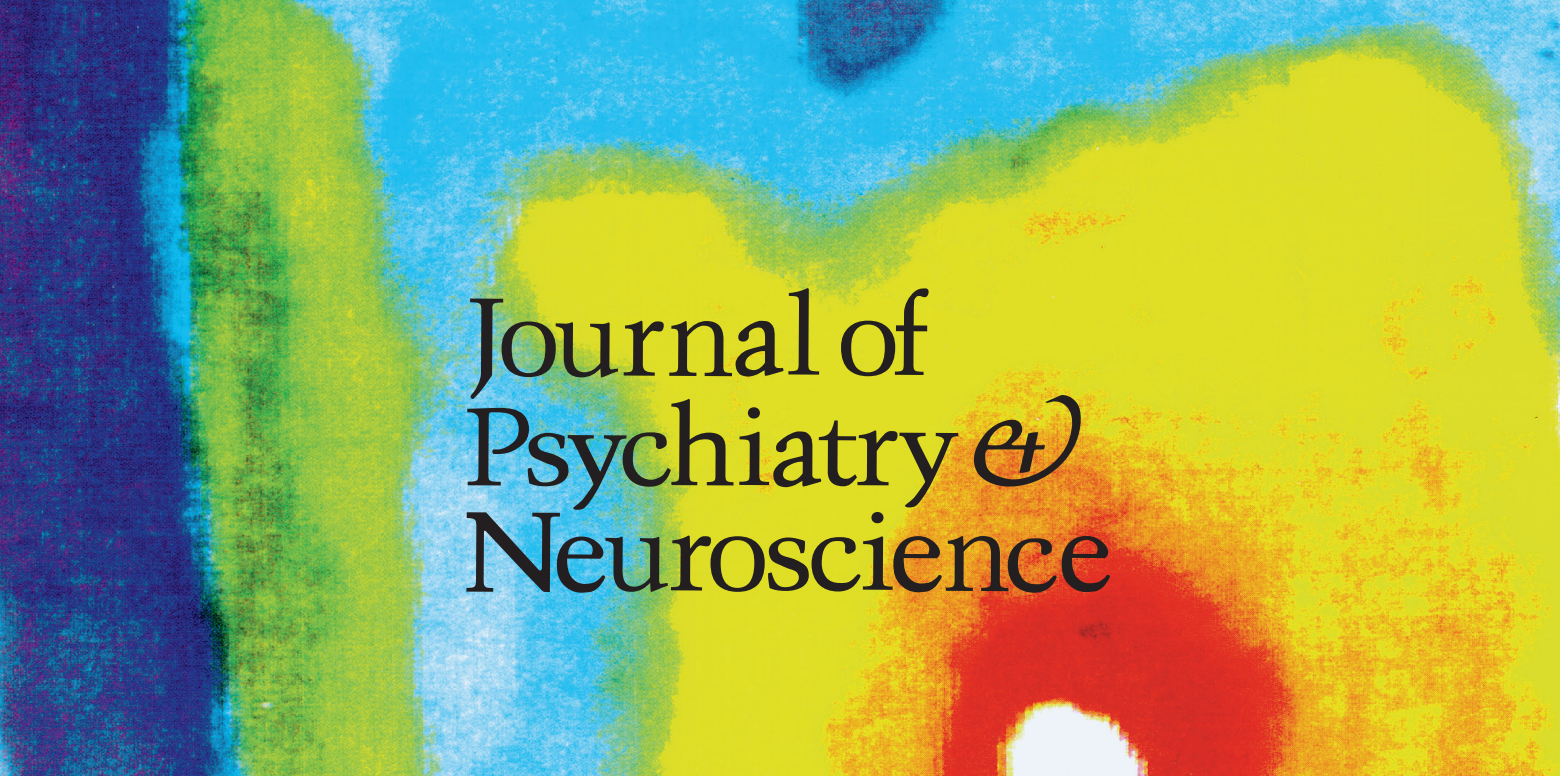

The 43rd Annual Meeting of the Canadian College of Neuropsychopharmacology November 4, 2021

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OVERVIEW OF EVENTS

10:30 am Opening of Meeting
10:45 am Opening Remarks – Dr. Jeff Daskalakis, CCNP President
10:50 am Introduction – Dr. Cecilia Flores, CCNP Vice-President
11:00 am CCNP 2020 Young Investigator Award Presentation
Caroline Ménard, PhD, Department of Psychiatry & Neuroscience, Université Laval: "Sex-specific vascular alterations and biomarkers underlie stress responses in mice mirrored in human depression"
11:50 am CCNP Next Generation Awardee
Andrea H. Pantoja Urban, MSc, Integrated Program in Neuroscience, McGill University: "Short and long-term effects of social defeat stress in adolescent female mice"
12:05 pm CCNP Next Generation Awardee
Orna Issler, PhD, Department of Neuroscience, Mount Sinai:"The sex-specific role for long noncoding RNAs in depression: from genome-wide patterns to behavioral readout"
12:20 pm Lunch/Break
12:50 pm CCNP 2020 Heinz Lehmann Award Presentation
Martin Alda, MD, FRCPC, Department of Psychiatry, Dalhousie University: "Personalized long-term treatment of bipolar disorder"
1:40 pm CCNP Next Generation Awardee
Mikaela K Dimick, BA, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health: "Cerebral blood flow and core mood symptoms in youth bipolar disorder: evidence for region-symptom specificity"
1:55 pm CCNP Next Generation Awardee
Sneha Chenji, PhD, Department of Psychiatry & Pediatrics, University of Calgary: "The effect of rTMS treatment on cortico-striatal-thalamo-cortical (CSTC) circuit connectivity in Tourette's syndrome: a pilot study"
2:10 pm Break
2:20 pm CCNP 2020 Innovations in Neuropsychopharmacology Award Presentation
Jeffrey Meyer, MD, PhD, FRCPC, Department of Psychiatry, University of Toronto: "Imaging markers of gliosis and monoamine oxidase in major depressive disorder: implications for personalized prevention and treatment"
3:10 pm CCNP Next Generation Awardee
Jasmine D. Cakmak, MSc, Neuroscience, Western University: "The functional and structural consequences of aberrant microglial activity in major depressive disorder"
3:25 pm CCNP Next Generation Awardee
Kayla D. Stone, PhD, Department of Psychiatry, University of Calgary: "Dorsolateral prefrontal cortex neurometabolite concentrations in pediatric mild traumatic brain injury"
3:40 pm Break
3:50 pm Keynote Speaker
Rémi Quirion, OC, CQ, PhD, FRSC, Chief Scientist of Quebec, Ministry of Economy & Innovation: "A less well travelled road: from neuroscientist to chief scientist and then came COVID-19"
4:50 pm Closing Remarks - Dr. Cecilia Flores, CCNP Vice President

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

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The Canadian College of Neuropsychopharmacology appreciates the ongoing support of Pfizer Canada Inc. for the Heinz

Lehman, Innovations in Neuropsychopharmacology and the Young Investigator Awards.

Role of histone 3.3 lysine 27 methylation in conferring enduring stress susceptibility. ***Angélica Torres-Berrío, Aarthi Ramakrishnan, Angélica Minier-Toribio, Eric M. Parise, Freddyson J. Martínez-Rivera, Caleb J. Browne, Orna Issler, Yentl Y. van der Zee, Omar Sial, Benjamin García, Kristian Helin, Simone Sidoli, Li Shen, Eric J. Nestler*. From the Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Torres-Berrío, Ramakrishnan, Minier-Toribio, Parise, Martínez-Rivera, Browne, Issler, van der Zee, Sial, Shen, Nestler); the Washington University School of Medicine in St. Louis, Saint Louis, MO, USA (Garcia); the Institute of Cancer Research, London, UK (Helin); and the Albert Einstein College of Medicine, New York, NY, USA (Sidoli).**

Background: Depression is a prevalent psychiatric disorder characterized by heterogeneous symptoms that can last a lifetime and remain even after several courses of antidepressant treatments. Vulnerability to depression is associated with long-lasting changes in the transcriptional profile of the nucleus accumbens (NAcc), a brain region involved in reward and mood regulation. **Methods:** Here, we characterized the enduring changes in histone modifications in the NAcc of mice exposed to chronic social defeat stress (CSDS), a validated model for the study of depression-like behaviours that separates mouse populations into susceptible (SUS) and resilient (RES) based on a social interaction test (SIT). Tissue from the NAcc of control, SUS, and RES mice was collected either 24 hours or 4 weeks after the SIT and processed for histone profiling via mass spectrometry. In parallel, we mapped the genome-wide enrichment of the most changed histone modifications using CUT&RUN and assessed for chromatin accessibility in a cell-specific manner using ATAC-Seq. **Results:** CSDS alters the methylation (me) dynamics of lysine (K) 27 of the histone variant H3.3 — the predominant form of H3 present in adult brain neurons. Specifically, we observed an increase in the abundance of H3.3K27me1 and a decrease in the abundance of H3.3K27me2 in the NAcc of SUS mice. Genomic distribution shows that H3.3K27me1 is primarily enriched in gene bodies and proximal promoters, suggesting its crucial role in determining stress-induced transcriptional profiles. In contrast, H3.3K27me2 is weakly deposited across intergenic regions. Using bioinformatics, we are currently identifying changes of chromatin accessibility and functional regulatory elements that coincide with H3.3K27me1 enrichment. **Conclusion:** Our results suggest that H3.3K27me1 and H3.3K27me2 are important chromatin "scars" that mediate enduring susceptibility to stress in the NAcc. Understanding the molecular basis of these adaptations and identifying the genomic regions affected will shed new light on persisting forms of stress-induced pathology.

Decreased medial prefrontal cortex glutamate levels in perimenopausal women. ***Sidney Yap, Jessica Luki, Christopher C. Hanstock, Peter Seres, Tami Shandro, Sarah Hanstock, Alynna Lirette, Huaying (Helen) Zhaoa, Katherine J. Aitchison, Jean-Michel Le Melledo*. From the Department of Psychiatry, University of Alberta, Edmonton, AB, Canada (Yap, Luki, S. Hanstock, Lirette, Zhaoa, Aitchison, Le Melledo); the Department of Medical Genetics, University of Alberta, Edmonton, AB, Canada (Aitchison); the Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada (Aitchison); the Edmonton Mood and Anxiety Disorders Program, University of Alberta Hospital, Edmonton, AB, Canada (Aitchison); the Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada (C. Hanstock, Seres); and the Royal Alexandra Hospital, Edmonton, AB, Canada (Shandro).**

Background: There is an increased risk of experiencing depression during perimenopause (PM), a period of rapidly changing female hormone concentrations. We hypothesize that this increased risk of depression is due to decreased Glu levels in the medial prefrontal cortex (MPFC) referenced to creatine in PM women compared with reproductive-aged (RD) women. Women at particular risk of developing major depression (MD) during PM are those with a history of mood sensitivity to female hormone fluctuations; i.e., women with a history of premenstrual dysphoric disorder (PMDD) and/or postpartum depression (PPD). Depressive symptomology has been associated with fluctuations of Glu levels in the MPFC in patients with MD as well as those with PMDD and PPD. Furthermore, the rapid antidepressant activity of ketamine, a glutamatergic modulator, has been linked to its activity at the level of the MPFC. The objective of our study was to compare MPFC Glu levels in healthy PM and RD women. **Methods:** MPFC Glu levels in healthy PM (n = 14) and healthy RD women (n = 16) were compared via magnetic resonance spectroscopy (MRS) scan using a 3 T magnet. Absence of depressive symptomology and psychiatric comorbidity was confirmed via semistructured interview (MINI Neuropsychiatric Interview). Participants were scanned during the early follicular phase of the menstrual cycle, specifically 1–5 days following commencement of the menstrual period. **Results:** Mean MPFC Glu concentrations were decreased in the PM group compared with the RD group (0.57 ± 0.06 v. 0.63 ± 0.06, $t = -3.84$, degrees of freedom [df] = 23.97, $p = 0.001$). **Conclusion:** PM is associated with decreases in MPFC Glu levels; this decrease may contribute to the increased risk of experiencing MD during PM. Further research should assess MPFC Glu levels in PM women with MD.

Novel treatments for autism-spectrum disorder based on genomics and systems biology. ***Danielle Baribeau, Evdokia Anagnostou*. From the Department of Psychiatry, University of Toronto, Toronto, ON, Canada (Baribeau); and the Department of Pediatrics, University of Toronto, Holland Bloorview Kids Rehabilitation Hospital, Toronto, ON, Canada (Anagnostou).**

Background: Autism-spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder with a complex underlying genetic architecture. There are currently no known pharmacologic treatments for the core ASD symptoms of social deficits and restricted/repetitive behaviour.

