/DCC pathway transcripts one week after treatment. Blood plasma testosterone was measured with ELISA to confirm ORX effectiveness.
Results AMPH and ALD induced robust CPP regardless of gonadal hormone status. Drug treatment did not alter discrimination learning; however, all ORX mice showed delayed task acquisition. AMPH and ALD groups showed impaired waiting impulsivity compared to saline controls during reaction time training; however, this effect was not observed in ORX mice. Go/No-Go task analysis is ongoing. AMPH downregulated DCC expression in dopamine neurons compared to saline, regardless of pubertal gonadal manipulation. Molecular experiments with ALD are ongoing.
Conclusion The rise in male pubertal gonadal hormones does not impact the effects of amphetamine in adolescence on reward and Netrin-1/DCC system soon after treatment termination but seems to modulate drug-induced alterations in learning and impulse control later in life, suggesting an interaction between sex hormones and drug of abuse in adolescent neurodevelopment.

Distinct Roles of Striatal Dopaminergic Subpopulations in Time Perception

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Introduction Disturbances in temporal perception, anticipation, and prediction are common features across disorders such as schizophrenia, ADHD, and Parkinson’s disease. This study examined how striatal dopaminergic neuron subpopulations, classified by dopamine receptor type, contribute to the perception of time and the acquisition of temporal tasks. We hypothesized that these subpopulations have distinct roles in temporal task performance and learning.
Methods Three cohorts of transgenic mice (total n = 26) were trained on a licking-based fixed-interval reward anticipation task (modified from Toda, 2017) for up to 60 sessions. Training was analyzed using a novel periodization framework to capture developmental aspects of task acquisition. Experimental groups included animals with selective dopamine transmission deficiencies, such as D1- and D2-type receptor knockouts (KOs).
Results Dopamine transmission-deficient animals displayed stage-specific impairments. Notably, we observed an inability to habituate to the task procedure among D2-type KO animals, and an inability to develop anticipatory licking behavior in full D1-type KO mice and in mice with D1-type receptors KO in D1/D2 receptor co-expressing neurons. Periodization analysis revealed distinct acquisition patterns corresponding to each dopamine pathway.
Conclusion Striatal dopaminergic subpopulations contribute differentially to time perception and temporal task acquisition processes - mechanisms relevant across multiple disorders. Identifying these roles extends our understanding of underlying neuronal mechanisms, which is essential for progress toward effective treatments for a wide range of cognitive dysfunctions.

Low-dose naloxone precipitates conditioned place aversion during chronic oral nicotine exposure in female Long-Evans rats

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Introduction: Imaging studies suggest that tobacco smoking can acutely increase endogenous opioid release in the brain. Conversely, preliminary reports suggest that, in rats receiving chronic nicotine, a naloxone (opioid antagonist) challenge can precipitate an aversive state revealed by conditioned place aversion. These earlier rodent findings were obtained in male rats, with nicotine delivered as a constant infusion via osmotic minipump. In contrast, we recently established a chronic oral nicotine regimen which provides a circadian pattern of nicotine exposure, more resembling that experienced by cigarette smokers. Here, we ask whether low doses of naloxone can precipitate a conditioned place aversion in female rats that are maintained on chronic oral nicotine.
Methods: Adult female rats were given single-bottle access to a 1% saccharin solution, with or without added nicotine (n=12 rats/group). Saccharin, at this concentration, appears motivationally neutral and helped to mask the bitter taste of nicotine. After three weeks, a conditioned place aversion (CPA) procedure was initiated while chronic drug exposure continued; this procedure included multiple interleaved conditioning sessions with acute naloxone and saline. Two subcutaneous doses of naloxone were tested: 0.1 mg/kg in Experiment 1, and 0.25 mg/kg in Experiment 2.
Results: As expected, neither of these low doses of naloxone induced a CPA in the nicotine-naïve chronic groups. In rats maintained on nicotine, however, naloxone produced a CPA at both doses (0.1 and 0.25 mg/kg, respectively: $p<0.05$ and $p<0.01$).
Conclusion: The present study extends earlier work by using female rats and a circadian pattern of chronic nicotine exposure. These findings suggest that chronic exposure to nicotine can render female rats highly sensitive to the aversive effects of the opioid antagonist naloxone. As such, our findings suggest that chronic nicotine administration, given here in a circadian pattern, can induce a form of dependence on endogenous opioids. Funding: CIHR

Amphetamine in Adolescence Induces a Sex-Specific Mesolimbic Dopamine Phenotype in the Adult Prefrontal Cortex

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Introduction: Drugs of abuse in adolescence impact brain maturation and increase psychiatric risk, with sex-specific sensitivities. Amphetamine in adolescent male, but not female mice, leads dopamine axons that typically innervate the nucleus accumbens to instead project to the prefrontal cortex (PFC), a process associated with drug-induced downregulation of the Netrin-1 receptor DCC. This study examines the impact of disrupted dopamine axon pathfinding on PFC dopamine dynamics in adulthood, and whether ectopic mesolimbic dopamine axons maintain their original anatomical and functional characteristics. We also explore if upregulating ventral tegmental area Dcc mRNA prevents these changes.
Methods: Between postnatal days (PND) 22 and 31, male and female mice were administered either saline or a recreational-like dose amphetamine (4 mg/kg, intraperitoneal). After each injection, mice were placed in designated compartments of a place-preference apparatus. Place preference was evaluated at PND32 and PND80. At PND81±15, GrabDA2h was microinjected into the PFC, and optical fiber was implanted. At PND101±15, dopamine dynamics were recorded using fiber photometry at baseline and after acute

intraperitoneal injections of saline and methylphenidate (10 mg/kg). Similar procedures were conducted in additional male group, except CRISPRa targeting Dcc or LacZ was microinjected into the ventral tegmental area at PND21.
Results: Male and female mice showed short- and long-term AMPH place-preference. AMPH-treated males exhibited increased PFC dopamine transporter (DAT) density, reduced baseline DA transients, increased amplitude, faster dopamine release, and a heightened PFC dopamine signal response to methylphenidate. No changes were observed in vesicular monoamine transporter 2 expression across the treatment groups. Dcc upregulation was associated with prevention of place-preference development and changes in dopamine dynamics.
Conclusion: The increase in DAT expression and changes in dopamine dynamics observed in the PFC of adult AMPH-treated male mice likely result from ectopic innervation of mesolimbic dopamine axons to the PFC, which seems to retain properties of their intended target.

Social Stress in Adolescence: A Longitudinal Analysis of Early Predictors and Outcomes

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Introduction: Adolescence is a key period for mental health, with adverse experiences like peer-victimization linked to higher psychiatric risk and impaired prefrontal and cognitive development. Though common and impactful, the predictors and neurobiological mechanisms of these outcomes are not fully understood. This study investigates how pre-existing behavioral traits interact with adolescent social stress and their long-term effects on social and cognitive function.
Methods: For the human study, data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort were used to construct a continuous "TF1 bullying score" at 12.5 years, based on self-reported frequencies of various bullying experiences. This score was correlated with peer victimization during childhood and adolescence and subsequently used to predict response inhibition in early adulthood. In the mouse study, behavioral assessments were conducted before and after exposure to accelerated social defeat in early adolescence. These results were integrated into scores reflecting "experience-seeking" and "sociability". In adulthood, in-vivo calcium imaging was employed to monitor prefrontal cortex neuronal activity while the mice learned and performed the Go/No-Go task.
Results: In humans, peer-victimization at age 12.5 strengthened the association between earlier (6.75) and later (13.1) peer problems and predicted lower response inhibition at age 24. In mice, “experience-seeking” in early adolescence predicted less sociability in adolescence, but only in defeated mice. In adulthood, mice exhibited either “active” or “passive” approaches on the Go/No-Go task. High “experience-seeking” and “sociability” scores were linked to an active strategy. Synchronized prefrontal cortex neuron activity was observed only in excited neurons of active solvers.
Conclusions: The impact of adolescent peer-victimization on social, cognitive, and neuronal activity outcomes is influenced by behavioral traits in early adolescence. The use of longitudinal, translational and multi-domain strategies and designs can identify common traits of vulnerability in humans and mice, potentially discovering biological causation.

Tracking Non-Motor and Motor Pathology Using a Dual-Hit Genetic LRRK2-G2019S and a-Synuclein Fibril Parkinson's Disease Model

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Introduction: This study aims to investigate the impact of the leucine-rich repeat kinase 2 (LRRK2)-G2019S mutation on alpha-synuclein pathology by tracking protein propagation alongside symptom onset within a dual-hit genetic Parkinson's Disease (PD) murine model. This hyper-kinase mutation is predicted to enhance subject vulnerability to A53T-preformed fibril (PFF)-induced pathology, specifically by increasing recruitment of endogenous alpha-synuclein.
Methods: Four groups of male and female wild-type and LRRK2-G2019S mice aged 12–13 weeks were infused with saline or A53T-PFF via unilateral intracerebroventricular injection (ICV). Subjects were monitored over a 12-month period, during which non-motor symptoms (depression, anxiety, cognitive changes) and motor symptoms (fine-, gross- movement) were tracked through behavioural testing (forced swim, tail suspension, sucrose preference, open field, novel object recognition, Y-maze, beam break, rotarod, digigait) at 1/2/3/4/8/12-months post-infusion. Whole brains processed through perfusion and additional tissue samples (brain punches, gut-colon and duodenum-, plasma) were collected one-day following testing at 1/4/8/12-months.
Results: Depression-like behaviour was observed in the LRRK2-G2019S A53T-PFF and LRRK2-G2019S vehicle groups, indicated by a lack of sucrose preference at 3/8-months (cohort-specific) and significantly greater immobility duration during tail suspension compared to controls at 4-months, respectively. Results from anxiety, cognitive, and motor tests have not shown significant findings yet, while analyses for fine and gross motor alterations are still in progress. Ongoing immunohistochemistry will assess the presence of aggregated alpha-synuclein throughout the brain, initially focusing on the raphe, amygdala, frontal cortex, substantia nigra pars compacta, and ventral tegmental area.
Conclusion: These findings suggest a persistent depression-like behaviour among LRRK2-G2019S mice treated with both vehicle and A53T-PFF, with no observed changes in anxiety-like behaviour or cognition. Ongoing behavioural and immunohistochemical analyses aim to clarify how LRRK2-G2019S influences alpha-synuclein pathology and its progression. Understanding this may be crucial for the development of targeted interventions.