However, there are dozens of clinical trials currently underway that are testing the impact of novel and existing agents on core and associated symptoms in ASD. **Methods:** We present a narrative synthesis of the historical and contemporary challenges to drug discovery in ASD. We then provide an overview of novel treatments currently under investigation from a genomics and systems biology perspective. **Results:** Data-driven network and cluster analyses suggest that alterations in transcriptional regulation, chromatin remodelling, synaptic transmission, neuropeptide signalling, and/or immunological mechanisms may contribute to or underlie the development of ASD. Agents and upcoming trials targeting each of these systems are reviewed. **Conclusion:** Identifying effective pharmacologic treatments for the core and associated symptom domains in ASD will require further collaboration and innovation in the areas of outcome measurement, biomarker research and genomics as well as systematic efforts to identify and treat subgroups of individuals with ASD who may be differentially responsive to specific treatments.

Dissecting the role of DCC-positive prefrontal cortex projections in susceptibility to social defeat stress in adulthood. ***Ashraf Mahmud, Giovanni Hernandez, Cecilia Flores*****. From the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Mahmud); the Douglas Mental Health University Institute, Montréal, QC, Canada (Hernandez); and the Department of Psychiatry, McGill University, Montréal, QC, Canada (Flores).**

Background: Depression-like behavioural states in humans are associated with elevated levels of the guidance cue receptor gene *DCC* in the prefrontal cortex (PFC). DCC receptors organize neuronal connectivity and plasticity in adulthood, by regulating dendritic arborization and synapse formation. In adult mice, downregulation of DCC levels in the PFC induces resilience to chronic social defeat stress (CSDS), indicating a causal role, but the underlying mechanisms are still unknown. Here we assessed whether DCC receptors play a role in stress susceptibility by altering the dendritic architecture of selective PFC pyramidal neuronal projections. **Methods:** We infused a retrograde tracer in the nucleus accumbens (NAcc) core, NAcc shell, or basolateral amygdala (BLA) of adult male mice to quantify the percentage of DCC-positive projection neurons in the PFC. Next, CSDS-induced changes in dendritic spine density in DCC-positive pyramidal neurons projecting to the NAcc shell were assessed by microinfusing an AAVrg-CAG-GFP virus into the NAcc shell of adult male mice before CSDS. A quantitative anatomic analysis in the PFC was performed 72 hours after CSDS. We also evaluated whether deleting *Dcc* in PFC-NAcc shell pyramidal projections alters susceptibility to CSDS, using adult *DCC*lox/lox male mice and a Cre-dependent retrograde virus. **Results:** *DCC*-positive neurons in prelimbic and infralimbic PFC subregions prominently innervate the NAcc core and NAcc shell, compared with a scant projection to the BLA. Also, compared with control and resilient groups, susceptible mice show reduced thin and/or mushroom spine density in apical, but not basal dendrites of prelimbic and infralimbic DCC-positive neurons, suggesting loss of both new and mature spines. Initial results show that *Dcc* deletion in PFC-NAcc shell pyramidal neurons induces resilience to CSDS. **Conclusion:** DCC receptors in adult PFC pyramidal-NAcc projecting neurons may play a causal role in susceptibility to social defeat stress by inducing changes in apical dendritic spine architecture.

Chronic desipramine induces norepinephrine projections to promote recovery in a mouse model of fluoxetine-resistant depression. ***Faranak Vahid-Ansari, Amin Zahrai, Mireille Daigle, Paul R. Albert*****. From the University of Ottawa Brain and Mind Research Institute, Ottawa, ON, Canada (Vahid-Ansari, Daigle, Albert); and the University of Ottawa, Ottawa, ON, Canada (Zahrai).**

Background: Reduction in monoamines has been implicated in major depressive disorder, for which selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the first-line treatment. However, many patients do not respond to SSRIs and are switched to augmentation or tricyclic antidepressants (TCAs). To elucidate rational strategies to overcome SSRI-resistant depression (SRD), we generated cF1ko mice. In these mice, the Freud-1/CC2D1A gene is deleted in adult 5-HT cells, leading to reduced 5-HT and SRD phenotypes. Here we address the response of cF1ko mice to the TCA desipramine, targeting 5-HT and norepinephrine systems. **Methods:** Using behavioural tests, we examined cF1ko and wild-type mice chronically treated with desipramine. Brain-wide norepinephrine (NE) projections, synapses and chronic cellular activation were detected by immunofluorescence for the NE transporter (NET), synaptophysin, and FosB, respectively, with GAD67/gephyrin or CaMKII/vGluT1–2/PSD95, used to detect GABAergic interneurons, glutamatergic neurons or postsynaptic densities, respectively. **Results:** Desipramine treatment restored depression-/anxiety-like behaviour of cF1ko mice to wild-type levels. Desipramine increased locus coeruleus NE neuronal activity and induced the restoration of NE innervation to excitatory and inhibitory neurons in the nucleus accumbens, hippocampal-CA1, and basolateral amygdala. **Conclusion:** cF1ko mice with reduced 5-HT activity show alterations in NE corticolimbic projections. Desipramine-induced behavioural recovery was associated with selectively restored NE innervation. These results suggest that treatment of patients with reduced 5-HT function or SSRI nonresponse using antidepressants targeting NE, like TCAs, may be an effective alternative to SSRIs. The cF1ko mice provide a clinically relevant genetic model of SSRI resistance to further investigate the efficacy and mechanisms of alternative antidepressant approaches.

The social and anxious-like behaviour of adolescent mice predicts the short and long-term effects of social stress in adolescence: a longitudinal approach. ***Philip Vassilev, Samuel Richer, Nicole Brown, Michel Giroux, Giovanni Hernandez, Cecilia Flores*****. From the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada**

(Richer, Brown); the Douglas Mental Health University Institute, Montréal, QC, Canada (Vassilev, Giroux, Hernandez, Flores); the Department of Psychiatry, McGill University, Montréal, QC, Canada (Vassilev, Flores); and the Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada (Vassilev, Flores).

Background: We have previously shown that male mice exposed to an accelerated social defeat stress (AcSD) procedure in early adolescence have impaired inhibitory control in adulthood. Interestingly, this cognitive impairment was observed in all mice stressed in adolescence, even if they did not exhibit social avoidance 24 hours after the last AcSD session — a widely used behavioural marker of susceptibility to social stress. Classifying mice as resilient or susceptible based solely on 1 behavioural measure at a single point in time may be insufficient to detect subtle individual differences. To address this issue, we used a longitudinal design to assess social and anxiety-like behaviour before and after exposure to AcSD in adolescence. **Methods:** We used the social preference (SP) and dark/light (D/L) tests to assess the social and anxious-like behaviour of adolescent mice at postnatal days (PND) 22–23. We then exposed mice to AcSD for 4 days starting at PND 25. Then, we assessed social behaviour again in the SP and social interaction tests (SIT), immediately after the last session of AcSD. Finally, we tested mice on the SIT and SP in adulthood (PND 60–61) and assessed inhibitory control in a go/no-go task. **Results:** Performance on the SP and D/L tests at PND 22–23 predicts social interaction 24 hours after AcSD. Mice with lower social preference and a more anxious-like phenotype are less vulnerable to AcSD-induced social avoidance. There is a strong correlation between social interaction in the SIT and SP after AcSD, suggesting that the effect of social stress generalizes beyond the defeat context itself. A hierarchical clustering analysis based on SIT and SP scores reveals a subpopulation of "susceptible" mice that are severely socially impaired. **Conclusion:** Our longitudinal approach allowed us to predict and better characterize the short and long-term effect of social stress in adolescence.

THC in adolescence dysregulates microRNA pathways involved in dopamine development. ***Giovanni Hernandez, Tanya Capolicchio, Michel Giroux, Katherina Estrada, Cecilia Flores*****. From the Douglas Mental Health University Institute, Montréal, QC, Canada (Hernandez, Capolicchio, Giroux); the Department of Psychology, McGill University, Montréal, QC, Canada (Estrada); the Department of Psychiatry, McGill University, Montréal, QC, Canada (Flores); and the Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada (Flores).**

Background: Cannabis is one of the most consumed substances among adolescents in North America. Its regular use during this developmental period is linked to an increased risk of cognitive impairments and psychiatric disorders later in life. However, the cellular and molecular processes underlying these effects, particularly the developing adolescent mesocorticolimbic dopamine system, still remain unknown. Dopamine maturation in adolescence is mediated by the Netrin-1 guidance cue receptor, DCC, whose expression is controlled by the microRNA, miR-218. Exposure to stimulant drugs of abuse in adolescence upregulates miR-218 in the ventral tegmental area (VTA) in male mice, reduces *Dcc* mRNA levels and disrupts mesocorticolimbic dopamine development and cognitive control in adulthood. **Methods:** Here we assessed whether tetrahydrocannabinol (THC), the main psychoactive component of cannabis, alters the miR-218/*Dcc* system in both male and female adolescent mice. Adolescent male and female C57/Bl6 mice (postnatal day 22) received intraperitoneal injections of THC — either 0, 2.5, 5, or 10 mg/kg once every other day for 10 days. One week after the last injection, miR-218 and *Dcc* mRNA expression were measured in the VTA using quantitative polymerase chain reaction (qPCR). **Results:** In males, exposure to 5 and 10 mg/kg, but not 2.5 mg/kg, of THC downregulated miR-218 in the VTA, inducing a concomitant increase in VTA *Dcc* mRNA levels. In females, THC did not alter miR-218 expression, but an increased *Dcc* mRNA level was observed following the 5 and 10 mg/kg doses. Interestingly, exposure to THC in both male and female mice leads to dose-dependent reduction in body weight. This change emerges during the adolescent treatment and persists throughout adulthood. **Conclusion:** Exposure to THC in adolescent male and female mice produces modifications in the molecular signalling pathways involved in protracted mesocorticolimbic dopamine maturation. We are currently examining these enduring effects on dopamine connectivity and behavioural endophenotypes associated with psychiatric vulnerability.

Stress susceptibility is related to changes in the hippocampal representation of conspecific location. ***Amanda Larosa, Xiong Long, Tian Rui Zhang, Alice S. Wong, Benjamin C.M. Fung, Tak Pan Wong*****. From the Neuroscience Division, Douglas Research Centre, Montréal, QC, Canada (Larosa, Long, Zhang, AS Wong, TP Wong); the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Larosa, Zhang); the Department of Psychiatry, McGill University, Montréal, QC, Canada (TP Wong); and the School of Information Studies, McGill University, Montréal, QC, Canada (Fung).**

Background: Depression is promoted by stress susceptibility, a factor that has been associated with enhanced hippocampal activity. The dorsal CA1 (dCA1) region of the hippocampus encodes spatial information, including the location of social targets. We sought to determine whether there are changes in dCA1 activity in mice with differing susceptibilities to chronic social defeat stress (CSDS) and whether they affect spatial representations of aggressors. **Methods:** In vivo calcium activity of dCA1 neurons expressing GCaMP6f were imaged with the UCLA Miniscope in C57/BL6 mice. Recordings were conducted on the day before CSDS and after episodes 2, 5, and 8 of CSDS, while animals were cohoused with a C57 (control group) or aggressor (stressed group) neighbour. We identified cells with increased activity when aggressors were close (near cells) or distant (far cells) by calculating the cosine similarity

index between calcium activity and head distance to aggressors. **Results:** Following CSDS, resilient animals showed an increase in mean dCA1 calcium activity following the fifth defeat episode (p = 0.0317). Of the recorded dCA1 neurons, about 12%–20% were characterized as near or far cells. Increased near cell activity after the eighth defeat episode was seen in resilient mice (p = 0.0362). Susceptible animals showed a decrease in the proportion of active near cells when the aggressor was distant (p = 0.0408) and a similar decrease in far cells when the aggressor was close (p = 0.0395) compared with resilient mice. **Conclusion:** CSDS susceptible mice show a mismatch between dCA1 activity and the egocentric representation of an aggressor's location. The previously reported stronger stress-related memory in susceptibility may not correspond to an accurate encoding of stress-related information. Such inaccuracy in the representation of aggressor location may be related to the abnormal cognitive processing seen in depression.

Individual differences in sucrose preference and ultrasonic vocalizations are temporally stable and uncorrelated in adult rats. ***Adithi Sundarakrishnan, Paul Clarke*****. From the Department of Pharmacology & Therapeutics, McGill University, Montréal, QC, Canada.**

Background: The sucrose preference test is a widely used measure of anhedonia in rat models of depression, yet depressed patients do not reliably show an analogous deficit. As an alternate affect-related measure, adult rat ultrasonic vocalizations (USVs) are attracting interest. It is unclear whether sucrose preference and ultrasonic vocalizations track the same emotional states. Therefore, as a first step, we have assessed whether sucrose preference and USV emission, tested separately, are correlated in "nondepressed" rats. **Methods:** Twenty-four experimentally naïve male Long–Evans rats were tested for 24 days, on alternating days of sucrose preference (12 d) and USV measurements (12 d). USVs were recorded in 20-minute sessions, and sucrose preference was measured using a simultaneous 2-bottle choice of tap water versus 0.3% sucrose solution in 1-hour sessions. To test the longer-term temporal stability of USVs, the rats then underwent a second round of USV measurements 3 months later. **Results:** Our 3 main measures (sucrose preference, 50-kHz call rate and relative prevalence of trill and flat call subtypes) all showed temporally stable individual differences across the 24-day testing period and at the 3-month follow-up. Correlational analysis revealed no significant associations between sucrose preference and all 3 USV measures. **Conclusion:** On measures of sucrose preference and USV emission, adult rats maintain interindividual differences over weeks or months. This trait-like stability helped to reveal a lack of association between sucrose preference and USV measures. This lack of association is potentially significant, given the limited validity of the sucrose preference test. Therefore, USVs should be explored as an alternative measure to sucrose preference in animal models of depression. **Funding:** Natural Sciences and Engineering Research Council of Canada and Canadian Institutes of Health Research.

A history of child abuse associates with fatty acid dysregulation in the anterior cingulate cortex of depressed suicides. ***Kelly Perlman, Raphaël Chouinard-Watkins, Arnaud Tanti, Giulia Cisbani, Massimiliano Orri, Gustavo Turecki, Richard P. Bazinet, Naguib Mechawar*****. From the McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montréal, QC, Canada (Perlman, Chouinard-Watkins, Tanti, Orri, Turecki, Mechawar); the Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada (Cisbani, Bazinet); the UMR 1253, iBrain, Université de Tours, INSERM, Tours, France (Tanti); and the Department of Psychiatry, McGill University, Montréal, QC, Canada (Turecki, Mechawar).**

Background: A history of child abuse (CA) strongly increases the lifetime risk of suffering from major depression and predicts an unfavourable course for the illness. Severe CA has been specifically associated with a widespread, robust, and lasting inhibition of oligodendrocyte function, coupled with impaired myelination of small-calibre axons in white matter of the human anterior cingulate cortex (ACC). Given that myelin is extremely lipid-rich, a possible explanation for this finding could be a disruption of the lipid profile that composes the myelin sheath. Furthermore, the composition of fatty acids (FA) in myelin phospholipids has been shown to influence its stability and permeability. Therefore, the objective of this study was to quantify and compare FA concentrations in postmortem ACC white matter in the choline glycerophospholipid pool (ChoGpl), a key myelin phospholipid pool, between adults with depression who died by suicide and had a history of CA, matched adults with depression who died by suicide without a history of CA, and healthy nonpsychiatric controls. **Methods:** Total lipids were extracted according to the Folch method, and lipids were separated into respective classes using thin-layer chromatography. FA methyl esters from the ChoGpl fraction were quantified using gas chromatography. **Results:** Our analysis revealed significant differences in FA concentrations between groups, primarily involving the FAs in the arachidonic acid synthesis pathway, which is further corroborated with ACC RNA-sequencing data. Furthermore, the concentration of most FAs was found to decrease with age. **Conclusion:** These findings warrant further investigation, in particular to establish the underlying mechanisms and to determine how they may contribute to the neurobiological vulnerability to psychopathology resulting from early-life adversity.

Dorsolateral prefrontal cortex neurometabolite concentrations in youth with and without mild traumatic brain injury. ***Kayla D. Stone, Rose Swansburg, Sneha Chenji, Frank P. MacMaster, Karen M. Barlow*****. From the Department of Psychiatry, University of Calgary, Calgary, AB, Canada (Stone, Swansburg, Chenji, MacMaster); the Addictions and Mental Health Strategic Clinical Network, Calgary, AB, Canada (MacMaster); the Department of Paediatrics, University of Calgary, Calgary, AB, Canada (MacMaster); and the Child Health Research Centre, University of Queensland, Brisbane, Australia (Barlow).**

Background: Mild traumatic brain injury (mTBI) is a major public health concern, affecting approximately 20% of youth, with persistent postconcussive symptoms (PPCS) in up to 30% of cases 1 month postconcussion. In adults, changes to energy metabolism and neuronal viability, as measured by creatine and *N*-acetyl-aspartate (NAA) concentrations in the brain, often ensue. Cognitive functions are often disrupted following mTBI too. However, the nature of these changes in youth with PPCS is not well understood. Our objective was to compare creatine and NAA concentrations in the dorsolateral prefrontal cortex (DLPFC) in symptomatic (n = 68) and asymptomatic (n = 34) youth approximately 40 days after mTBI, and in typically developing youth (n = 20) without mTBI. **Methods:** Magnetic resonance spectroscopy was used to measure concentrations of creatine and NAA in the DLPFC. Cognitive function was measured using the CNS Vital Signs neurocognitive index. **Results:** Symptomatic participants had higher creatine and NAA concentrations than typically developing controls ($p < 0.04$), but not higher than asymptomatic participants ($p > 0.1$), in the left DLPFC. There was no difference in cognitive performance among the 3 groups ($p = 0.06$). Cognitive performance was not significantly related to DLPFC creatine or NAA concentrations. **Conclusion:** These findings highlight the delicate neurobiological changes that occur post-mTBI in youth, particularly in youth with PPCS. Large-scale, longitudinal magnetic resonance spectroscopy studies in youth with mTBI are needed to corroborate these findings.

A dissonance between health care utilization costs and research funding for eating disorders in Canada. ***Kayla D. Stone, Gina Dimitropoulos, Frank P. MacMaster*. From the Department of Psychiatry, University of Calgary, Calgary, AB, Canada (Stone, MacMaster); the Department of Pediatrics, University of Calgary, Calgary, AB, Canada (MacMaster); the Faculty of Social Work, University of Calgary, Calgary, AB, Canada (Dimitropoulos); the Mathison Centre for Mental Health, Calgary, AB, Canada (Dimitropoulos, MacMaster); and the Addictions and Mental Health Strategic Clinical Network, Calgary, AB, Canada (MacMaster).**

Background: Eating disorders are common and potentially life-threatening, affecting more than 1.7 million Canadians at any given time. Unfortunately, eating disorder research is underfunded, and many Canadians are suffering the consequences. Our objective was to synthesize research funding and health care utilization costs for people with eating disorders in Canada. We compared these values to that of other common neuropsychiatric/neurodevelopmental conditions (e.g., schizophrenia, bipolar disorder, and autism-spectrum disorder). **Methods:** Health care utilization costs were obtained from the Canadian Institute of Health Information, while research funding (from 2014–2019) was obtained from tri-council funding databases (Canadian Institutes of Health Research [CIHR], Social Sciences and Humanities Research Council of Canada [SSHRC]). Means are reported. **Results:** In 2018/2019 (most recent reported data), health care utilization costs equated to $22 935 per individual affected with an eating disorder, 1.6 times more than what was spent on schizophrenia and 2 times more than what was spent on bipolar disorder (data were unavailable for individuals with autism-spectrum disorder). Combined CIHR and SSHRC funding from that same year provided only $0.70 per affected Canadian with an eating disorder compared with $50.17, $7.32, and $57.31 per affected Canadian with schizophrenia, bipolar disorder, and autism-spectrum disorder, respectively. **Conclusion:** Despite significant health care utilization costs, research funding for eating disorders remains low. There is a need for increased research funding in the field of eating disorders in Canada, as the current research-related investments hinder progress in developing neuroscientifically sound treatments for these populations.

Assessing active monoamine oxidase-A in live cells using selective fluorophore-tagged activity-based probes. ***Shusheng Wang, Jennifer N.K. Nyarko, Maa O. Quartey, Ryan M. Heistad, Christopher P. Phenix, Darrell D. Mousseau*. From the Department of Chemistry, University of Saskatchewan, Saskatoon, SK, Canada (Wang, Phenix); and the Cell Signalling Laboratory, Department of Psychiatry, University of Saskatchewan, Saskatoon, SK, Canada (Nyarko, Quartey, Heistad, Mousseau).**

Background: Monoamine oxidase-A (MAO-A) is central to the biology of amine function and was the first target used in the pharmacotherapeutics of depression. While targeting MAO-A remains an option, particularly in cases of refractory depression, there is still much to be learned about this enzyme. There are 2 isoforms of MAO — MAO-A and MAO-B — each with different cellular and tissue distributions and different affinities for monoaminergic neurotransmitters (e.g., serotonin, dopamine, and noradrenaline). Both isoforms can generate hydrogen peroxide as a reaction byproduct, which is thought to contribute to cytotoxicity. MAO protein expression and catalytic activity often do not correlate, and none of the current protocols can dependably differentiate active from inactive MAO-A (or MAO-B). Obviously, this could give rise to misleading conclusions about a role for MAOs in a given context. Activity-based probes (ABPs) are designed to target the catalytic sites of active enzymes. **Methods:** Exploring this concept, we synthesized 3 fluorescent ABPs. **Results:** Our probes bind MAO-A selectively and irreversibly, and with high affinity. This was shown using recombinant MAO-A and MAO-B proteins, endogenous (LnCAP cells) and overexpressed (N2a cells) MAO proteins, and confocal imaging. **Conclusion:** Our MAO-A ABPs will help understand the contribution of active MAO-A in cell function and could address some of the ambiguities in the MAO literature. Our ABPs also could provide a clearer understanding of the role of MAOs in the progressing of diseases such as depression and could inform on the most appropriate timing for the efficacious use of MAO therapeutics in the clinic

Short and long-term effects of social defeat stress in adolescent female mice. *Andrea H. Pantoja Urban, Samuel Richer, Amelie Mittermaier, Michel Giroux, Cecilia Flores*. **From the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Pantoja-Urban, Richer); the Douglas Mental Health University Institute, Montréal, QC, Canada (Pantoja-Urban, Richer, Giroux, Flores); the Department of Psychiatry and Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada (Mittermaier); and the Department of Psychiatry, McGill University, Montréal, QC, Canada (Flores).**

Background: Social stress in adolescence is associated with psychiatric vulnerability, but not all individuals are equally affected. The protracted development of dopamine (DA) innervation to the prefrontal cortex (PFC) is vulnerable to the detrimental effects of social stress, and its alteration is associated with cognitive deficits in adulthood. Male mice exposed to a modified version of the accelerated social defeat stress (AcSD) model in adolescence showed altered PFC DA connectivity and cognitive control in adulthood. These changes occur regardless of whether AcSD induces social avoidance in adolescence. **Methods:** We investigated the anatomic and behavioural consequences of AcSD in adolescent female mice. Female C57BL/6J mice exposed to AcSD in adolescence were assessed in a social interaction test to measure approach and/or avoidance behaviour 24 hours later and were categorized as "susceptible" or "resilient." In adulthood, (i) mice were tested in the go/no-go paradigm to measure inhibitory control or (ii) their brains were processed to quantify DA connectivity in the PFC using stereology. **Results:** Similar to adolescent males, most AcSD-exposed female mice show resilience to social avoidance. However, in adulthood, female mice categorized as resilient but not as susceptible show impaired inhibitory control and disorganized PFC DA connectivity. Interestingly, AcSD in adolescent female, but not male, mice leads to increased body weight throughout adulthood. **Conclusion:** There is a sex-specific impact of AcSD in adolescence on PFC DA development, inhibitory control, and possibly metabolism. Stress-induced social avoidance in adolescence determines risk to develop adult inhibitory control deficits in female, but not male, mice.

Pharmacogenomic testing for adults with intellectual disability and autism-spectrum disorder. *Kazunari Yoshida, Yona Lunsky, James L. Kennedy, Pushpal Desarkar, Daniel J. Mueller*. **From the Centre for Addiction and Mental Health, Toronto, ON, Canada; and the Department of Psychiatry, University of Toronto, Toronto, ON, Canada.**

Background: Adults with intellectual disability (ID) and/or autism-spectrum disorder (ASD) often present with mental health difficulties and challenging behaviours (e.g., aggression and self-injurious behaviour), which frequently require pharmacological treatment (e.g., antipsychotics and antidepressants). However, there have been limited efforts to optimize pharmacological treatment in this population. Although there is ample evidence that pharmacogenomics (PGx) testing can improve pharmacological treatment for depression and psychotic disorders, PGx studies have been scarce in adults with ID/ASD. Therefore, we aim to evaluate the feasibility and acceptability of PGx testing in this population. **Methods:** We aim to recruit 100 adults (aged ≥ 18 yr) with ID/ASD in a cross-sectional design. Saliva will be collected for PGx testing, and clinical assessments will be performed at baseline. At around week 6, we will inform the participants' primary physicians of the PGx testing results, and ask them to fill out a questionnaire for objective 3 listed below. The protocol of this study is now under review by REB. Our objectives are as follows: 1) to assess the feasibility of PGx testing; 2) to explore how frequently individuals prescribed antipsychotics or antidepressants have functional "anomalies" of the analyzed drug metabolizing genes (e.g., CYP2D6 and CYP2C19); and 3) to investigate physicians' understanding of and acceptability with PGx and the possibility of future clinical application of PGx for adults with ID/ASD. **Results:** Pending. **Conclusion:** This study has the potential to substantially improve pharmacotherapy, which will contribute to advance personalized medicine, in this marginalized population.