Imaging monoacylglycerol lipase: a first-in-human positron emission tomography study with [18f]magl-2102

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Introduction: Monoacylglycerol Lipase (MAGL) plays a critical role in the endocannabinoid system by metabolizing 85% of 2-arachidonoylglycerol, the primary cannabinoid 1 receptor ligand. Understanding MAGL in vivo is vital, given its potential as a therapeutic target across multiple clinical indications. A novel reversible radiotracer, [^{1}8F]MAGL-2102, was developed and validated preclinically, demonstrating strong potential for human use. This study presents the first-in-human positron emission tomography (PET) evaluation of [^{1}8F]MAGL-2102, with objectives of characterizing in vivo binding, biodistribution, and pharmacokinetics.
Methods: Four healthy volunteers (mean age: 31.25 ±11.58, 1 male, 3 female) underwent dynamic PET scan following administration of [^{1}8F]MAGL-2102 (171.03 ±14.46 MBq) along with arterial blood sampling. Stable standardized uptake values (SUV) were calculated across brain regions and Logan graphical analysis were used for kinetic modelling.
Results: [^{1}8F]MAGL-2102 PET scans demonstrated blood brain barrier penetration, with a low but stable SUV of ~0.6 throughout the scan. Tracer distribution was highest in cortical regions (SUV range: 0.66-0.73) and lowest in white matter (0.42), which are slightly lower than prior preclinical studies (SUV peak: 1.2). Logan graphical analysis showed linearity, consistent with reversible radioligand kinetics. Minimal tracer metabolism was observed, with ~88% of the parent compound remaining intact at the end of the scan. Plasma free fraction was 0.75 ±0.28%.
Conclusion: Our preliminary PET study suggests [^{1}8F]MAGL-2102 shows lower brain uptake in humans compared to non-human primates, along with low plasma free fraction (<1%) likely reflecting high plasma protein binding. This may limit tracer availability to cross the blood-brain barrier and could partly explain the lower brain SUV observed in humans. Additional studies are warranted to validate the stability of [^{1}8F]MAGL-2102 for imaging MAGL in humans, representing a critical step toward developing a more effective tracer for accurate in vivo MAGL quantification and supporting the development of targeted cannabinoid therapies for neuropsychiatric disorders.

Longitudinal Association between Traditional Cardiovascular Risk Factors and Suicide Risk among Canadian Youth with Bipolar Disorder

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Introduction: In cross-sectional studies, traditional cardiovascular risk factors are associated with higher risk of suicide attempts (SA) in adults and youth with bipolar disorder, but there is a dearth of longitudinal studies. We therefore undertook a prospective study on this topic.
Methods: Participants included 95 youth with bipolar disorder, ages 13-21 years, followed up over 23.0±12.6 months. Lifetime non-suicidal self-injury (NSSI) and SA, and current cardiovascular risk score based on blood pressure, body mass index, and cigarette smoking, were determined at baseline. Current NSSI and SA were

examined at follow-up visits. Cox proportional hazards regression examined the predictive effects of baseline cardiovascular risk scores with NSSI and SA during follow-up, controlling for age and sex.

Results: There were 34% of youth with NSSI, and 13% with SA during follow-up. Higher baseline cardiovascular risk scores were significantly associated with increased risk of post-baseline NSSI (HR = 1.30 [1.04, 1.62], pFDR = 0.02), but there was a non-significant association for SA (HR = 1.29 [0.71, 2.35], pFDR = 0.21).
Conclusions: Higher cardiovascular risk may comprise a risk indicator for future NSSI and SA among youth with bipolar disorder. Still larger sample are warranted to enable adequate statistical power for predicting SA and more robust covariate modeling. If such future studies replicate the current findings, this would underscore the potential value of therapeutic interventions for optimizing cardiovascular risk to reduce suicide risk.

The Role of The Orbitofrontal Cortex (OFC) in Integral and Independent Learning of a 2D Auditory Space

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Introduction: Thus, this experiment seeks to elucidate the role of the orbitofrontal cortex (OFC) in facilitating integral representation. As such, we developed a Pavlovian task to determine the extent to test rats' ability to learn the stimulus dimensions as interdependent.
Methods: Here, 20 rats are presented with combinations of a set of auditory stimuli forming a putative cognitive grid (12x12) of 144 configural cues, 2 of which are rewarded via saccharine. We sought to determine whether temporary DREADD-induced inactivation of the OFC across the learning phase of the task would inhibit associations between the compound stimuli and saccharine. We injected AAV8- CaMKIIa-hM4Di-mCherry (experimental, n=11) or AAV8-CaMKIIa-mCherry (control, n=9) bilaterally into the OFC 4 weeks before the experiment. Rats then underwent 34 days of training, with DREADD Agonist 21 and saline injections occurring through the first 16 days. To learn the stimulus set, all configural cues were presented for 3 seconds at a time before immediately transitioning to an adjacent cue; cues are adjacent in that each presented cue differs in frequency from the one preceding it by an increment of one along one of the two dimensions that define them, where an increment represents a change by a factor of 1.3 in either direction. Injections were counterbalanced across experimental groups and extinction tests. Learning was assessed through reward anticipation and performance on two extinction tests (days 17 and 34).
Results: Findings suggested that OFC inactivation may inhibit integral learning, thereby reducing reward prediction accuracy and delaying acquisition in post-inactivation trials.

Neurobiological Effects of Psilocybin-Assisted Psychotherapy in Treatment Resistant Bipolar Depression: An Emotion-Processing fMRI Pilot Study

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Introduction: Psilocybin-assisted psychotherapy (PAP) has emerged as a promising intervention for individuals with treatment-resistant depression (TRD). Previous studies investigating PAP have excluded participants with a history of mania, hypomania, or psychosis. In TRD, PAP has been associated with increased amygdala reactivity, a neural change that predicted greater antidepressant effects. It is theorized that transiently increasing amygdala activity may allow participants to access previously suppressed emotions and process them in psychotherapy. In contrast, mood stabilizers and antipsychotics are known to blunt amygdala responsiveness, thus dampening emotions.
Methods: We are conducting an emotion-processing fMRI pilot study in twenty participants with moderate to severe treatment-resistant bipolar II depression (TRBD), each receiving a single 25 mg oral dose of psilocybin alongside structured psychological support (Clinical Trial: NCT06506019). Our primary objective is to determine whether increased amygdala activity during a validated emotional facial affect task following PAP is associated with improvements in depressive symptoms. Secondary objectives include evaluating overall feasibility, safety, and clinical outcomes. Resting state and task fMRI scans are completed at baseline, one day post-treatment (Day 1; primary imaging endpoint), and one month post-dose (secondary imaging endpoint to assess sustained changes).
Results: Recruitment for the trial is ongoing (n=8 enrolled to date). An interim analysis evaluating antidepressant effects and adverse events was completed. PAP was associated with substantial reductions on the Montgomery-Asberg Depression Rating Scale (MADRS), with mean (standard deviations) scores decreasing from 33 (5) at baseline to 14 (8) at week one and 15 (9) at week four. PAP was generally well tolerated, with transient adverse events resolving within 48 hours. No cases of treatment-emergent mania, hypomania, or psychosis were observed.
Conclusions: PAP appears to be a feasible and well-tolerated intervention in TRBD, associated with meaningful reductions in depression severity.

Heterogeneity in response to N-acetylcysteine in vascular mild cognitive impairment

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Introduction Oxidative stress (OS) contributes to vascular mild cognitive impairment (vMCI), and the antioxidant N-acetylcysteine (NAC) has been proposed to mitigate cognitive decline. However, our randomized clinical trial (NCT03306979) found no overall effects of NAC on executive function in vMCI. Despite this, variability in response to NAC prompted post-hoc analyses to identify clinical predictors of NAC response.
Methods A 24-week, randomized clinical trial included participants with vMCI (=-1SD norms in executive function, memory, working memory, or attention with cardiovascular disease). Baseline clinical variables were selected a priori and assessed for their effects on executive function z-score changes between NAC and placebo using univariate analyses. Variables with at least a 0.37 difference between their levels (based on observed improvements in executive function across all participants) were considered potential predictors. A multivariate regression model with selected variables estimated NAC's effects under both treatments' scenarios. An index score was calculated as the difference in predicted changes in executive function between the NAC and placebo models. Participants were grouped into quartiles according to their index scores, and treatment effects were compared across groups.
Results A total of 53 participants (mean[SD] Age=67.7[7.9], %male=66%, BMI=27.2[5.5], MoCA=22.6[3.2]) completed the trial. Analysis found that younger age, higher BMI, non-APOE4 status, lower Apathy Evaluation Scale-self scores, elevated homocysteine levels, and ACE inhibitor use were associated with greater improvements in executive function with NAC. Mean treatment effect [95%CI] for each quartile were: Q1=-0.68[-1.18,-0.15], Q2=-0.16[-0.62,0.34], Q3=0.08[-0.57,0.72], Q4=1.01[0.28,1.86]. A likelihood ratio test showed that the treatment effect significantly varied across quartiles ($p<0.001$). Percent responders (improvement >0.37 in executive function z-scores) among participants who received NAC were: Q1=0%, Q2=25%, Q3=62.5%, Q4=100% (?²(3)=10.4, p=0.02).
Conclusion These findings show significant variability in response to NAC among vMCI patients, with certain subgroups showing more pronounced benefits. This highlights the need for personalized therapeutic strategies targeting OS in vMCI.