A three-factor model of commonly comorbid early onset psychiatric disorders: temperament, adversity, and dopamine. *Maisha Iqbal, Sylvia M.L. Cox, Natalia Jaworska, Maria Tippler, Natalie Castellanos-Ryan, Sophie Parent, Alain Dagher, Frank Vitaro, Mara Brendgen, Michel Boivin, Robert O. Pihl, Sylvana M. Côté, Richard E. Tremblay, Jean R. Séguin, Marco Leyton*. **From the Department of Neurology & Neurosurgery, McGill University, Montréal, QC, Canada (Iqbal, Tippler, Dagher, Leyton); the Department of Psychiatry, McGill University, Montréal, QC, Canada (Cox, Leyton); the Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada (Jaworska); the University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada (Jaworska); the School of Psychoeducation, Université de Montréal, Montréal, QC, Canada (Castellanos-Ryan, Parent, Vitaro); the CHU Ste-Justine Research Center, Montréal, QC, Canada (Vitaro, Brendgen, Côté, Tremblay, Séguin, Leyton); the Department of Psychology, Université de Québec à Montréal, Montréal, QC, Canada (Brendgen); the Department of Psychology, Université Laval, Québec, QC, Canada (Boivin); the Institute of Genetic, Neurobiological and Social Foundations of Child Development, Tomsk State University, Tomsk, Russia (Boivin, Pihl); the Department of Psychology, McGill University, Montréal, QC, Canada (Leyton); the Department of Social & Preventative Medicine, Université de Montréal, Montréal, QC, Canada (Côté); the Departments of Pediatrics & Psychology, Université de Montréal, Montréal, QC, Canada (Tremblay); the School of Public Health and Sports Science, University College Dublin, Dublin, Ireland (Tremblay); Institut national de la santé et de la recherche médicale (INSERM), Paris, France (Tremblay); and the Department of Psychiatry and Addictology, Université de Montréal, Montréal, QC, Canada (Séguin).**

Background: Commonly comorbid early onset psychiatric disorders might reflect the varying expression of overlapping risk factors. The mediating processes remain poorly understood, but 3 factors show some promise: adolescent externalizing (EXT) traits, early-life adversity, and midbrain dopamine autoreceptors. The present study investigated whether greater predictive power is attained when these features are combined. **Methods:** Participants had been followed since birth and were invited to participate in our study based on EXT trait scores between the ages of 10 and 16, as measured with the Social Behavioural Questionnaire. In early adulthood (age 18.5 ± 0.6 yr) participants were assessed with the Structured Clinical Interview for DSM-5, completed the Childhood Trauma Questionnaire (CTQ), and had a 90-minute high-resolution positron emission tomography (PET) scan with [18F]fallypride. Fifty-two psychotropic medication-free young adults (30 females, 22 males) completed the study. Follow-up interviews were conducted 1, 2 and 3 years later. Binomial logistic regression analyses tested whether midbrain [18F]fallypride BPND values, EXT and CTQ scores predicted the presence of lifetime DSM-5 diagnoses. All analyses were run for lifetime diagnoses at the time of or before the PET scan and again including diagnoses obtained during the follow-up interviews. **Results:** At the index interview, 23% of participants met criteria for at least 1 lifetime DSM-5 disorder. The 3-factor model predicted their presence with an overall accuracy of 90.4% (p = 0.000024) and explained 91.5% of the area under the receiver operating characteristic curve (95% confidence interval 0.824–1.000). When limited to EXT disorders specifically, the model was not more powerful than when targeting all disorders (p = 0.54). The model remained significant upon addition of new diagnoses that developed during the follow-up period (p = 0.000035). **Conclusion:** A combination of EXT traits, early-life adversity and poorly regulated dopamine transmission might increase risk for diverse early-onset psychiatric disorders. The present data raise the possibility that these features can predict susceptibility prospectively.

Imaging the endogenous opioid response to acute cannabis smoking in humans using positron emission tomography with [11C]carfentanil. ***Kelly Smart, Patrick D. Skosnik, David Matuskey, Nabeel Nabulsi, Jim Ropchan, Zachary Felchner, Henry Huang, Kelly P. Cosgrove, Ansel T. Hillmer.*** **From the Yale PET Center, Yale School of Medicine, New Haven, CT, USA (Smart, Matuskey, Nabulsi, Ropchan, Felchner, Huang, Hillmer); and the Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA (Anderson, Skosnik, Cosgrove, Hillmer).**

Background: The major psychoactive compound in cannabis, Δ9-tetrahydrocannabinol (THC), induces release of endogenous opioids in preclinical models, which may contribute to both analgesic and reinforcing effects. Our objective was to determine whether endogenous opioid release is detected in humans following cannabis smoking using positron emission tomography (PET) with the μ opioid receptor (MOR) agonist radioligand [11C]carfentanil. **Methods:** Seven healthy volunteers (age 30.1 ± 9.1 yr, 3 female) with limited past recreational cannabis use completed PET scans with [11C]carfentanil (515 ± 162 MBq) at baseline and after smoking cannabis (5.6 ± 0.57% THC, 0.01 ± 0.00% cannabidiol). Ratings of subjective drug response were collected, and the Cold-Pressor Task was performed to assess pain response pre- and postcannabis. Difference in [11C]carfentanil binding potential (BPND, simplified reference tissue model) between baseline and postcannabis scans was assessed as an index of endogenous opioid release. Secondary analyses explored correlations between baseline BPND, drug response and pain tolerance. **Results:** There were no significant reductions in [11C]carfentanil BPND postcannabis, indicating that no evidence of endogenous opioid release was detected. BPND was higher in the anterior cingulate postcannabis (p = 0.04) and not statistically different in other regions. Change in BPND postcannabis ranged from –0.5 ± 5.3% in the frontal cortex to 7.0 ± 7.1% in the anterior cingulate. Baseline amygdala BPND was negatively correlated at trend level with ratings of "high" postcannabis (r = -0.75, p = 0.08), such that people with lower MOR availability at baseline tended to have stronger subjective intoxication responses. Baseline BPND in the amygdala and thalamus was correlated with greater pain tolerance postcannabis (p < 0.04). **Conclusion:** In healthy volunteers with low levels of recreational cannabis use, we did not find evidence of endogenous opioid release following smoked cannabis using [11C]carfentanil PET. Low THC content may have limited the ability to detect such effects. Baseline MOR availability in the amygdala, reflecting either receptor expression or endogenous endorphin levels, may be linked to pain tolerance and subjective response to cannabis.

Pharmacogenetics of lethal opioid overdose. ***Leen Magarbeh, Ilona Gorbovskaya, Bernard Le Foll, Reuven Jhirad, Richard Wells, Daniel J. Müller.*** **From the Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada (Magarbeh); the Centre for Addiction and Mental Health, Toronto, ON, Canada (Gorbovskaya, Le Foll, Müller); Department of Psychiatry, University of Toronto, Toronto, ON, Canada (Le Foll, Müller); and the Office of the Chief Coroner and Ontario Forensic Pathology Service, Toronto, ON, Canada (Jhirad, Wells).**

Background: Deliberate or accidental overdose of opioids is a severe health care problem. According to the Public Health Agency of Canada, more than 5000 Canadians lost their lives between April and December 2020 as a result of opioid-related overdose; 96% of those deaths were accidental. We hypothesize that genetic factors involved in metabolism and drug action play an important role in opioid-related deaths. **Methods:** We will identify cases of interest (unintentional opioid-overdose deaths) and obtain blood samples of the deceased through the Office of the Chief Coroner of Ontario and Ontario Forensic Pathology Service (OCC/OFPS). For this pilot study, we aim to collect data on 200 people and will investigate genetic variants for association with opioid-related deaths. We aim to conduct genotyping of marker

genes related to opioid pharmacokinetics (*CYP2D6*, *CYP2B6*, *CYP3A4*, *CYP2C19*, *UGT2B7*, *ABCB1*) and marker genes related to opioid pharmacodynamics (*OPRM1*, *COMT*, *DRD*). Finally, we will create a polygenic risk score in an attempt to identify patients at greater risk for opioid overdose. **Results:** We have obtained 41 blood samples from methadone-only fatalities from the OCC/OFPS. We have genotyped 25 samples for the *CYP2B6**4, *9 variants and 41 samples for the *OPRM1* A118G variant. Our preliminary analysis shows a minor allele frequency of 30% for both the *CYP2B6**4 and *9 alleles, and 5% for the *OPRM1* 118G allele. Notably, we detected differences in the distribution of *CYP2B6**9 between males and females in our sample ($p = 0.009$, $\chi^2 = 9.455$). **Conclusion:** We have found an underrepresentation of slow metabolizers of *CYP2B6* and a 3-fold underrepresentation of the 118G allele carriers of *OPRM1* in our methadone-overdose cases compared with the general population. Recruitment and data analyses are ongoing.

Scalp-to-cortex distance in rTMS treatment responders versus nonresponders in youth with major depressive disorder. ***Sneha Chenji, Rose Swansburg, Frank P. MacMaster*****. From the Department of Psychiatry, University of Calgary, Calgary, AB, Canada (Chenji, Swansburg, MacMaster); and the Department of Pediatrics, University of Calgary, Calgary, AB, Canada (MacMaster).**

Background: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that enables the modulation of brain activity using magnetic pulses. The distance between the scalp and the brain surface affects the strength of the rTMS signal (treatment dose). Previously we found that youth with major depressive disorder (MDD) had significantly greater scalp-to-cortex distance in the left dorsolateral prefrontal cortex (DLPFC) than healthy controls. In this study, we aimed to investigate if scalp-to-cortex distance influences rTMS treatment response in youth with MDD. **Methods:** Thirty-two youth with MDD (age 13–22 yr; 17 males) were included from our recent rTMS clinical trial (NCT01731678). Treatment response was defined as greater than 50% reduction in Hamilton Depression Rating Scale (Ham-D) scores. Scalp-to-cortex distance for the left DLPFC and dominant primary motor cortex were obtained using FreeSurfer (v5.3) and AFNI. Significance was set at $p < 0.05$. **Results:** There were no significant differences in scalp-to-cortex distance of treatment responders ($n = 18$) compared with nonresponders ($n = 14$) in the DLPFC ($F_{1,18} = 0.282$, $p = 0.602$) or the primary motor cortex ($F_{1,18} = 0.462$, $p = 0.505$). However, higher scalp-to-cortex distance in the DLPFC (site of rTMS stimulation) was associated with lower treatment response as indicated by HAM-D percent change in treatment responders ($r = –0.565$, $p = 0.044$), but not in nonresponders ($r = –0.363$, $p = 0.336$). There were no significant associations between scalp-to-cortex distance and treatment dose in responders or nonresponders. **Conclusion:** Responders to rTMS treatment, with greater reduction in depression severity (as captured by percent change in HAM-D scores) showed associations with lower scalp-to-cortex distance in the left DLPFC.

The Effect of rTMS treatment on cortico–striatal–thalamo–cortical (CSTC) circuit connectivity in Tourette syndrome: a pilot study. ***Sneha Chenji, Cynthia Kahl, Rose Swansburg, Kayla D. Stone, Frank P. MacMaster*****. From the Department of Psychiatry, University of Calgary, Calgary, AB, Canada (Chenji, Kahl, Swansburg, Stone, MacMaster; and the Department of Pediatrics, University of Calgary, Calgary, AB, Canada (MacMaster).**

Background: Dysfunction in the cortico–striatal–thalamic–cortical (CSTC) circuit has been associated with Tourette syndrome (TS). Previously, we found a 60% reduction in tic severity when low-frequency repetitive transcranial magnetic stimulation (rTMS) was applied to an overactive region in the CSTC circuit called the supplementary motor area (SMA). In this study, we aimed to investigate the effects of rTMS on functional connectivity within the CSTC circuit. We hypothesized that there would be greater connectivity between the SMA and bilateral motor cortices following rTMS treatment. We also expected lower connectivity between motor cortices and the striatum following treatment. **Methods:** Ten children with TS (age 9–15 yr; 8 males, 2 females) participated in an open-label phase-I clinical trial (NCT02356003). Low-frequency (1 Hz) rTMS using a neuronavigated robot was applied to bilateral SMA over 15 sessions (100% resting motor threshold, 1800 pulses). Functional magnetic resonance imaging (fMRI) during a bilateral finger tapping task was obtained at baseline and following rTMS treatment (echo time 30 ms, repetition time 2 s, slice thickness 3.6 mm, no slice gap, interleaved acquisition). Regions of interest included bilateral SMA, primary motor cortices, striatum, basal ganglia, thalamus and cerebellum. Images were preprocessed using SPM and analyzed in CONN toolbox. **Results:** At baseline, higher connectivity was noted between the subcortical and the cortical regions (SMA and motor cortices; $p < 0.05$, uncorrected). Following rTMS treatment, we found no connectivity between the subcortical and cortical regions. Additionally, we did not find significant connectivity between the SMA and motor cortices after treatment. Instead, higher connectivity was noted between bilateral cerebellum (crus I), bilateral motor cortices and the right SMA ($p < 0.05$, corrected for false discovery rate). **Conclusion:** Low-frequency rTMS to the SMA alters functional connectivity within the CSTC circuit. Moreover, the cerebellum appears to show connectivity with motor cortex and the SMA after rTMS treatment in children with TS.

Nicotine self-administration behaviour under continuous versus intermittent access conditions in rats. ***Hajer E. Algallal, Anne-Noël Samaha*****. From the Department of Biomedical Sciences, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada (Algallal); the Department of Pharmacology and Physiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada (Samaha); and le Groupe de recherche sur le système nerveux central, Université de Montréal, Montréal, QC, Canada (Samaha).**

Background: Tobacco smoking is the main cause of preventable disease in Western Europe and North America. Nicotine is the principal psychoactive agent in tobacco, underlying its addictive properties. Most preclinical studies on the effects of voluntary nicotine use have used self-administration procedures that provide continuous nicotine access during each self-administration session (long-access or LgA). However, many smokers consume cigarettes intermittently, rather than continuously throughout each day. **Methods:** Here we gave female and male rats continuous (LgA, 6 h/d) or intermittent access (IntA; 12 min on, 60 min off, for 6 h/d) to intravenous nicotine (15 μg/kg/infusion) for 12 daily sessions. We then compared the groups on intake, responding for nicotine under a progressive ratio schedule of reinforcement, and cue- and nicotine-induced reinstatement of nicotine-seeking behaviour after abstinence (measures of relapse). **Results:** Nicotine self-administration behaviour was similar across the sexes and so they were pooled for analysis. LgA rats took more nicotine than IntA rats. However, the 2 groups later showed similar responding for nicotine under progressive ratio and similar cue- and nicotine-induced reinstatement. **Conclusion:** Intermittent nicotine use is just as effective as continuous use in producing addiction-relevant behaviours, despite significantly less nicotine exposure.

Acute stress causes rapid alteration in cortical functional connectivity. ***Donovan M. Ashby, Alexander McGirr*****. From the Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada (Ashby); the Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada (McGirr); and the Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, AB, Canada (McGirr).**

Background: Alterations in functional connectivity are an emerging indicator for depression and related disorders. Acute stressors are commonly used in rodents to examine how the stress response produces neurobiological changes that may be related to anxiety and depression, however it is not known whether acute stress produces functional connectivity changes across brain networks in rodents. **Methods:** Calcium activity dynamics across the entire dorsal cortical surface were repeatedly recorded through an imaging window affixed to the exposed skull of awake, headfixed mice (n = 25) expressing a calcium biosensor in neurons (Thy1-jRGECO1a). After a 1-week habituation to head fixation, mice were exposed to a 1-hour footshock stress (100x3sx0.4mA shocks) or homecage control. Cortical activity was recorded before stress and at multiple time points after stress. Correlations in calcium activity in selected ROIs were measured in the slow (0.3–4 Hz) and theta/α (4–12 Hz) power bands and compared using a general linear model (GLM). **Results:** Baseline cortical activity showed reliable network structure, with several discrete modules identifiable by higher correlated activity. After stress, functional connectivity was altered at multiple time points with significantly elevated connectivity between modules, while within-module connectivity was comparatively unaltered. Changes in functional connectivity normalized 24 hours after acute stress. **Conclusion:** A single acute stressor in mice produces widespread functional connectivity similar to the alterations observed with chronic stress in animal models as well as clinical depression. Results are discussed with reference to the biological mechanisms of the stress response that may mediate this transient alteration in functional connectivity.

Blood–brain barrier alterations and vascular biomarkers underlie chronic stress responses in female mice mirrored in human depression. ***Laurence Dion-Albert, Alice Cadoret, Ellen Doney, Fernanda Neutzling Kaufmann, Katarzyna A. Dudek, Beatrice Daigle, Lyonna F. Parise, Flurin Cathomas, Nalia Samba, Natalie Hudson, Manon Lebel, Signature Consortium, Matthew Campbell, Gustavo Turecki, Naguib Mechawar, Caroline Menard*****. From the Department of Psychiatry and Neuroscience, Université Laval and CERVO Brain Research Center, Québec, QC, Canada (Dion-Albert, Cadoret, Doney, Kaufmann, Dudek, Daigle, Lebel, Menard); the Fishberg Department of Neuroscience and the Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Parise, Cathomas); Sorbonne Université, Paris, France (Samba); the Smurfit Institute of Genetics, Trinity College Dublin, Lincoln Place Gate, Dublin, Ireland (Hudson, Campbell); the Institut universitaire en santé mentale de Montréal, Centre intégré universitaire de santé et service sociaux de l'Est-de-l'Île-de-Montréal, Montréal, QC, Canada (Signature Consortium); and the Department of Psychiatry, McGill University and Douglas Mental Health University Institute, Montréal, QC, Canada (Turecki, Mechawar).**

Background: Major depressive disorder (MDD) will affect 20% of individuals and is now considered the leading cause of disabilities worldwide. Prevalence and symptoms of depression all point toward major sex differences. Most studies explored biological mechanisms underlying MDD exclusively in males, which may explain the high rate of relapse and treatment resistance. We reported that chronic social stress induces blood–brain barrier (BBB) leakiness through loss of tight junction protein Claudin-5 (Cldn5) in the nucleus accumbens (NAcc), a mood regulation centre, of male mice, leading to passage of circulating inflammatory mediators into the brain and establishment of depression-like behaviours. We investigated if stress-induced loss of BBB integrity is occurring in a sex- and region-specific manner, which could explain differences in MDD symptomatology. **Methods:** In rodents, repeated exposure to chronic social defeat stress (CSDS) through physical encounter with a larger aggressive mouse induces a depression-like phenotype characterized by anhedonia and social avoidance. We combined behavioural, molecular, morphological, and functional studies and discovered sex-specific BBB alterations induced by chronic stress exposure. **Results:** After 10-day exposure to CSDS, Cldn5 gene and protein expression is unchanged in the NAcc of stress-susceptible females but decreased in the prefrontal cortex (PFC), a brain region regulating decision making and social behaviours, when compared with

unstressed controls. Importantly, this sexual dimorphism of stress-induced neurovascular adaptations was confirmed in postmortem human brain samples from individuals with depression, adding translational value to our findings. Viral-mediated functional manipulation of Cldn5 loss in the female PFC confirmed the causal link of BBB disruption in the establishment of depressive behaviours and possibly sex-specific MDD symptomatology. **Conclusion:** By characterizing sex- and region-specific neurovascular alterations underlying stress susceptibility in mice and human depression we provide valuable clues and highlight the need to consider sex as a biological variable while defining the role of brain barriers in psychiatric diseases.

Improvement in anxiety and depressive symptoms in older adult users of medical cannabis: a retrospective observational study using validated assessment scales. *Shankar Tumati, Andrew Davis, Krushnaa Sankhe, Krista L. Lanctôt, Nathan Herrmann*. **From the Neuropsychopharmacology Research Group, Sunnybrook Research Institute, Toronto, ON, Canada (Tumati, Sankhe, Lanctôt, Herrmann); the Department of Economics, Acadia University, Wolfville, NS, Canada (Davis); the Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada (Lanctôt); and the Department of Psychiatry, University of Toronto, Toronto, ON, Canada (Lanctôt).**

Background: A substantial number of older adults (≥ 65 yr) seek medical cannabis (MC) for anxiety and depressive symptoms. However, the effectiveness of MC for these symptoms in older adults is not clear. The objective of this retrospective observational database study was to assess self-reported changes in anxiety and depressive symptoms using validated assessment scales in older adults. **Methods:** From October 2014 to April 2021, a Canadian MC clinic collected anonymized data on patient characteristics and indications for MC at intake. The current study included patients who reported primarily seeking therapy for anxiety symptoms (assessed with the Generalized Anxiety Disorder Scale 7-item [GAD-7]) or depressive symptoms (assessed with the Patient Health Questionnaire 9-item scale [PHQ-9]). At follow-up, in addition to the GAD-7 or PHQ-9, self-perceived changes in mood were also assessed. Change in symptom scores were assessed with a paired *t* test. **Results:** The study included 867 older adults (mean age 71.5 ± 5.9 yr, 58.5% female) out of 9103 patients of all ages. Among older adults, the primary reason for seeking therapy was anxiety symptoms in 229 patients (26.4%, mean age 71.5 ± 6.3 yr, 64.2% female) and depressive symptoms in 123 patients (14.2%, mean age 70.7 ± 5.7 yr, 48.8% female). At the follow-up visit, GAD-7 scores declined from 10.8 ± 5.2 to 8.5 ± 5.4 (n = 54, mean age 74.7 ± 7.5 yr, 57.4% female, mean follow-up 92.2 ± 60.4 d; t = –3.85, p < 0.001), and PHQ-9 scores declined from 14.1 ± 5.7 to 9.4 ± 5.8 (n = 38, mean age 73 ± 5.8 yr, 44.7% female, mean follow-up 105.6 ± 85.8 d; t = –5.58, p < 0.001). Patients with and without follow-up did not differ on intake scores of GAD-7 and PHQ-9. Improved mood was indicated by 72.5% (n = 51) and 47.2% (n = 36) of patients with anxiety and depressive symptoms, respectively. **Conclusion:** This preliminary evidence from a convenience sample indicates that MC may improve anxiety and depressive symptoms in older adults and supports the need for well-designed randomized controlled trials.

Clinical efficacy of rTMS treatment and functional connectivity in youth with major depressive disorder. *Clara Tapia, Sneha Chenji, Kayla Stone, Rose Swansburg, Kristina Kim Lyngberg, Helen Carlson, Signe Lauren Bray, Daniel Kopala-Sibley, Katherine Rittenbach, Frank P. MacMaster*. **From the Department of Psychiatry, University of Calgary, Calgary, AB, Canada (Tapia, Chenji, Stone, Swansburg, Lyngberg, Kopala-Sibley, Rittenbach, MacMaster); the Department of Clinical Neuroscience, University of Calgary, Calgary, AB, Canada (Carlson); the Department of Radiology, University of Calgary, Calgary, AB, Canada (Bray); and the Department of Pediatrics, University of Calgary, Calgary, AB, Canada (MacMaster).**

Background: Accurate targeting of repetitive transcranial magnetic stimulation (rTMS) for major depression is a pressing question in the field. Studies have shown that negative functional connectivity between the dorsolateral prefrontal cortex (DLPFC; target site) and the subgenual cingulate is associated with greater clinical efficacy in adults, but this has not been explored in youth with major depressive disorder (MDD). **Methods:** Twenty-six youth with MDD (age 13–22 yr, 13 males) completed 10-Hz rTMS treatment (NCT01731678) and had good-quality resting-state functional magnetic resonance imaging (fMRI) scans at baseline. We used FSL and FEAT to preprocess fMRI scans and extract functional connectivity between the target site (DLPFC) and the subgenual cingulate. Treatment response was determined at > 50% reduction in Hamilton Depression Rating Scale (HAM-D) scores and correlated with functional connectivity. **Results:** There were no significant differences in functional connectivity between responders (n = 15) and nonresponders (n = 11) (t_{14} = –1.53, p = 0.147). Clinical efficacy, as determined by higher percent reduction in HAM-D, showed a weak association with positive DLPFC–subgenual connectivity (r = 0.39, p = 0.051). **Conclusion:** Our findings suggest that positive (not negative) functional connectivity between the DLPFC and subgenual cingulate is associated with clinical efficacy in youth with MDD. It is possible that youth with MDD differ in their connectivity pattern compared with adults. Connectivity-based rTMS targeting in youth with MDD needs to be explored further.

Corticolimbic DCC co-expression networks are linked to behavioural endophenotypes of psychiatric risk. *Jose Maria Restrepo, Irina Pokhvisneva, Zihan Wang, Sachin Patel, Michael J. Meaney, Patricia P. Silveira, and Cecilia Flores*. **From the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Restrepo); the Douglas Mental Health University Institute, Montréal, QC, Canada (Restrepo, Pokhvisneva, Wang, Patel, Meaney, Silveira, Flores); the Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute,**

McGill University, Montréal, QC, Canada (Pokhvisneva, Wang, Patel, Meaney, Silveira); the Department of Neurology and Neurosurgery, McGill University, Douglas Mental Health University Institute, Montréal, QC, Canada (Meaney, Flores); the Department of Psychiatry, McGill University, Montréal, QC, Canada (Meaney, Silveira); and the Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Brenner Centre for Molecular Medicine, Singapore (Meaney).