Generalization of the interoceptive morphine stimulus to other opioids in rats trained on appetitive or inhibitory learning contingencies.

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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.

Pharmacogenomics of Antipsychotic-Induced Weight Gain: A Systematic Review of Studies Since 2018

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Introduction: Antipsychotic-induced weight gain (AIWG) is a significant clinical concern, affecting approximately 30% of patients treated with antipsychotics. The objective of this systematic review is to summarize recent pharmacogenomic findings on AIWG published since 2018 and to test the hypothesis that specific genetic variants contribute to its development.
Methods: Following PRISMA guidelines, peer-reviewed human studies on the pharmacogenetics of AIWG published in English from May 2018 to March 2025 were included. MEDLINE, Embase, and PsychInfo were systematically searched. Two reviewers independently screened studies and reached consensus on inclusion. Eligible studies examined genetic associations with AIWG and included details on design, diagnosis, antipsychotic treatment, sample size, ancestry, genotypes, and AIWG outcomes.
Results: Forty-nine studies met inclusion criteria. In candidate gene studies, the strongest associations with AIWG were observed for MTHFR rs1801133 ($p=0.001$), DRD2 rs1799732 (OR=2.91, 95%CI: 1.42–5.94, $p=0.003$), CYP2D6 ($p=0.001$), HTR2C rs1414334 ($p=0.002$), MC4R rs489693 (OR=0.20, 95%CI: 0.11–0.38, $p=0.01$), and ADRA2A rs553668 (OR=0.07, 95%CI: 0.01–0.54, $p=0.0019$). Among studies using polygenetic risk scores (PRS) and genome-wide association studies (GWAS) analyses, notable variants associated with AIWG included rs1525085 in the DGKB gene (OR=8.51, 95%CI: 2.57–28.16, p=3.15×10??) and rs78310016 near CTD-2201E18.1 (OR=3.98, 95%CI: 1.75–9.06, p=3.66×10?8). Other significant loci were rs10422861 in PEPD, rs3824417 in PTPRD, rs7736552 near MAN2A1, rs11074029 in SLCO3A1, and rs117496040 near DEFB1. Also, PRS analysis demonstrated that higher genetic liability for body mass index (BMI) predicted AIWG.
Conclusion: Polymorphisms in traditional candidate genes (e.g. DRD2, HTR2C, MC4R, ADRA2A, CYP2D6) continue to be investigated for association with AIWG. More recently, GWAS have identified associations in novel genes (e.g. DGKB, CTD-2201E18.1, PEPD, PTPRD, MAN2A1, SLCO3A1, DEFB1) that offer new insights into AIWG. Furthermore, PRS analyses showed that BMI risk predicts AIWG. These results enhance understanding of AIWG's genetic architecture and support future personalized treatment strategies.

Cortical differences in psychiatric disorders don't relate to those from rare genetic variants and may be influenced by non-genetic factors

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Introduction: Rare copy number variants (CNVs) increase risk for neurodevelopmental and psychiatric disorders (NPDs) and alter cerebral cortex structure. However, it is unknown whether cortical differences associated with CNVs are related to the risk they confer for NPDs. We aimed to compare the differences between genetic risk and psychiatric diagnosis in terms of their association with cortical thickness (CT) and surface area (SA), two neurobiologically distinct metrics.
Methods: We characterized case-control CT and SA differences from T1-weighted MRIs in ~730 individuals (general-population and clinical-cohorts, age: 6-80 years, 50.5% male) carrying one of the 18 NPD-linked CNVs and aneuploidies and 870 matched controls (age: 6-80 years, 49.5% male), following ENIGMA protocols. We compared these with ENIGMA summary statistics for 8 NPDs (Attention-deficit/hyperactivity-disorder, autism, bipolar-disorder, clinical high-risk for psychosis, conduct-disorder, major-depression, obsessive–compulsive-disorder, schizophrenia), including medicated/unmedicated subgroups where possible.
Results: Rare CNVs were preferentially associated with total-SA, while NPD diagnoses were preferentially associated with mean-CT. Larger effects on mean-CT, but not total-SA, were seen in medicated NPD subgroups; and first-degree relatives at risk for NPDs show little to no effect on mean-CT. For regional cortical differences, CNVs were preferentially associated with effects in sensorimotor areas (earlier-developing), while NPDs showed higher effects in association areas (later-developing). Regional SA differences for NPDs were detectable mainly in young participants. CNV findings aligned with twin and SNP heritability estimates, which were higher for SA and sensorimotor regions, suggesting a general property of the genetic architecture of the cerebral cortex.
Conclusion: This systematic comparison of CT and SA identified a differential impact of CNVs and psychiatric diagnoses on these two metrics. Cortical differences in psychiatric disorders don't seem to relate to those from individual genetic variants, and may be influenced by non-genetic factors like medication and the lived experience of the disorder.

Development of a Minimal Clinically Important Difference in Treatment Resistant Schizophrenia

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Introduction: RCTs are increasingly evaluated for clinical or “real world” importance. Defining meaningful measurement changes is critical to determine sample sizes, interpret treatment group results and understand outcome-changes over time. The minimum clinically important difference (MCID) emerged as a measure of minimum change in an objective score corresponding to clinically significant change (Jaeschke et al., Control Clin Trials, 1989;10:407-415). MCIDs are calculated using two types of approaches. Anchor-based methods compare measurement scores of patients reporting meaningful change (according to a validated anchor) with those who do not. Distribution-based methods rely on statistical distributions of measurement scores. Objectives: 1) Quantify MCIDs for change in PANSS scores using different approaches, 2) explore applications to hospitalized patients with treatment resistant schizophrenia (TRS).
Methods: PANSS ratings on days 1 and 7 from 68 Clozapine and Risperidone Enhancement (CARE) study participants (Honer et al., NEJM, 2006;354:472-482) were used to derive distribution-based MCIDs. These were calculated using the reliable change index, standard error of the mean and minimum detectable change. While PANSS and clinical global impression-severity scale (CGI-S) admission and discharge ratings for 355 TRS-patients at the British Columbia Psychosis Program (BCPP) were used to determine anchor-based MCIDs, where a 1-unit score change in CGI-S was used to anchor "responders". MCIDs were calculated using within-subject change, between-subject change and ROC-based measurements.
Results: Combining MCID methodologies, a MCID for total PANSS corresponded to a change of 13.38 points; 4.86 points for positive PANSS; 4.83 for negative PANSS and 7.37 points for general PANSS. Participants reaching MCID thresholds for total PANSS and PANSS subscales during their admission to the BCPP had greater improvement in social and occupational functioning assessment scale scores ($p<0.001$, for all), suggesting greater functional improvement.
Conclusion: Ongoing analyses of changes in day-to-day function in hospitalized TRS patients may help develop a MCID for clinical trial evaluation.

Differentiating Between Successor Representation and Model-Based Learning in Rats

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Introduction: The Successor Representation family of algorithms has become a popular conceptualization of reinforcement learning in biological organisms. By representing transitions in terms of probabilistic temporally discounted future state occupancies, these algorithms forgo the intensive planning of model-based reinforcement learning approaches. When paired with a replay mechanism as in SR-replay, Successor Representation algorithms maintain a similar level of flexibility to model-based learning. However, information related to transition sequences is unavailable because of the lack of a planning mechanism. While previous research has distinguished between Successor Representation and Model-Based algorithms in humans, no equivalent behavioural procedure is currently available for the study of animals.
Method: In the present study, (n = 22, 14 female) Long-Evans rats underwent a novel sequence-unblocking procedure. In training, a blocked stimulus is presented before a neutral stimulus, which predicts a rewarded stimulus. The stochastic control group disperses the blocked stimulus across trials such that the blocked stimulus is a worse predictor of the neutral stimulus. After the training phase, rodents are probed with the

blocked stimulus in extinction and magazine entry is recorded to measure expectation of the saccharine-solution reward.

Result: After accounting for baseline responding, experimental rodents respond significantly more than the stochastic control ($F(1, 86) = 8.79$, $p < 0.01$**, $\eta^2 = 0.05$) during the extinction test. The increase in responding can be observed at the time-bin corresponding to when the reward was previously delivered during training ($t(86) = 2.17$, $p = 0.02$*, $d = 0.219$).
Conclusion: Contrary to SR-replay accounts of behaviour, the results are consistent with the use of a planning mechanism. Because the blocked stimulus cannot be used to directly predict the reward at test, a sequential planning process could be used to predict the absent neutral stimulus and then the absent rewarded stimulus. SR-Replay does not satisfy this requirement.