Background: Deficits in the cognitive capacity to control and override impulsive behaviours are prevalent in numerous neuropsychiatric conditions. Altered connectivity and communication between brain corticolimbic regions are essential for behaviours requiring inhibitory control, but the underlying neurobiological processes, as well as early markers of vulnerability, are yet to be discovered. Interestingly, genetic variability within the Netrin-1/DCC signalling pathway is tightly associated with a wide range of psychiatric disorders characterized by abnormal corticolimbic connectivity and deficits in inhibitory control. **Methods:** Owing to the prominent role of the Netrin-1/DCC signalling pathway in corticolimbic development, we generated an expression-based polygenic score (ePRS) consisting of single nucleotide polymorphisms (SNPs) within genes co-expressed with the axon guidance cue receptor, DCC, in 2 key regions of the corticolimbic circuitry, the prefrontal cortex (PFC) and nucleus accumbens (NAcc). We investigated the association of the ePRS with impulsivity-related phenotypes in 3 ethnically diverse community samples of children as well as the functional/biological properties of the co-expression networks that comprise the ePRS. **Results:** Lower ePRS scores were associated with higher measurements of impulsive choice in 6-year-old children tested in the information sampling task (n = 197) and impulsive action in 6- and 10-year-old children tested in the Stop Signal Reaction Time Task (n = 398 and n = 4392, respectively). The gene networks that comprise the ePRS show a prominent role in core neurodevelopmental processes and are enriched in brain areas that show protracted maturation. Interestingly, 60.3% of the genes in the co-expression networks are loss-of-function intolerant genes. **Conclusion:** Our results show that an ePRS based on corticolimbic DCC co-expression networks can serve as a novel type of marker for impulsivity-related phenotypes in children. The numerous genes within the co-expression networks that are loss-of-function intolerant (characteristic of genes that confer risk to psychiatric disorders) suggests the potential use of the ePRS to predict genetic susceptibility to endophenotypes linked to developmental psychiatric conditions.

Cell-type specific open chromatin signatures in the brains of individuals diagnosed with major depressive disorder and died by suicide. ***Anjali Chawla, Corina Nagy, Matthew Suderman, Malosree Maitra, M.A. Davoli, Jenny Yang, Gustavo Turecki*****. From the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Chawla); the McGill Group for Suicide Studies, Douglas Mental Health University Institute, Montréal, QC, Canada (Chawla, Nagy, Maitra, Davoli, Yang, Turecki); the Department of Psychiatry, McGill University, Montréal, QC, Canada (Nagy, Turecki); the MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK (Suderman); and the Genome Quebec Innovation Centre, Department of Human Genetics, McGill University, Montréal, QC, Canada (Turecki).**

Background: For psychiatric diseases, including major depressive disorder (MDD), the genetic variants identified by genome-wide association studies (GWAS) tend to be enriched in the noncoding regions of the genome with cell-type specificity. To identify active gene regulators and cell-type-specific heritability enrichments for MDD-associated single nucleotide polymorphisms (SNPs), we performed single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq) in the postmortem human brains of individuals who, during an episode of major depression, had died by suicide. **Methods:** We profiled the dorsolateral prefrontal cortex of 44 cases and 44 sex- and age-matched psychiatrically healthy controls. To mitigate batch effects of capture and sex, we developed a machine-learning approach that uses sex-specific chromatin features and 1000 genome common variants for in silico splitting of the multiplexed libraries. Cell types were annotated using the accessibility of promoters and enhancers of cell-type marker genes. Further, the snATAC-seq data were integrated with snRNA-seq data produced from the same individuals to identify active regulators of gene expression changes associated with depression. **Results:** We captured hundreds of thousands of nuclei from the prefrontal cortex resulting in the largest snATAC-seq data set in the brain to date. We elucidated brain cell-type-specific proximal and distal gene regulators. Our preliminary analysis resulted in differentially accessible chromatin sites in cortical cell types of MDD cases and controls. In the excitatory neurons, differentially closed chromatin sites in MDD cases enriched for biological pathways, including cognition, social behaviour, and synaptic transmission, while differentially open chromatin of MDD cases enriched for pathways known to regulate antidepressant response. Further, we uncovered novel transcription factor binding motifs that were differentially accessible in the cell types of MDD cases. **Conclusion:** Generating cell-type-specific open chromatin landscapes pinpointed promoters and enhancers that regulate differential gene expression in depression. In overlapping MDD-associated GWAS SNPs with differentially accessible chromatin, we found disease- and sex-specific heritability enrichments in certain cortical cell types.

Sex differences in the metabolic outcomes of high-fat diet in perinatal cannabis-exposed mice. ***Nada A. Sallam, Colleen S. Peterson, Stephanie L. Borgland*****. From the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt (Sallam); and the Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada (Sallam, Peterson, Borgland).**

Background: With the increased legalization of cannabis use, the prevalence of past-month cannabis consumption by pregnant women almost doubled between 2002 and 2017 in the United States, particularly during the first trimester. Studies on the long-term outcomes of perinatal cannabis exposure (PCE) are limited. Although cannabis ingestion triggers short-term hyperphagia, the incidences of obesity and metabolic dysfunction are lower in frequent cannabis users. It is unknown whether PCE will influence the outcomes of high-fat diet (HFD) consumption in adult offspring. **Methods:** Pregnant female mice voluntarily consumed edible cannabis extract, equivalent to THC (5 mg/kg/d) or vehicle (coconut oil) from gestational day 1.5 until postnatal day (PD) 10. At least 6 litters, culled to a maximum of 6 mice/litter, from each pregnancy group were examined. Dams' body weight, food intake and maternal behaviour were monitored until weaning. Body weight and locomotor activity of the pups were recorded at 4 and 2 time points, respectively. Starting at 7 weeks old, offspring received HFD or control diet for 12 weeks. Body weight, adiposity, plasma hormones, glucose tolerance and insulin sensitivity were examined in male and female offspring. **Results:** While PCE did not alter the dams' weight gain, food intake, pregnancy duration, or litter size, it reduced the pups' body weight at PD6 and PD11, but not at later ages, and decreased their general locomotor activity at PD10. In adult offspring, PCE induced insulin resistance independent of weight gain in female but not male offspring on control diet in parallel with higher plasma glucagon. However, PCE protected against HFD-induced elevations in blood glucose, insulin, c-peptide, leptin, resistin, and amylin and reduced fat deposition in the inguinal area in female offspring. **Conclusion:** PCE negatively affects insulin sensitivity of adult offspring on a control diet but partially protects against HFD-associated metabolic dysfunction in a sex-specific manner.

Role of dopamine D2 and D3 receptors in conditioned memory modulation. ***Thomas Lapointe, Francesco Leri*****. From the Department of Psychology, University of Guelph, Guelph, ON, Canada.**

Background: Exposure to conditioned stimuli (CS) predictive of foot shock enhances memory consolidation, a process of memory stabilization that is central to learning. There is evidence that dopamine D2 and D3 receptors modulate several responses to CS, including freezing and step-through passive avoidance. Therefore, this study explored whether these DA receptors are involved in the memory-enhancing action of a CS predictive of foot shock. **Methods:** Male Sprague Dawley rats trained on a signalled active avoidance task (8 d; 30 trials/d; 0.8 mA) were exposed to the avoidance CS immediately following the sample phase of the spontaneous object recognition (SOR) task. Different groups were pretreated with the β-noradrenergic receptor antagonist propranolol (0, 10, 20 mg/kg), DA D2 antagonist pimozide (0, 0.2, 0.6 mg/kg), or D3 antagonist NGB-2904 (0, 0.1, 5 mg/kg). All groups were tested for object memory 72 hours later, in drug-free conditions. **Results:** Immediate postsample exposure to the avoidance CS in the absence of shock enhanced object memory, and this effect was dose-dependently blocked by propranolol, thus confirming that this conditioned effect on object recognition is indeed facilitated by a modulation of consolidation. We then tested pimozide and NGB-2904, both of which dose-dependently blocked the effect of postsample CS exposure on object memory, while having no effect on avoidance behaviour. **Conclusion:** These results indicate an important role for DA D2 and D3 receptors in conditioned enhancement of memory consolidation.

Role of small nucleolar RNAs in antidepressant treatment. ***Rixing Lin, Aron Kos, Julien Dine, Laura Fiori, Yair Ben-Efraim, Juan Pablo Lopez, Jean-Francois Theroux, Zahai Aouabed, Pascal Ibrahim, Tak Pan Wong, El Cherif Ibrahim, CAN-BIND working group, Alon Chen, Gustavo Turecki*****. From the McGill Group for Suicide Studies, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montréal, QC, Canada (Lin, Fiori, Theroux, Aouabed, P. Ibrahim, Turecki); the Department of Stress Neurobiology and Neurogenetics, Max Planck Institute of Psychiatry, Munich, Germany (Kos, Lopez, Chen, Dine); the Max Planck Society–Weizmann Institute of Science Laboratory for Experimental Neuropsychiatry and Behavioural Neurogenetics, Rehovot, Israel and Munich, Germany (Ben-Efraim, Chen, Dine); the Aix-Marseille Université, CNRS, Institute Neuroscience Timone, Marseille, France (E.C. Ibrahim); and the Department of Psychiatry, McGill University, Montréal, QC, Canada (Wong).**

Background: Major depressive disorder (MDD) is a prevalent global disorder treated primarily by antidepressants; however, less than 50% of patients experience full remission even after multiple attempts. Thus, a better understanding of the underlining molecular mechanisms of antidepressant response is needed. Small nucleolar RNAs (snoRNAs) have been shown to be involved in a diverse range of gene regulatory mechanisms, making them an interesting category of RNA to investigate in the context of antidepressant response. **Methods:** We performed small RNA sequencing from peripheral blood samples collected from 3 independent clinical cohorts consisting of subjects with MDD treated with antidepressants for 8 weeks. We followed up by investigating candidate snoRNA expression in human and mice neuronal tissues as well as in vitro assays investigating mechanistic roles of our candidate snoRNAs. Lastly, we overexpressed our candidate snoRNAs in mice anterior cingulate cortex (ACC) and investigated behavioural outcomes. **Results:** From our clinical data, SNORD90 was found to be significantly upregulated in responders to antidepressants. It was also upregulated in neuronal tissue from human and mice exposed to antidepressants. In vitro overexpression and knock-down of SNORD90 indicated that it is downregulating NRG3 expression. Previous research has shown that NRG3 interferes with vesical docking in pyramidal neurons and that NRG3 knockout increases glutamatergic signalling in mice. We investigated if SNORD90-mediated knock-down

of NRG3 influences glutamatergic signalling. We overexpressed SNORD90 in mice ACC, via viral injection, and observed a downregulation of NRG3 and consequently increased glutamatergic signalling. Following the same aforementioned experimental approach, we also observed an overall decrease in anxiety and depressive-like behaviours in mice with overexpressed SNORD90 in the ACC. **Conclusion:** We found that SNORD90 is upregulated following antidepressant treatment. It downregulates NRG3 expression, which in turn increases glutamatergic signalling in the ACC and is associated with an anti-anxiety and antidepressive phenotype.

Extinction of conditioned memory modulation. ***Travis Francis, Francesco Leri*****. From the Department of Psychology, University of Guelph, Guelph, ON, Canada.**

Background: It has been established that exposure to drug conditioned stimuli (CS) can enhance memory consolidation, indicating that drug CS not only produce changes in behaviour, but can also impact cognition. Therefore, it is possible that conditioned memory modulation, like other conditioned responses, will display extinction. The current study used classical and operant conditioning techniques to test this hypothesis in male Sprague Dawley rats performing an object location (OL) memory task. **Methods:** To establish the CS in experiment 1, rats were injected with heroin (0, 0.3, 1 mg/kg, subcutaneously) and immediately placed in operant chambers for 1 hour, once a day for 5 consecutive days. We found that exposure to the heroin CS 4 days after conditioning dose-dependently enhanced OL memory. In addition, when tested after 6 exposures to the CS without receiving heroin, the ability of the CS to modulate memory was significantly reduced. In experiment 2, rats were trained to intravenously self-administer heroin (0.05 mg/kg/inf) on a continuous reinforcement schedule for 12 days. **Results:** We found that exposure to the heroin CS established through both operant and Pavlovian conditioning 4 days after training enhanced OL memory ($p < 0.05$), and when tested after 6 exposures to the CS without receiving heroin, the operant and Pavlovian ability of the CS to modulate memory was attenuated ($p > 0.05$). **Conclusion:** Taken together, these data indicate that conditioned memory modulation, similarly to other conditioned drug effects, displays both Pavlovian and instrumental extinction.