The contribution of Hippocampal GluN2D-containing NMDARs to stress resilience

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Introduction: Major depressive disorder (MDD) affects more than 300?million people worldwide, yet not all who experience stress develop MDD, highlighting the importance of understanding neural mechanisms of stress resilience. We hypothesized that GluN2D-containing NMDA receptors in the dorsal CA1 (dCA1) of hippocampus confer stress resilience.
Methods: Both male and female mice were subject to chronic social defeat stress (CSDS), with mice attacked and cohoused with aggressors of the same sex. Social interaction test (SIT) was used to differentiate stress resilient mice and susceptible mice after CSDS. Open field test (OFT) was performed as a stress-related behavior. We used western blot to compare the expression of hippocampal extrasynaptic GluN2D in mice of different susceptibility. CIQ, a GluN2C/D positive allosteric modulator, was infused into the dorsal CA1 (dCA1) of hippocampus during CSDS to examine the role of GluN2D in stress resilience. We also overexpressed GluN2D in dCA1 pyramidal neurons using a lentiviral vector before CSDS as an alternative approach.
Results: We found significantly lower SI ratio in SIT and center time in OFT in stressed group compared to non-stressed group. In male mice, we found a higher expression of extrasynaptic GluN2D in the dorsal hippocampus of resilient mice. After dCA1 CIQ infusion before each episode of social defeat, we found a higher center time in OFT compared with vehicle group in male mice. In both male and female mice after dCA1 GluN2D overexpression, we found a higher social interaction ratio in SIT and a higher center time in OFT compared to mice without virus injection. The results indicate a pro-resilient role of dCA1 GluN2D-containing NMDARs.
Conclusion: GluN2D-containing NMDARs in dCA1 plays a pro-resilience role. Knockdown of GluN2D in mice of both sexes will be performed, and the involvement of GluN2D in the pro-resilience role of extrasynaptic NMDARs activation will be explored.

Characterizing Sex Differences in Cannabis Withdrawal During 28 Days of Cannabis Abstinence

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Introduction: While past research suggests that females experience greater cannabis withdrawal severity compared to males, these data are derived from studies that employed cross-sectional, retrospective designs or surveyed minimal abstinence periods (< 28 days). Since cannabis withdrawal can last for several weeks with fluctuations in severity, we examined sex differences in cannabis withdrawal severity during 28 days of cannabis abstinence and hypothesized that females would demonstrate more severe cannabis withdrawal throughout this time.
Methods: Males and females, between 18-80 years old, with cannabis use disorder (CUD) or using cannabis = 4 times per week and no current comorbid DSM-5 disorder were enrolled. Participants underwent 28 days of cannabis abstinence supported by contingency management and weekly behavioural support sessions. Cannabis withdrawal symptoms were assessed at baseline and then weekly using the Marijuana Withdrawal Checklist (MWC). Cannabis abstinence was verified biochemically with twice-weekly urine analysis.
Results: Twenty-eight participants completed the study (n=5 males and n=3 females dropped out). Twenty-three participants (n=14 male and n=9 female) remained successfully abstinent, 5 participants (n=2 male and n=3 female) relapsed. Overall, 23 participants are included in our final analysis. After controlling for baseline MWC scores and recency of cannabis use, a repeated measures ANOVA revealed a significant time effect ($F4, 76 = 2.92$, $p = 0.03$) in MWC total scores, and a significant time*sex interaction ($F4,76 = 4.14$, $p < 0.01$). Between-group sex differences were nonsignificant ($F1,19 = 1.18$, $p = 0.29$). Male withdrawal severity followed the previously established trajectory, where symptoms peaked at day 7 and dissipated by day 28. Female withdrawal severity followed a different trajectory and remained stable between days 0 and 28.
Conclusions: Our preliminary findings demonstrate distinct cannabis withdrawal trajectories between males and females and a significant interaction between time and sex. Such results highlight the need for developing sex-specific CUD interventions.

The role of protein kinase A in the nucleus accumbens core in D1 receptor agonist-induced locomotor stimulation in rats

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Introduction: The nucleus accumbens core (NAcc core) expresses Gaolf coupled D1 receptors (D1R), and in this brain structure D1Rs play a key role in locomotion. The canonical signaling pathway downstream of the D1Rs features increased production of cyclic AMP (cAMP), which subsequently activates protein kinase A (PKA) and extracellular signal-regulated kinases 1 and 2 (ERK1/2). In this study, we investigated the dynamics of PKA activation in the NAcc core during locomotion. We also asked whether recently developed non-catechol D1R agonists activate PKA in the NAcc core and promote locomotion. We hypothesized that PKA activity in the NAcc core is necessary for the locomotor stimulant response.
Methods: PKA activity in NAcc core dMSNs was monitored using a virally expressed FRET-based biosensor and fiber photometry in male Long Evans rats. In addition to the PKA biosensor, some rats also received a

PKA inhibitor (PKI) or an inactive mutated form of PKI protein as a control. Animals were acutely tested with three non-catechol D1R agonists (each at 0, 0.1, 0.5, and 1 mg/kg SC), and the catechol agonist SKF 81297 serving as a positive control. Biosensor activity and locomotion were recorded for 60 minutes post-injection.
Results: None of the three non-catechol D1R agonist increased biosensor activity or locomotor activity at the doses tested. SKF 81297 increased PKA activity in the NAcc core and significantly enhanced locomotor activity. The locally-injected PKA inhibitor blocked the SKF 81297-induced increase in PKA activity, while increasing the locomotor stimulant effect of SKF 81297. Western blots confirmed that the PKA inhibitor increased ERK1/2 phosphorylation in the NAcc core.
Conclusion: Non-catechol D1 receptor agonists may need to be tested at higher doses than those used in this study to fully assess their effects. Inhibiting PKA in the NAcc core enhanced SKF 81297-induced locomotion, potentially reflecting a shift to intracellular signalling via ERK1/2. Funding: CIHR

Simultaneous Monitoring of cAMP and ß-Arrestin Signaling in the Striatum Evoked by Dopamine D1 Receptor Agonists

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Introduction: Dopamine D1 receptors (D1Rs), which couple to Gas-olf proteins, are highly expressed in the prefrontal cortex and striatum and play a key role in neuropsychiatric disorders. In striatal medium spiny neurons, D1Rs signal primarily via Golf /cAMP but can also recruit ß-arrestin isoforms, mediating receptor desensitization and initiating G protein-independent pathways. While these pathways are well described in vitro, their in vivo dynamics remain poorly understood, and no ß-arrestin biosensor has been validated in living animals. In this study, we compared two D1R agonists with distinct functional selectivity profiles in vitro. Specifically, SKF 81297 is a full cAMP and ß-arrestin agonist, whereas Compound 7 (Cp7) signals preferentially via the Gas-olf/cAMP pathway. We asked whether these in vitro signalling properties (i.e. cAMP vs. ß-arrestin) would transfer to the living brain, providing new insight into pathway-specific D1R signaling in vivo.
Methods: Using virally-expressed biosensors and fiber photometry, we simultaneously monitored cAMP and ß-arrestin signaling in the striatum of adult rats. To this end, adeno-associated viruses (AAVs) encoding cAMP (cADDis) or ß-arrestin (Borealis) biosensors were injected into the left and right caudate putamen, and an optical recording fiber was implanted at each AAV injection site. Rats were acutely challenged with SKF 81297, Cp7 or vehicle, following acute pretreatment with saline or the D1R antagonist SCH 39166 (0.1 or 0.5?mg/kg, SC). Biosensor activity and locomotor behavior were recorded for 45 minutes post-injection.
Results: SKF 81297 produced greater cAMP and ß-arrestin responses than Cp7. The D1R antagonist SCH 39166 dose-dependently reduced SKF-induced locomotion. This antagonist also altered agonist-induced signaling in a time-dependent manner.
Conclusions: These findings provide the first in vivo demonstration of concurrent cAMP and ß-arrestin signaling induced by D1R agonists in vivo, highlighting the utility of real-time dual-sensor recording for dissecting GPCR signaling dynamics and their potential behavioral impact. Acknowledgments: CIHR & Montana Molecular

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The role of microglial GPR120 in anxiodepressive behavior, energy metabolism and microglia reactivity in response to chronic unpredictable stress

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Introduction: GPR120 (also known as FFAR4) is a G protein–coupled receptor that senses long-chain omega-3 fatty acids which are known to have beneficial effects on anxiety and depression. Neuroinflammation is a key player in the development of neuropsychiatric and metabolic disorders and is highly mediated by microglia. Activation of GPR120 triggers potent anti-inflammatory effects in both peripheral macrophages and microglia. Dysfunction or deficiency of this receptor has been linked to metabolic disorders due in part to increased inflammation. Chronic unpredictable stress elicits neuroinflammation, activate microglia and promote anxiety and depressive-like behaviors. We hypothesized that microglia GPR120 deficiency exacerbates neuroinflammation and stress-induced behavioral alterations.

Method: Adult male and female microglia-specific GPR120 knock-out (CX3CR1^{CreER}GPR120$^{fl/fl}$) and controls (CX3CR1^{CreER}GPR120$^{+/+}$) underwent 2 weeks of a daily unpredictable restraint stress or absence thereof, 4 weeks after tamoxifen injections. Weight and food intake were measured along with behavioral tests assessing anxiety- and depressive-like phenotypes (elevated-plus maze, open field, forced swim, social interaction, sucrose preference & novel object). Microglial morphology and phagocytic activity were evaluated via IBA-1 and CD68 immunohistochemistry in PFC and nucleus accumbens.
Results: Microglia GPR120 loss of function in both sexes increased body weight and food intake and heightened anxiety-like behaviors under stress. GPR120 KO increased the number of microglia, their reactivity and increased CD68 co-expression in the PFC of male mice. Microglia CD68 expression was also enhanced in female GPR120 KO mice submitted to chronic stress.
Conclusion: These findings highlight the impact of GPR120 in regulating microglial reactivity and phagocytosis, neuroinflammation, and behavioral outcomes. *Supported by a CIHR grant to SF and TA.*

Investigating Sex Differences in the Relationship between Brain Fatty Acid Amide Hydrolase Levels and Depression, Anxiety, and Stress in Social Anxiety Disorder: A PET study with [11C]CURB.

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Introduction: Social anxiety disorder (SAD) affects nearly three million Canadians, with higher prevalence reported in females. Treatment response remains limited, necessitating new interventions. Inhibition of the

endocannabinoid system enzyme, fatty acid amid hydrolase (FAAH), is a treatment target of interest. Sex differences have also been reported regarding the endocannabinoid system and FAAH. This analysis used positron emission tomography (PET) imaging of the FAAH probe,
[11C]CURB, to investigate the relationship between brain FAAH and Depression Anxiety Stress Scale (DASS) scores across males and females with SAD.
Methods: Participants completed a [11C]CURB PET scan, a magnetic resonance imaging (MRI) scan, the DASS, and genotyping of the FAAH C385A polymorphism. Regions of interest were delineated and brain FAAH levels were quantified using the lk3 parameter. Differences in DASS scores between males and females were evaluated with independent samples t-tests. Partial correlations assessed the relationship between whole brain FAAH and DASS scores controlling for genotype.
Results: Thirty-one participants (M/F assigned at birth=10/21; 26.32±5.9 years old) were included. Females reported higher anxiety, depression, and stress scores compared to males ($p<0.05$). FAAH was not correlated with DASS scores in the full sample ($0.12 < r < 0.30$; $0.11 < p < 0.52$). In females, FAAH was positively correlated with anxiety ($r=0.59$, $p<0.01$), but not depression ($r=-0.06$, $p=0.80$) or stress ($r=0.18$, $p=0.46$). In males, there were no significant correlations observed regarding anxiety ($r=-0.23$, $p=0.55$), depression ($r=0.44$, $p=0.24$), or stress ($r=-0.06$, $p=0.87$).
Conclusion: These preliminary findings suggest potential sex-related differences in the relationship between brain FAAH levels and anxiety scores in individuals with SAD. Brain FAAH was positively correlated with anxiety subscale scores in females, while the DASS correlations failed to meet significance in males, warranting further investigation with a larger sample. These results support the importance of sex considerations in future investigations of treatments targeting the endocannabinoid system in SAD.

High-Frequency rTMS for Negative Symptoms and Cognitive Function in Schizophrenia: A Multisite Sub-Analysis Examining Clinical and Anticholinergic Correlates

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Introduction: High-frequency repetitive transcranial magnetic stimulation (rTMS) may improve negative symptoms and cognition in schizophrenia, but findings are mixed. This study investigates the effects of rTMS on negative symptoms, cognition, and functioning, and explores whether anticholinergic burden moderates rTMS-related cognitive outcomes.
Methods: A sub-analysis was performed on data from an open-label, single-arm trial conducted in Canada and Germany over a three-year period. Seventy-two patients with schizophrenia who received three weeks of 10 Hz rTMS over the left dorsolateral prefrontal cortex (five days per week) and completed baseline, post-

treatment, and 105-day follow-up assessments were included. Assessments consisted of but not limited to the Positive and Negative Syndrome Scale (PANSS), Digit Symbol Substitution Test (DSST), d2 Test of Attention, Trail Making Test Parts A and B (TMT-A/B), Social and Occupational Functioning Assessment Scale (SOFAS) and Global Assessment of Functioning (GAF). Anticholinergic Cognitive Burden (ACB) of medication was calculated at baseline.
Results PANSS negative scores improved significantly (p < .001; d = 0.96–1.36; 95% CI [–10.12, –4.54]), with =20% symptom reduction in 44% post-treatment and 71% at follow-up. The d2 Test showed persistent but smaller gains in processing speed and attention (TN, TN-E, CP: p < .001; d = 0.18–0.33), with reduced error rates (rrb = 0.47–0.55). DSST raw scores increased from 77.8 to 83.5 and 89.2 (rrb = 0.42–0.45). TMT-A, (rrb = 0.42-0.52); TMT-B (rrb = 0.48–0.49), TMT-Total (rrb = 0.55) also improved but did not correlate with negative symptom improvement. SOFAS (d = 0.60) and GAF (rrb = 0.47–0.85) also improved. ACB was not significantly associated with cognitive outcomes, but a negative association trend was observed in some cognitive domains.
Conclusion: Sustained improvement in negative and cognitive symptoms may occur after rTMS in schizophrenia, though the role of anticholinergic medication burden warrants further investigation.

Validating an Insomnia Polygenic Risk Score in Youth with Major Depression: Genes to Clinical Correlates

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Introduction: Despite the well-established deleterious psychiatric correlates of sleep disturbance in youth with major depression, no studies have explored polygenic risk (PRS) for insomnia in this population. This study aims to validate the generalizability of insomnia-PRS in a clinical sample of youth with major depression. We hypothesize that insomnia-PRS will be associated with sleep disturbance in the overall sample and with more severe psychiatric characteristics in youth with major depression.
Methods: Participants included 374 youth aged 13-20 (247 with lifetime major depression [135 bipolar disorder, 112 major depressive disorder] and 127 controls). Insomnia-PRS was computed from adult genome-wide association study data. Sleep disturbance was derived from most severe lifetime insomnia and hypersomnia items from the Kiddie Schedule for Affective Disorders and Schizophrenia Depression Rating Scale. General linear models or logistic regressions examined main effects of insomnia-PRS on sleep disturbance and psychiatric correlates (i.e., mood symptom severity, anxiety, suicide risk, global functioning), controlling for age, sex and the first two genetic principal components.

Results: Insomnia-PRS was higher in youth with major depression vs. controls (p=0.03, d=0.24), and was significantly associated with insomnia severity in youth with major depression (p=0.03, ?²p=0.02). Greater insomnia-PRS was associated with greater lifetime mania symptom severity in youth with bipolar depression only (BD only; p=0.03, ?²p=0.03). In females, but not males, insomnia-PRS was associated with insomnia severity (p=0.02, ?²p=0.03), mania severity (p=0.02, ?²p=0.05), and depression severity (p=0.02, ?²p=0.03). There were no significant findings for hypersomnia.
Conclusion: This study extended prior findings linking adult-derived insomnia-PRS with insomnia in youth with major depression, with evidence of sex differences and differences related to bipolar disorder. These findings, while preliminary, provide evidence that variability in adult-derived insomnia-PRS is sensitive to differences in sleep and mood symptoms in youth.

Evidence of microglial involvement in the childhood abuse-associated increase in perineuronal nets in the ventromedial prefrontal cortex

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Introduction: Microglia, known for their diverse roles in the central nervous system, have recently been recognized for their involvement in degrading the extracellular matrix. Perineuronal nets (PNNs), a specialized form of this matrix, are crucial for stabilizing neuronal connections and constraining plasticity. Our group recently reported increased PNN densities in the ventromedial prefrontal cortex (vmPFC) of depressed individuals that died by suicide in adulthood after experiencing childhood abuse (DS-CA) compared to matched controls.
Methods: To explore potential underlying mechanisms, we employed a comprehensive approach in similar well-characterized postmortem vmPFC samples (Douglas-Bell Canada Brain Bank), combining a human matrix metalloproteinase and chemokine array, isolation of CD11b-positive microglia and enzyme-linked immunosorbent assays (ELISA).
Results: Our findings indicate a significant downregulation of matrix metalloproteinase (MMP)-9 and tissue inhibitors of metalloproteinases (TIMP)-2 in both whole vmPFC grey matter and isolated microglial cells from DS-CA samples. Furthermore, our experiments reveal that a history of child abuse is associated with diminished levels of microglial CX3CR1 and IL33R in both vmPFC whole lysate and CD11b+ isolated cells. However, levels of the CX3CR1 ligand, CX3CL1 (Fractalkine), did not differ between groups.
Conclusion: While these data suggest potential long-lasting alterations in microglial markers in the vmPFC of individuals exposed to severe childhood adversity, direct functional assessments were not conducted. Nonetheless, these findings offer insight into how childhood abuse may contribute to PNN alterations via microglial-related mechanisms.

Integration of appetitive features in the orbitofrontal cortex during food-based choices

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Introduction Understanding how the brain assigns value to potential rewards is central to neuropsychopharmacology, with implications for decision-making in both health and neuropsychiatric disorders. The orbitofrontal cortex (OFC) is thought to integrate sensory and contextual features of available food options to compute subjective values guiding choice. We investigated how OFC neuronal populations combine multiple appetitive features during economic decision-making.
Methods We recorded from 485 OFC neurons in rats performing a food-based choice task where offers varied in food type and quantity. Each session (~300 trials) allowed for the precise estimation of stable preferences. Neural coding of individual features, integrated value signals, and ensemble dimensionality were examined during the evaluation of offers and the execution of decisions.
Results OFC neurons encoded both individual features (type, quantity, spatial location) and emerging value signals during offer presentation. Dimensionality analyses revealed maximal integration of these attributes before choice commitment, followed by a shift toward value-dominated coding as decisions were finalized. This dynamic transformation suggests the OFC constructs a multi-attribute representation that underlies valuation and selection.
Conclusion Our findings highlight neural computations in the OFC that transform sensory and contextual information into subjective value estimates guiding behaviour. These mechanisms provide insight into the neurobiological substrates of decision-making relevant to understanding altered valuation processes in neuropsychiatric conditions like substance use disorders (SUDs).