Adiposity in schizophrenia, illness and antipsychotics: a systematic review and meta-analysis. ***Sri Mahavir Agarwal, Emily Smith, Raghunath Singh, Jiwon Lee, Laura Colucci, Ariel Graff-Guerrero, Gary Remington, Margaret Hahn*****. From the Schizophrenia Division, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada (Agarwal, Smith, Singh, Lee, Colucci, Graff-Guerrero, Remington, Hahn); the Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada (Agarwal, Smith, Lee, Graff-Guerrero, Remington, Hahn); and the Department of Psychiatry, University of Toronto, Toronto, ON, Canada (Agarwal, Graff-Guerrero, Remington, Hahn).**

Background: Although a relationship between schizophrenia, antipsychotic medication, and metabolic dysregulation is now well established, the effect of adiposity is less well understood. By synthesizing findings from imaging techniques that measure adiposity, our systematic review and meta-analysis (PROSPERO CRD42020192977) aims to determine the adiposity-related effects of illness and treatment in this patient population. **Methods:** We searched MEDLINE, EMBASE, PsychINFO and Scopus for all relevant case–control and prospective longitudinal studies from inception until February 2021. Measures of adiposity, including percent body fat (%BF), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT), were analyzed as primary outcomes. **Results:** Our search identified 29 articles that used imaging methods to quantify adiposity among patients with schizophrenia-spectrum disorders. Analyses revealed that patients have greater %BF (mean difference [MD] 3.09%, 95% confidence interval [CI] 0.75–5.44), SAT (MD 24.29 cm^2, 95% CI 2.97–45.61) and VAT (MD 33.73 cm^2, 95% CI 4.19–63.27) compared with healthy controls. Antipsychotic treatment was found to increase SAT (MD 31.98 cm^2, 95% CI 11.33–52.64) and VAT (MD 16.30 cm^2, 95% CI 8.17–24.44) with no effect on %BF. However, change in %BF was higher for antipsychotic-free or antipsychotic-naïve patients compared with treated patients. **Conclusion:** Our findings indicate that patients with schizophrenia-spectrum disorders have greater adiposity than healthy controls, which is increased by antipsychotic treatment. Young, antipsychotic-naïve patients may be particularly susceptible to this effect. Future studies should explore the effect of specific antipsychotics on adiposity and its relation to overall metabolic health.

Prefrontal cortical circuit dysconnectivity following early developmental ventral hippocampal perturbations. ***Moushumi Nath, Sanjeev K. Bhardwaj, Tak Pan Wong, Lalit K. Srivastava*****. From the Basic Neuroscience Division, Douglas Research Centre, Montréal, QC, Canada (Nath, Bhardwaj, Wong, Srivastava); and the Department of Psychiatry, McGill University, Montréal, QC, Canada (Wong, Srivastava).**

Background: The ventral hippocampus (vHPC) projects to the prefrontal cortex (PFC) and contributes to PFC maturation in early development. This pathway becomes involved in cognitive functions. Abnormal development and dysfunction in this pathway, characterized by abnormal connectivity patterns, is implicated in schizophrenia pathology and cognitive deficits. Our objective was to elucidate developmental cellular mechanisms underlying abnormal vHPC–PFC connectivity. **Methods:** To investigate the effects of early vHPC perturbations on PFC maturation, we used transgenic mouse lines in which the vHPC was disconnected from the PFC through excitotoxic lesioning or cell-type specific viral ablations in adolescent mice. The effects on the PFC were assessed using electrophysiology in adult animals. Whole-cell recordings in PFC slices were conducted on pyramidal cells and visually identified fluorescent parvalbumin (PV)-expressing interneurons to characterize cellular functional

changes. **Results:** Early vHPC excitotoxic lesioning resulted in altered PFC pyramidal cell firing output, increased excitatory inputs and decreased inhibitory inputs onto pyramidal cells. This altered excitatory/inhibitory input balance was replicated when CaMKII-expressing vHPC cells were virally ablated, but not when PV-expressing vHPC cells were ablated, suggesting the ablation of excitatory vHPC projections mediate PFC deficits. In contrast, PFC PV interneurons show a reduced ability to sustain high-frequency firing, and a decrease in excitatory inputs onto PV cells. Moreover, PV PFC cells, but not pyramidal PFC cells, show reduced NMDA-receptor mediated current. **Conclusion:** These results showcase the differential effects of early vHPC perturbations on pyramidal and interneuron activity. Together, the altered firing activity patterns and imbalanced excitatory/inhibitory transmission of pyramidal cells and PV-interneurons could be substrates for altered PFC cognitive functions that characterize early vHPC perturbations.

The sex-specific role for long noncoding RNAs in depression: from genome-wide patterns to behavioural readout. ***Orna Issler, Yentl Y. van der Zee, Chunfeng Tan, Junshi Wang, Aarthi Ramakrishnan, Benoit Labonte, Carol A. Tamminga, Yan Dong, James W. Murrough, Li Shen, Eric J. Nestler*. From the Department of Neuroscience, Mount Sinai, New York, NY, USA (Issler, van Der Zee, Ramakrishnan, Labonte, Murrough, Shen, Nestler); the Department of Psychiatry, UT Southwestern, Dallas, TX, USA (Tan, Tamminga); and the Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA (Wang, Dong).**

Background: Depression is a common, chronic and debilitating disorder. Women are twice as likely to suffer from depression as men, yet the molecular mechanisms contributing to this sex difference remain poorly understood. Long non-coding RNAs (lncRNAs) are a class of regulatory transcripts, which represent a substantial portion of the human genome. We explored the sex-specific role of lncRNAs in depression. **Methods:** We bioinformatically analyzed a genome-wide profile of lncRNAs from postmortem depressed and control humans of both sexes. We identified specific target lncRNAs with potential sex-specific roles in depression. Using viral tools, we expressed these lncRNAs in the prefrontal cortex (PFC) of mice from both sexes followed by behavioural testing, slice electrophysiological recording, and RNA-sequencing analysis. **Results:** We found that lncRNAs are robustly regulated in a sex-specific manner in postmortem brain tissue from depressed subjects. Using genome-wide correlation analysis, we identified sex-specific lncRNAs linked to depression risk. One of these targets, LINC00473, is gene downregulated in the cortex of depressed females only. Expressing LINC00473 in mouse PFC induced stress resilience in females only, which mirrored the human sex-specific phenotype, and was accompanied by changes in synaptic function and gene expression. An additional key lncRNA we identified is upregulated in the depressed female brain, and we named it FEDORA (FEmale DepressiOn lncRnA). We found that expressing FEDORA promoted depression-like behaviours only in female mice, and these changes are linked to alteration in the gene expression, synaptic functions, and myelin sheath thickness. **Conclusion:** This work establishes that lncRNAs play key roles in depression and contribute to the sex differences of this disorder. These findings provide a fundamentally new view of molecular neuroadaptations that contribute to depression risk and may lead to the identification of novel targets for treatment and diagnosis.

Dorsal raphe nucleus dopaminergic neurons project to the orbitofrontal cortex. ***Duncan Noble, Aida Mohammadkhani, Min Qiao, Stephanie L. Borgland*. From the Department of Pharmacology and Physiology, University of Calgary, Calgary, AB, Canada.**

Background: The dorsal raphe nucleus (DRN) is heterogeneous nucleus in the midbrain pons that is an important source of neuromodulators. While the DRN provides the largest source of serotonergic neurons in the brain, it also expresses dopaminergic neurons. While serotonergic neurons of the DRN project widely throughout the brain, less is known about the afferent targets of DRN dopaminergic neurons. Given that DRN dopaminergic neurons are activated in response to natural rewards as well as aversive stimuli and can reflect the learning and expression of incentive salience, we hypothesized that these neurons may project to the orbitofrontal cortex (OFC), a region that is involved in the representation and regulation of reward value. **Methods:** We administered Lumafluor Green retrograde beads to the medial and lateral OFC of DATcre TdTomato mice and examined colocalization of retrobeads with TdTomato fluorescence in dopaminergic neurons of the OFC. We also administered AAV-hSyn-DIO-ChR2-eYFP to the DRN of DATcre TdTomato mice to target expression of channelrhodopsin to dopaminergic neurons and examined enhanced yellow fluorescent protein (eYFP) expression at terminals in the OFC. **Results:** We observed Lumifluor beads in both DRN dopaminergic and serotonergic neurons. There was no significant difference in the number of dopaminergic neurons labelled from the medial OFC compared with the lateral OFC. We observed eYFP-like fibres in the medial and lateral OFC. **Conclusion:** DRN dopamine neurons project to the medial and lateral OFC. Future studies will address if this projection releases detectable dopamine in the medial or lateral OFC and the behavioural function of the DRN dopaminergic projection to the OFC.

The functional and structural consequences of aberrant microglial activity in major depressive disorder. ***Jasmine D. Cakmak, Linshan Liu, Stefan E. Poirier, Betsy Schaefer, Raju Poolacherla, Amer M. Burhan, Priyadharshini Sabesan, Keith St. Lawrence, Jean Théberge, Justin W. Hicks, Elizabeth Finger, Lena Palaniyappan, Udunna C. Anazodo*. From the Department of Neuroscience, Western University, London, ON, Canada (Cakmak, Palaniyappan); the Department of Imaging, Lawson Health Research Institute, London, ON, Canada (Liu); the Department of Medical**

Biophysics, Western University, London, ON, Canada (Poirier, Sabesan, St. Lawrence, Théberge, Hicks, Anazodo); the London Health Sciences Centre, London, ON, Canada (Schaefer); the Department of Anesthesia and Perioperative Medicine, Western University, London, ON, Canada (Poolacherla); the Department of Psychiatry, Western University, London, ON, Canada (Burhan); and the Department of Clinical Neurological Sciences, Western University, London, ON, Canada (Finger).

Background: Major depressive disorder (MDD) is a highly debilitating mental illness that has been linked with increases in markers of both peripheral and central inflammation, as well as with changes in brain functional and structural connectivity, particularly between the insula and the subgenual anterior cingulate cortex (sgACC). Here, we directly relate inflammation and dysconnectivity in MDD by concurrently measuring microglial activity by [18F]N-2-(fluoroethoxyl) benzyl-N-(4phenoxypyridin-3-yl)acetamide ([18F]FEPPA) positron emission tomography (PET), the severity of MDD, and disrupted functional/structural connectivity among the insula/sgACC nodes. **Methods:** Twelve patients with MDD and 23 healthy controls completed a hybrid [18F]FEPPA PET/MRI acquisition, from which relative standardized uptake values of [18F]FEPPA activity and Pearson *r*-to-*z* scores representing functional connectivity were extracted from the insula and sgACC. Diffusion tensor imaging metrics were extracted from the cingulum bundle, a key white matter bundle relevant for the features of MDD. Regressions were performed to relate microglial activity with functional connectivity, structural connectivity, and Hamilton Depression Rating Scale (HAM-D) scores. **Results:** We found significantly increased [18F]FEPPA uptake in patients with treatment-resistant late-life depression compared with healthy controls in the left sgACC ($p = 0.012$). Patients had an overall reduction in connectivity between the sgACC and the insula ($p > 0.05$). The left sgACC [18F]FEPPA uptake significantly related to both functional connectivity with the insula ($p = 0.044$ whole sample; $p = 0.015$ patients; $p = 0.035$ controls) as well as the structural connectivity of the cingulum bundle ($p = 0.023$). Furthermore, [18F]FEPPA uptake predicted severity scores on HAM-D ($p = 0.039$ left insula; 0.037 right insula). **Conclusion:** We present evidence linking a network-level dysfunction relevant to the pathophysiology of depression to increased microglial activity in MDD. To our best knowledge, this is the first study to jointly assess the associations in MDD.