Speech Markers as Longitudinal Predictors of Youth Mental Health: A Systematic Review

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Introduction: Severe mental disorders in young people (0–25 years) are often preceded by subtle changes in communication and thinking, detectable in speech. Speech markers are promising for early detection; however, no systematic review has evaluated their prospective utility in predicting mental disorders in youth. We systematically reviewed longitudinal studies assessing speech markers as predictors of major mental disorder onset or symptom progression in youth.
Methods: We searched for longitudinal studies using recorded speech samples from youth or family members to predict diagnostic changes or symptom severity in major depressive disorder (MDD), psychosis, ADHD, substance use disorder, bipolar disorder, OCD, and eating disorders. Risk of bias was assessed using the Newcastle Ottawa Scale. Our protocol was pre-registered [CRD42024579798].
Results: Of 2,259 articles, 11 studies met inclusion criteria, covering MDD (n=3), psychosis (n=5), and ADHD (n=3). No eligible studies were found for OCD, substance use, bipolar, or eating disorders. Both manual and computational speech analyses were used, with speech samples from parents and youth. Predictive speech markers included parental expressed emotion (MDD, ADHD), formal thought disorder (psychosis), and acoustic/linguistic features (psychosis, ADHD). Study quality was moderate to good (mean score: 5.5/8).
Conclusions: Externally validated longitudinal studies on the predictive value of speech markers of youth-onset mental disorders are scarce, restricted to a few target disorders, and do not allow to account for the

developmental stage. Nonetheless, existing studies highlight the potential of applying Natural Language Processing methods to speech samples from both youth and parents for early identification.

Investigating TNF and anxiety as predictors of agitation in Alzheimer's disease dementia

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Introduction: Agitation is a prevalent and challenging neuropsychiatric symptom in Alzheimer's disease dementia (ADD), affecting up to 70% of individuals. Anxiety frequently co-occurs with agitation and may contribute to its severity. Tumour necrosis factor (TNF), a pro-inflammatory cytokine, has been implicated in neuroinflammatory pathways underlying both symptoms. It was hypothesized that higher anxiety would be associated with greater agitation severity, with TNF moderating this relationship.

Methods: This cross-sectional analysis used baseline data from participants enrolled in a randomized, placebo-controlled crossover trial of nabilone for agitation in AD conducted across long-term care homes and geriatric psychiatry clinics in Ontario, Canada. Agitation severity was measured using the Cohen-Mansfield Agitation Inventory (CMAI), anxiety using the Neuropsychiatric Inventory – Nursing Home (NPI-NH) anxiety score, and serum TNF concentration was quantified via multi-ELISA. A moderation analysis using a multiple linear regression examined whether TNF interacted with anxiety to predict agitation severity, adjusting for age, sex, and standardized Mini-Mental State Examination (sMMSE) scores.

Results: Participants (n=38) with ADD (sMMSE =24) were aged =55 years and had clinically significant agitation (NPI-NH agitation/aggression =3). Multiple linear regression showed that greater anxiety (ß=2.555, SE=1.219, p=.045) and poorer cognition (ß=-1.419, SE=0.430, p=.003) were both associated with higher agitation. However, TNF alone was not a significant predictor of agitation (ß=1.643, SE=1.017, p=.117). The moderation analysis revealed that TNF did not moderate the relationship between anxiety and agitation (ß=-0.080, SE=0.142, p=.579).

Conclusion: These findings suggested that anxiety was associated with increased agitation severity in ADD, independent of TNF levels. Although TNF did not significantly moderate this relationship, further investigation of biomarkers of neuroinflammation in larger samples may be warranted. Understanding these relationships may inform biomarker-driven targeted treatments for agitation in ADD.

Nucleus accumbens medial shell D1 and D2 medium spiny neurons encode the valence of conditioned stimuli in a sex-dependent manner

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Introduction Assigning emotional valence to environmental stimuli enables survival by promoting approach of beneficial stimuli and avoidance of noxious ones, a process thought to be dysregulated in many psychiatric disorders. The nucleus accumbens (NAc) is posited to translate information about valence into appropriate behavioural responses, and its main neuron populations, D1 and D2 dopamine receptor expressing medium spiny neurons (MSN), are suggested to play opponent roles in representing valence.
Methods We tested this hypothesis with fibre photometry Ca^{2+} imaging in male and female D1-Cre and A2a-Cre mice during a classical conditioning paradigm in which distinct auditory cues were followed by either foot shock (CSS), food reward (CSR), or no outcome (CS-) in the same context.
Results We find that as they acquire motivational significance, the reinforced cues elicit bidirectional responses in both cell types, with CSS driving an increase in neuronal activity and CSR driving a decrease in neuronal activity, which suggests that both cell types may encode the valence of conditioned stimuli. Notably, the suppression of activity during CSR in both cell types is prominent in females but not males. By contrast, both cell types respond to unconditioned stimuli with an increase in activity scaling to stimulus magnitude regardless of valence or sex, suggesting salience encoding. Additionally, response to unsignaled outcomes is greater than to signaled outcomes in D2 but not D1 MSNs, suggesting a contribution of prediction error to D2 MSN activity.
Conclusion Our findings confirm that there is little functional opposition between NAc D1 and D2 MSNs, and highlight the importance of studying reward and aversion together rather than separately and accounting for sex as a biological variable, since we find more evidence of valence encoding than previous studies examining each valence in isolation, as well as sexual dimorphism which had not yet been described.

Ultrasonic vocalizations in anticipation of social interaction in female Long-Evans rats

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Introduction: 50-kHz ultrasonic vocalizations (USVs) are reported to track affective states in adult rats. However, existing studies have focused almost exclusively on males. These 50-kHz calls are emitted in various rewarding contexts, including in anticipation of a play partner. Studies often interpret increased call rates across days as evidence of anticipation, but this approach does not account for partner effects. Here, specific USV measures (i.e., call rate, call subtype prevalence) were assessed in female rats tested alone and in anticipation of social interaction with a same-sex partner. Additionally, we examined whether corticosterone administration would induce a depressive-like state, as previously shown in male rats, and also inhibit anticipatory USV emission.
Methods: Cagemate pairs of female Long-Evans rats received either tap water or corticosterone (100 µg/mL, CORT) in the drinking water for 18 days (n = 8 rat pairs/group); intended to induce a depressive-like state. During the final 6 days of CORT administration, each rat was briefly socially isolated and then tested daily in a ‘partner’ and a ‘no-partner’ session, presented in counterbalanced order. Each session started with a 2-minute pre-access (waiting) period, followed by a 5-min opportunity to interact with an unfamiliar partner (partner) or no partner (no-partner).
Results: Rats anticipating a social partner emitted more 50-kHz USVs, with a preferential increase in the "flat-trill" 50-kHz call subtype, and a decrease in the "short" call subtype. Corticosterone administration had no detectable effect on the 50-kHz call rate or call subtype profiles.

Conclusion: Although we were unable to detect a depressive-like state after chronic low-dose oral corticosterone, we show for the first time that adult female rats emit specific 50-kHz call subtypes during social anticipation. The latter finding suggests that specific ultrasonic vocalizations may serve as markers of affective state in female, as well as male, rats. Funding: CIHR

Emission of 50-kHz ultrasonic vocalizations in anticipation of a sexual partner in male rats

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Introduction: Adult rats emit 50-kHz ultrasonic vocalizations (USVs) during reward anticipation. The specific 50-kHz call subtypes recruited during anticipation of a sexually-receptive partner have not been characterized. Here, we investigated whether certain USV measures (i.e., call rate, call subtype prevalence) were modified in male rats while they anticipated access to a sexually-receptive female. We also examined whether withdrawal from a chronic amphetamine regimen, intended to induce a depressive-like state, would inhibit the anticipation-associated changes in USV measures.
Methods: Thirty-two male Long-Evans rats were randomly allocated to receive either once-daily saline or amphetamine (2 mg/kg IP) for 14 days. For the next eight days, all rats were tested in sessions comprising a 2-min pre-access period followed by 5-min access period. During the latter, half the rats in each drug group were permitted to interact with an unfamiliar sexually-receptive female, while the remainder had no interaction partner (hence, n = 8 rats/subgroup).
Results: Compared to control (no-partner) animals, those anticipating a sexually-receptive female partner emitted more 50-kHz calls and emitted a greater percentage of two specific 50-kHz call subtypes: split calls and composite calls. Withdrawal from chronic amphetamine administration had no detectable effect on the call rates or call subtype prevalence.
Conclusion: In contrast to previous reports using the same chronic amphetamine regimen, signs of amphetamine withdrawal were not detected. Independent of amphetamine history, male rats became more vocal while they anticipated a sexual reward. During sexual anticipation, two 50-kHz call subtypes became more prevalent: split and composite calls. These two calls subtypes are typically rare (i.e., not highly prevalent) and as a result are underreported in the literature. Our findings support the idea that subtypes other than the previously studied “flat” and “trill” can potentially serve as markers of affect. Funding: CIHR

Is Netrin-1–Mediated Protection Against Amphetamine Sensitivity in Females Requires Gonadal Hormones?

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Introduction: Adolescent amphetamine exposure disrupts dopamine system maturation in male mice by downregulating the axon guidance cue Netrin-1 in dopaminergic regions, resulting in long-term impulse control deficits, instead female mice exhibit protection through Netrin-1 upregulation in these regions. This study investigates whether pubertal ovarian hormones mediate this female-specific protective mechanism.
Methods: Female mice underwent ovariectomy (OVX) – or sham – surgery at postnatal day (PND) 21 to prevent pubertal onset. At PND 35, mice received a recreational-like regimen of amphetamine (4 mg/kg, i.p., every other day for 10 days), or saline, using the conditioned place preference paradigm to assess drug rewarding effect. Brains were collected to assess Netrin-1 expression in dopamine regions, 7 days post-exposure — when dopamine axon targeting is occurring. Uteri weight was measured to validate ovarian OVX manipulation.
Results: Amphetamine produced rewarding effects regardless of pubertal status (main effect of drug treatment: $F(1,39) = 14.00$, $p < 0.001$, 95% CI [7.74 to 25.97]). However, sham but not OVX females exhibited significant amphetamine-induced Netrin-1 upregulation in the ventral tegmental area (pubertal manipulation x drug interaction: $F(1,39) = 6.927$, $p = 0.013$, 95% CI [0.165 to 1.280]), demonstrating that pubertal ovarian hormones are necessary for compensatory Netrin-1 signaling.
Conclusion: These findings reveal a critical role of pubertal ovarian hormones in regulating Netrin-1-mediated neuroprotection during adolescent dopamine circuit development. Disruption of this hormone-dependent mechanism may contribute to addiction vulnerability in females.

Classification of social behavioral responses in stress and non-stress adult mice with high precision

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Introduction: Conventional analysis of social behavior following stress exposure in mice relies on binary zone-based measures that provide limited insight into the complexity of social engagement patterns. To better characterize social behavior following stress exposure in mice, this study introduces a bidimensional analytical framework that extends beyond the limits of conventional analysis.
Methods: We integrated a time-based social interaction ratio with the average distance to the CD1 aggressor to propose a composite index that offers a more comprehensive assessment of social engagement during the social interaction test. By treating distance as a continuous variable, this approach moves beyond binary zone-based measures and enables a more refined phenotyping of individual differences along the resilience–susceptibility spectrum. This advancement is made possible through the use of open-source, multipose-estimation tools such as DeepLabCut and DeepOF, which allow for high-resolution tracking and precise behavioral quantification.
Results: The proposed index distinguishes between socially hesitant mice—those entering the interaction

zone while maintaining a relative distance from the CD1 aggressor—and mice that display robust sociability by both entering the zone and closely approaching the aggressor.
Conclusion: Our framework refines current preclinical models by capturing subtle behavioral adaptations to social stress. This ultimately improves their translational value for studying the neural and behavioral correlates of stress-related psychiatric disorders.

Systematic Review of gene-environment interactions in schizophrenia susceptibility

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Introduction: Schizophrenia is a heterogeneous disease in which both genetic and environmental risk factors have been implicated in its pathophysiology; however, neither fully explain the disease independently. Evidence suggests that gene-environment interaction (GxE) could influence schizophrenia susceptibility, yet a comprehensive synthesis of these findings is lacking. Here, we aim to systematically review the literature on GxE interaction and its role in the development of schizophrenia.
Methods: We conducted a comprehensive search of Ovid MEDLINE, Ovid EMBASE, and Ovid PsychInfo databases with no date restrictions. We included original English-language studies investigating GxE interactions in schizophrenia spectrum disorders. Two reviewers independently screened studies, extracted data, and assessed quality using the Newcastle-Ottawa Scale, following PRISMA guidelines. We excluded studies investigating GxE interaction in the first episode of psychosis or the clinically high-risk population.
Results: Seventeen studies met the inclusion criteria. Due to heterogeneity in study design the genetic and environmental measures investigated, we grouped the studies based on the environmental exposures they examined: birth-related complications (65%), childhood adversity (29%), urban factors (29%), cannabis use (12%), infection (12%), and other (18%). Overall, five studies reported positive findings, including interactions between maternal cytomegalovirus x GWAS hits, Toxoplasma *gondii x COMT* gene, high birth weight and DISC1 pathway genes, schizophrenia polygenic risk score (PRS-SCZ) and exposome score, and GWAS and winter birth. Three studies reported mixed results: PRS-SCZ and childhood adversity, PRS-SCZ and polyenvironmental risk score, and 128 variants with high birth weight.
Conclusion: The study supports the relevance of GxE interaction in schizophrenia susceptibility. Although methodological heterogeneity and reliance on European ancestry cohorts limit the generalizability of the findings, more recent studies have leveraged advances in genetics and biostatistics to account for the polygenic nature of schizophrenia and conduct a cumulative assessment of a broader range of environmental exposures. Thus, large-scale, diverse and standardized studies are warranted.

Large Language Models in psychiatry: evaluating AI's rating capabilities of formal thought disorder

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Introduction: Schizophrenia and other psychiatric disorders are associated with significant disruptions in thought, language, and speech, collectively Formal Thought Disorder (FTD) typically evaluated using clinical rating scales like the Thought and Language Index (TLI). Here we investigate whether Large Language Models (LLMs), particularly small-to-medium sized local open-weight models, can reliably perform structured rating of FTD as measured using the TLI. Assessments by clinicians can be subjective, prone to inter-rater variability and bias, and difficult to scale because they require a live interview with a patient, which could be resolved by using LLM ratings.
Methods: We prompted open-weight LLMs (Qwen 2.5 14B and Qwen 3 14B) to act as a clinician and assign TLI scores. The base prompt consisted of the task instructions, documentation of the TLI scale, description of the 3 images, and example transcripts and reference TLI scores. To evaluate performance, we used a real-world dataset of 191 transcribed interviews with three picture descriptions from patients with schizophrenia, schizophrenia spectrum disorder (SSD), and healthy controls. The LLM-generated ratings were compared against human clinician scores using mean absolute error (MAE), correlation, and intraclass correlation coefficient (ICC).
Results: Our results show a moderate overall correlation (0.44) between LLM and human clinician TLI scores with Poverty of Speech performing the best (0.61). All average differences were within one step of the TLI scale (0.25). Distractibility did not correlate well because our dataset contained no occurrences of it.
Conclusion: Our results showed that LLMs can approximate professional assessment of TLI item scores with moderate correlation, even without fine-tuning. However, we also discovered inherent limitations of LLMs such as only being able to process one modality (text), missing out on key verbal and visual nuances.

Associations of Polygenic Risk for Alzheimer's Disease with Cerebral Blood Flow in Youth: Focus on Bipolar Disorder and Sex Differences

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Introduction: Bipolar disorder (BD) confers elevated risk for Alzheimer's disease (AD). Given that AD-related processes begin decades before symptom onset, it is important to explore early markers of AD risk. Cerebral blood flow (CBF) declines up to 5% annually in AD patients. Additionally, youth with BD have higher CBF demands, and lower CBF is associated with greater depression severity. The current study investigated the association of a polygenic risk score for AD (AD-PRS) with CBF in youth with BD and heathy controls (HC).
Methods: CBF was collected for 100 youth aged 13-20 (n=58 BD; n=42, HC) via arterial spin labelling MRI. AD-PRS was calculated from adult genome-wide association studies. Region of interest (ROI; global, anterior cingulate cortex, and middle frontal gyrus gray matter CBF) and voxel-wise analyses used general linear models to assess the association of AD-PRS with CBF in the overall sample, within diagnosis and sex, and interaction effects. Covariates included age, sex, and the first two genetic principal components.

Results: In ROI analyses, higher AD-PRS was associated with higher global CBF in males. In voxel-wise analyses, higher AD-PRS was associated with lower CBF in the right cerebral white matter within BD (ß=-0.46, p<0.001). Higher AD-PRS was associated with lower CBF in the right middle temporal gyrus in females (ß=-0.40, p=0.008), and higher CBF in the left lateral occipital cortex in males (ß=0.65, p=0.003). In interaction analyses, higher AD-PRS was associated with lower CBF in females but higher CBF in males in the left lateral occipital cortex (ß=-0.40, p<0.001) and left frontal pole (ß=-0.34, p=0.003).
Conclusion: Genetic risk for AD may influence CBF as early as youth, with preliminary evidence of sex- and diagnosis-specific patterns. Longitudinal studies are needed to examine how age-related changes may shape the association of AD-PRS with CBF across the lifespan.

Region-Specific Neural Oscillations in the Prelimbic Cortex During Social Tasks in Female Fmr1 KO Mice

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Introduction: Fragile X syndrome (FXS) is the most common inherited cause of autism spectrum disorder, with social interaction deficits as a core feature. The underlying neural mechanisms, particularly in females, remain poorly understood. The prelimbic cortex (PL), a subregion of the medial prefrontal cortex, is critical for integrating social cues and guiding adaptive behaviors. While global EEG has revealed large-scale network dysfunctions in FXS, it lacks the spatial resolution to assess oscillatory dynamics within specific circuits. This study uses local EEG recordings in juvenile female Fmr1 knockout (KO) mice and wild-type (WT) controls to identify region- and circuit-level disruptions in PL activity during social tasks.
Method: EEG activity was recorded from the PL using a stand-alone, open-source electrophysiology system and customized tungsten monopolar electrodes. Reference and ground electrodes (stainless steel screws) were positioned in the parietal cortex and the contralateral hemisphere relative to the recording site. EEG activity was recorded in the home cage and during behavioral testing, and EEG power was computed for each condition.
Results: In the two-chamber test, 7 WT and 6 KO juvenile mice were evaluated. Both groups showed decreased alpha EEG power during the task, with no significant differences between genotypes. Behaviorally, both WT and KO mice spent significantly more time with a stranger mouse than with a novel object, indicating preserved social approach behavior.
Conclusion: In summary, juvenile female Fmr1 KO mice did not differ from WT controls in PL alpha oscillatory dynamics or basic social approach in the two-chamber test. Further research with larger cohorts is needed to clarify any disruptions in FXS.

Glutamatergic basis of diminished sensitivity to linguistic context in first-episode psychosis

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Introduction: Disorganized speech is a prominent and persistent symptom of schizophrenia, a key feature of which is the deficit in processing linguistic context. In this study, we aimed to identify the neurochemical basis of context processing deficits in first-episode psychosis (FEP); we hypothesized that glutamate alterations in the dorsal anterior cingulate cortex (dACC) underlies insensitivity to linguistic context.
Methods: We included 39 FEP patients (33 men) and 33 socio-demographically matched healthy controls (22 men), recruited between February 2017 and February 2022 as part of the TOPSY clinical trial. All patients had less than 2 weeks of antipsychotic exposure. Linguistic contextual sensitivity was quantified using GPT-3-based lexical predictability from naturalistic speech. Concentrations of metabolites in dACC were measured with 7-T proton magnetic resonance spectroscopy (MRS). We then conducted general linear models to examine the interaction between diagnosis and glutamate in predicting contextual sensitivity, with additional regression models controlling for clinical, linguistic, and cognitive variables.
Results: A significant interaction was observed between diagnosis and glutamate in predicting contextual sensitivity [$F(3,68) = 3.50$; $p = 0.020$, $R2 = 0.13$]. In FEP patients, lower glutamate levels were associated with reduced contextual sensitivity ($R = 0.34$; $p = 0.033$), a pattern not seen in controls ($p = 0.53$). This relationship remained significant after adjusting for clinical symptoms, other linguistic features, and cognitive scores, underscoring its robustness and specificity. Notably, N-acetylaspartate (NAA), glutathione, and glutamine, despite their close links to glutamatergic metabolism, were not significantly associated with contextual sensitivity.
Conclusion: In minimally treated psychosis, reduced glutamate in the dACC is associated with impaired use of linguistic context during speech. This relationship is specific to glutamate and contextual sensitivity, not other clinical measures or glutamate-related metabolites. These results highlight a glutamatergic basis for disorganized speech in schizophrenia and suggest that contextual insensitivity could reflect dACC glutamate variations in early psychosis.

Targeted Optogenetic Stimulation of Serotonin Induces Axonal Regrowth and Behavioral Recovery from Cortical Stroke

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Introduction: Post-stroke depression (PSD) is one of the most common adverse effects of stroke that affects around one-third of stroke patients. PSD can cause poor stroke recovery, anxiety, cognitive impairment, and increase chance of developing second stroke. Depression is commonly linked with serotonin (5HT) deficiency;

thus, PSD patients are often treated with selective serotonin reuptake inhibitors (SSRIs), which reduce PSD symptoms by enhancing 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.
Methods: In this study, we use bilateral optogenetic stimulation to directly increase 5HT release to the stroke site to achieve a treatment effect. Pet-ChR2 mice that express channelrdhodopsin-2 (ChR2) in 5-HT neurons and wildtype (WT) mice were given stroke (endothelin-1 injections, 2x1ul, in 2ug/ul=800 pmol/ul) at the left medial prefrontal cortex (mPFC) and bilateral light fibre implants at the cingulate gyrus (CG). After 2-week surgery recovery, all mice had chronic 20-Hz optogenetic stimulation (3x5min/day for 5-days; and 24hr before each behavioral test). We used behaviour tests to assess treatment effect and utilized immunofluorescence staining to assess cellular changes.
Results: Within a week, Pet-ChR2 mice showed significant reduced anxiety- and depression-like behaviors compared to WT in all behaviour tests. Stroke causes significant reduction of 5HT innervation at the stroke site and imbalanced brain activity between two brain hemispheres. At 4-weeks post-stroke, imbalanced cell activity and 5HT axon loss remained present in the left mPFC in WT mice, but opto-stimulation in Pet-ChR2 mice achieved more balanced brain activity and a strong recovery of 5HT axon density.
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.

Cannabis and Tobacco Co-Use and its Association with Striatal Brain Morphometry: Leveraging Data from the ENIGMA Addiction Working Group

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Introduction: The striatum plays a central role in the pathophysiology of addiction. Studies report that cannabis use is associated with greater striatal grey matter volume (GMV), while tobacco use is associated with both greater and lower striatal GMV. However, their combined effects on striatal GMV remain unclear. Using two independent MRI processing methods, we investigated the main and interaction effects of cannabis and tobacco use on striatal GMV.
Method: Men and women from 8 ENIGMA Addiction sites (N=302) were parsed into 4 groups; individuals with: co-use (CT, n=38); cannabis-only use (CO, n=34); tobacco-only use (TO, n=61), and controls (CTL, n=169). Striatal GMV was assessed using (1) Freesurfer-extracted region-specific estimates and (2) voxel-based morphometry in FSL using a striatal mask. Analyses employed 2 x 2 ANCOVAs controlling for necessary covariates.
Results: With Freesurfer, a main effect of cannabis use emerged in the right nucleus accumbens, which was

replicated using FSL (ps=0.05). With FSL, main effects of cannabis use were found in the putamen and caudate (ps=0.01), which were modulated by tobacco use (ps=0.02). Post-hoc comparisons revealed: CT = CTL > TO in the putamen and caudate (ps=0.04); and CTL > CO (ps=0.06) and CT > CO (p=0.03) in the caudate.

Conclusions: We demonstrated, for the first time, that people who co-use have greater striatal GMV compared to people using either substance alone, whereas individuals using only one substance have lower striatal GMV compared to controls. Future research should investigate the clinical correlates of co-use in relation to this distinct pattern of striatal morphology.

Brain connectivity predictors of response to transcranial magnetic stimulation in major depression: results from the CARTBIND clinical trial

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Introduction: Major depression is highly heterogeneous, with over one-third of patients not responding to frontline treatments. Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for treatment resistant depression interindividual variability in response underscores the need to identify predictive biomarkers.

Methods: In secondary analyses of the Canadian rTMS Treatment and Biomarker Network in Depression (CARTBIND) trial that included 175 patients (65.7% female, mean [SD] age = 41.4[11.4]) with usable images and response data, we train logistic regression models with elastic net regularization and 10-fold cross-validation to predict response to rTMS from clinical, structural, and functional connectivity (FC) MRI data. Resting-state FC features include connectivity of the left dlPFC with cortical regions. Structural connectivity was measured using the Morphometric INverse Divergence (MIND). Model performance was assessed using area under the curve (AUC).

Results: Models including clinical features and MIND structural connectivity achieved high performance levels, with AUCs improving from 0.59 (clinical only) to 0.89 (clinical and MIND top features). Top positive predictors included interhemispheric-prefrontal connections; negative predictors involved temporal-occipital pathways. Adding FC features also improved response prediction performance compared to clinical models. The best performing FC models (clinical and top left dlPFC FC features) produced an AUC of 0.88. Lower left dlPFC connectivity with the left anterior cingulate, insula, and medial temporal regions and higher left dlPFC connectivity with select visual and motor regions and left posterior cingulate predicted higher likelihood of response.

Conclusion: Functional and structural connectivity features combined with clinical data show promise for predicting response to brain stimulation in major depression. Cross-trial analyses and replication are needed to validate generalizability in future studies.

Preliminary Study of LPS-Stimulated Immune Markers and Synaptic Density in a Trans-Diagnostic Sample from the Toronto Adolescent and Youth (TAY) Cohort

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Introduction: Pre-clinical studies show that stress triggers immune dysregulation, leading to elevated levels of pro-inflammatory cytokines and microglial activation. This response is linked to excessive synaptic pruning and reduced synaptic density, potentially raising vulnerability to mental illness. However, this pathway is poorly understood in humans, highlighting the need for translational research. Here, we explored the link between innate immune response and synaptic density in youth seeking mental health treatment.

Method: A subset of participants from the TAY cohort completed a PET study with [^{1}8F]SynVesT-1, a radiotracer for presynaptic density, and provided blood samples that were immunologically challenged ex vivo using lipopolysaccharide (LPS) stimulation to generate a panel of immune markers. MRI was used to delineate six corticolimbic regions of interest. Time-activity curves were analyzed using a simplified reference tissue model 2 to estimate non-displaceable binding potential (BPND), serving as an index of synaptic density.
Results: Fifty participants consented to the PET study, of which 33 (20.9 years old, 14M, 19F) had blood drawn for analysis. Eighty-eight percent of participants met DSM-5 criteria for each of depression and anxiety, and 46% for each of PTSD and substance use disorders. LPS stimulation significantly increased levels of multiple cytokines (TNF-a, IL-1ß, IL-6, TNFRI, IFN-?, CCL2). A greater fold change in TNFRI (Tumor Necrosis Factor Receptor I) from baseline to LPS condition was associated with lower [18F]SynVesT-1 BPND in prefrontal cortex ($r = -0.376$, $p = 0.031$), anterior cingulate cortex ($r = -0.351$, $p = 0.045$), and striatum ($r = -0.358$, $p = 0.041$).
Conclusion: This is the first study to investigate the relationship between synaptic density and peripheral provoked immune markers in mental-health treatment seeking youth. Greater response to the immune challenge was associated with reduced synaptic density. Further studies are needed to understand the diagnostic and phenotypic links between markers of peripheral inflammation and synaptic density.

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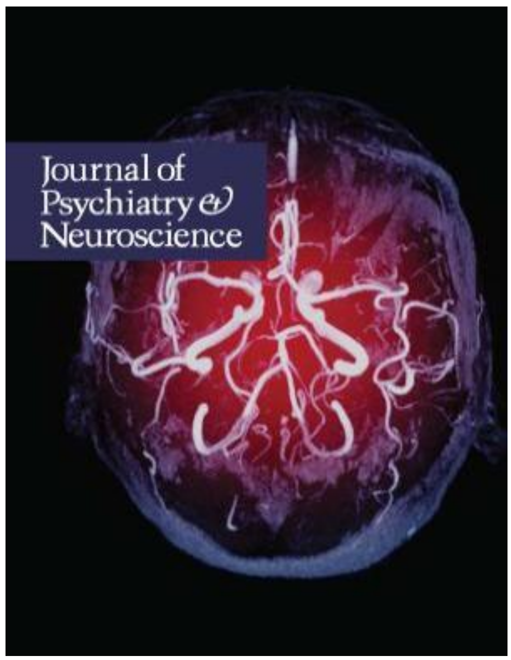

The JPN Editorial held a workshop during the lunch break entitled:

“Publish ~~or perish~~ and flourish: a fireside chat with the JPN Editorial Board”

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We are pleased to announce that CCNP's 48th Annual Meeting

is scheduled for September 23 – 25, 2026

and will be held in Toronto, Ontario!

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