Sex differences and therapeutic effects of miR-218 during prefrontal cortex development. ***Alice Morgunova, Michel Giroux, Giovanni Hernandez, Cecilia Flores*****. From the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Morgunova); the Douglas Mental Health University Institute, Montréal, QC, Canada (Giroux, Hernandez, Flores); the Department of Psychiatry, McGill University, Montréal, QC, Canada (Flores); and the Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada (Flores).**

Background: MicroRNA miR-218 is a potent expression regulator of genes known to control adolescent prefrontal cortex (PFC) development and is reduced in the PFC of adults with depression who died by suicide and in adult male mice susceptible to chronic stress-induced social avoidance. **Methods:** We assessed miR-218 in female mice over PFC development and the effect of administered intranasal spray of antisense oligonucleotides targeting miR-218 in adolescence on long-term behaviour. We measured miR-218 expression levels in PFC punches and circulating whole blood using quantitative reverse transcription polymerase chain reaction in female mice at postnatal days P21, P35 and P75. Antisense oligonucleotides solution (antagomiR-218 or a scrambled sequence) was administered via a single intranasal spray in adolescent mice. In adulthood, behavioural assays, including the elevated plus maze, were used to characterize motor and anxiety-like traits. **Results:** Developmental trajectory of miR-218 expression in the PFC in females was found to rapidly rise in early adolescence, reaching adult-like levels by mid adolescence ($F_{2,23} = 11.38$, $p = 0.0004$, one-way analysis of variance), which is in contrast to miR-218 expression in the male PFC, which increased gradually during early and mid adolescence until adulthood. Intranasal spray of antagomiR-218 in adolescence shows an anxiolytic-like effect observed on elevated arms maze in adulthood ($p = 0.033$, $n = 20$), consistent with effects observed following adolescent antagomiR-218 intra-PFC injections. **Conclusion:** These studies suggest that targeting miR-218 in adolescence has lasting effects on behaviour into adulthood, potentially having therapeutic application. However, effects may differ between males and females because of the sexually dimorphic trajectory of miR-218 in the PFC.

Actions of acute and persistent optogenetic stimulation of serotonin neurons in a post-stroke depression mouse model. ***Min Zhang, Faranak Vahid-Ansari, Paul R. Albert*****. From the Department of Neuroscience, University of Ottawa, Ottawa, ON, Canada (Zhang); and the Ottawa Hospital Research Institute, Ottawa, ON, Canada (Vahid-Ansari, Albert).**

Background: Selective serotonin reuptake inhibitors (SSRIs), which ameliorate depression by enhancing serotonin (5-HT) levels, are the first-line treatment for post-stroke depression (PSD). However, SSRIs are effective in only 50% of depressed patients, with a 2–3 week latency for antidepressant response, in part due to autoinhibition of 5-HT neurons. We tested whether direct optogenetic stimulation of 5-HT neurons would produce a more rapid antidepressant effect. **Methods:** Ischemic stroke was induced via a unilateral injection of endothelin-1 into the left medial prefrontal cortex. For optogenetic stimulation, an optic fibre was implanted at 20°, ending above the dorsal raphe nucleus in Pet-ChR2 transgenic mice expressing channelrhodopsin-2 (ChR2) in 5-HT cells, with ChR2-negative littermates as control. A battery of tests assessed anxiety- (3) and depression-like (2) behaviour. The effect of light intensity (1mW and 3mW at fibre tip) on 5-HT activation and behaviour was tested in separate cohorts. Immediate actions of 5-HT stimulation during testing

were monitored using sequential 3–5′ OFF-ON-OFF epochs of constant light stimulation. Chronic optogenetic stimulation was done in another cohort for 1 week of daily 5′ home-cage stimulation before behavioural testing. **Results:** Mild 1mW stimulation induced an immediate anxiolytic effect, and significant antidepressant effect in 1 of the 2 depression tests. Moderate 3mW stimulation produced an immediate and significant anxiogenic effect while strengthening the antidepressant response. Home-cage chronic stimulation at 3mW before behavioural testing produced a significant baseline antidepressant effect before acute stimulation and during testing. **Conclusion:** Our results suggest that acute optogenetic stimulation of the 5-HT system produces an antidepressant effect in a light-intensity-dependent manner. Repeated stimulation over 5 days was also shown to produce a sustained antidepressant effect in the PSD mice. Future studies will focus on the brain regions responsible for these changes through immunohistochemistry and further refine our targeting to minimize anxiogenesis and increase antidepressant behaviour.

Impact of prenatal exposure to THC on neonatal brain anatomy and behaviour in mice. ***Lani Cupo, Annie Phan, Elisa Guma, Daniel Gallino, Jérémie Fouquet, Gabriel A. Devenyi, M. Mallar Chakravarty*****. From the Computational Brain Anatomy Laboratory, Cerebral Imaging Centre, Douglas Mental Health University Institute, Montréal, QC, Canada (Cupo, Phan, Guma, Gallino, Devenyi, Chakravarty); the Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada (Cupo, Phan, Guma, Gallino, Chakravarty); and the Cerebral Imaging Centre, Douglas Mental Health University Institute, Montréal, QC, Canada (Fouquet).**

Background: Cannabis is used in more than 10% of pregnancies. Nevertheless, the impact of prenatal exposure to the psychoactive Δ-9-tetrahydrocannabinol (THC) on brain anatomy and behaviour in neonates is poorly characterized. To address this gap, we investigated how exposure to THC early in pregnancy affects brain anatomy and behaviour in mouse pups. Longitudinal in-vivo magnetic resonance imaging (MRI) was leveraged to noninvasively investigate the trajectories of brain development during the first week of life. To understand the impact of THC on behaviour, we measured ultrasonic vocalizations (USVs) pups emit when separated from their dam, lending insight into alterations in social and anxiety-like behaviours. **Methods:** Dams were injected with saline or 5 mg/kg THC daily from gestational day 3 to 10. On postnatal days (PND) 3, 5, 7, and 10, structural MRI scans were acquired from 2 male and 2 female pups per litter. On PND 12, ultrasonic vocalizations were acquired from pups separated from dams and littermates. Longitudinal deformation-based morphometry assessed altered trajectories of volumetric development in pups. Differences between groups were assessed using linear mixed effects models examining fixed effects for the interaction between age and condition and random effects for subject and litter. We assessed USVs with a shift-function examining group differences at deciles of call length. Multiple comparisons were corrected with the false discovery rate. **Results:** Preliminary results from 8 saline (all male) and 8 THC (4 males, 4 females) pups suggest that relative to the control condition, THC-exposed pups exhibit altered developmental trajectories in the prefrontal cortex, hippocampus, and cerebellum, with initial overgrowth (PND 3–7), followed by volume reduction thereafter. Additionally, THC pups make more calls longer than 50 ms, suggestive of anxiety-like behaviour. **Conclusion:** The full sample is required to clarify sex differences and substantiate preliminary results.

Morphine as an interoceptive negative feature discriminative stimulus alters morphine reward in female rats. ***Caitlin J. Nolan, Davin R. Peart, Adiia P.S. Stone, Julia S. Keating, Audrey E. Barta, Allyson K. Andrade, Jude A. Frie, Jennifer E. Murray*****. From the Department of Psychology, University of Guelph, Guelph, ON, Canada (Nolan, Barta, Andrade, Murray); the Collaborative Neurosciences Graduate Program, University of Guelph, Guelph, ON, Canada (Nolan, Andrade, Frie, Murray); the Department of Molecular and Cellular Biology, University of Guelph, Guelph, ON, Canada (Peart, Stone, Keating); and the Department of Biomedical Sciences, University of Guelph, Guelph, ON, Canada (Frie).**

Background: Interoceptive stimuli elicited by drugs form associations with exteroceptive cues. Feature positive (FP) and feature negative (FN) occasion setters disambiguate associations between exteroceptive conditioned stimuli (CSs) and appetitive unconditioned stimuli (USs). Here, we investigate how a history of morphine affects later morphine reward. **Methods:** Male and female rats were assigned to FP, FN, or saline-control training groups and received daily intermixed morphine or saline injections before each training session. On morphine sessions, FP rats received white noise CS presentations that were followed by access to sucrose US, but sucrose was withheld on saline sessions. The FN rats learned the reverse contingency. Saline-controls received only saline injections and intermixed sucrose/no-sucrose sessions. Rats then underwent place conditioning. Morphine was paired with a distinctive context of a 2-sided chamber; saline was paired with the other context. When rats were tested for place preference, they had access to both sides of the chamber but did not receive injections of saline or morphine. **Results:** Training with morphine as an occasion setter resolved the ambiguity of reward-predictive exteroceptive cues. In male rats, regardless of learning history, rats spent more time on the morphine-paired side of the chamber. In female rats, however, a history of FN learning inhibited the rewarding properties of morphine relative to FP learning. **Conclusion:** These data indicate that a history of learning sex-dependently affects the rewarding value of morphine. The rewarding properties of morphine can be inhibited by the formation of a negative association between the stimulus effects of morphine and the availability of an appetitive US following the presentation of a CS, with female rats more sensitive to this inhibition than males. Attenuation of morphine reward by inhibitory training may be relevant to the treatment of opioid use disorder in women.

Verbal memory in patients with first-episode psychosis: effects of dosage and anticholinergic burden of antipsychotics. ***Agnès Belkacem, Katie M. Lavigne, Caroline Makowski, M. Mallar Chakravarty, Ridha Joober, Ashok Malla, Jai Shah, Martin Lepage*. From the Douglas Research Centre, McGill University, Montréal, QC, Canada (Belkacem, Lavigne, Chakravarty, Joober, Malla, Shah, Lepage); the Montréal Neurological Institute-Hospital, McGill University, Montréal, QC, Canada (Lavigne); and the Department of Radiology, University of California San Diego, La Jolla, California, USA (Makowski).**

Background: Antipsychotics are commonly used to reduce symptoms of psychosis. However, they are not as effective in treating cognitive deficits and negative symptoms as they are in treating positive symptoms. In fact, verbal memory deficits are common in patients with first-episode psychosis (FEP) and have a significant impact on functional outcomes. Recent findings suggest that high doses and high anticholinergic burden of antipsychotics may actually contribute to verbal memory deficits in FEP. **Methods:** As part of a longitudinal study over a 1-year period with a large sample and 2 time points, this study aimed to examine changes over time in verbal memory performance in patients with FEP compared with controls and to determine whether poor performance in verbal memory is associated with high antipsychotic dosage and anticholinergic burden. We hypothesized that patients would show lower verbal memory performance over time compared with controls. We expected a negative association between antipsychotic dosage and verbal memory performance and that patients with the highest anticholinergic burden would have the poorest performance on verbal memory. **Results:** Patients with FEP followed by the PEPP-Montréal clinic (n = 328) and nonclinical controls (n = 128) completed a neurocognitive battery at 2 time points that included a detailed measure of verbal memory. Generalized estimating equations analysis revealed a significantly reduced verbal memory performance over time in patients with FEP compared with controls. A multiple linear regression revealed that dosage and anticholinergic burden were negatively associated with verbal memory performance in patients with FEP. An analysis of variance showed that the patients with a high anticholinergic burden had the poorest verbal memory performance. **Conclusion:** Despite the effectiveness of antipsychotics in relieving psychotic symptoms, it appears that over the long term and at high doses they may have a detrimental effect on cognitive performance. Greater clinical consideration of the anticholinergic burden of antipsychotics should be addressed in psychiatric patients.

Sex differences in dendritic morphology in the valproic acid (VPA) model of autism. ***Olivia O.F. Williams, Madeleine Coppolino, Cecilia B. Micelli, Melissa L. Perreault*. From the Department of Biomedical Sciences, University of Guelph, Guelph, ON, Canada.**

Background: Autism-spectrum disorders (ASD) are increasingly prevalent in North America. Robust sex differences are observed in prevalence, etiology and presentation for ASD, yet little research has elucidated the mechanisms underlying these sex differences. The protein glycogen synthase kinase-3β (GSK-3β), is downregulated in rats administered valproic acid (VPA) and implicated in disorders of cognitive impairment, and therefore may have importance in neuronal morphology. In this study, sex differences in neuronal morphology and the expression/activity of the GSK-3a/β isoforms were evaluated in rats administered VPA. **Methods:** Pregnant Sprague Dawley rats (Charles River, QC) were injected 500 mg/kg of VPA or saline (n = 2/group). Postnatal day 0–1 male and female pups were separated by sex, and cortex and hippocampal tissue was dissected. Cells were plated at a density of 1×10^6 cells/well Corning 6-well plates for Western blotting, and 2.5×10^5 cells/well Corning 24-well plates with a 12mm glass cover slip for immunocytochemistry (IHC). We performed IHC (MAP2 1:1000) for Scholl analysis and Western Blot analysis (GSK-3a/β 1:10,000, pGSK-3a/β and GAPDH 1:8000) on day in vitro (DIV) 21, 4 neurons were counted for each N, and replicates of 2 were done for Western blotting. **Results:** Preliminary data showed a decrease in the mean number of intersections for both male and female VPA-derived cortical cells, 30–100 radials away from the soma, compared with saline-derived cells (VPA: mean 3.77 ± 0.06; slaine: mean 9.92 ± 0.11; n = 16 cells/group). In the VPA-derived hippocampal neurons only, males showed a greater number of intersections 20–80 radials away from the soma (FVPA: mean 8.89 ± 0.20; MVPA: mean 13.36 ± 0.30; n = 8 cells/group). **Conclusion:** Phosphorylation of GSK-3a/β, reflective of a decrease in activity, in the cortex was increased for both male and female VPA-derived neurons and in VPA females only in the hippocampus. Total GSK-3a/β expression in males and females was decreased in VPA-derived cortical and hippocampal cells.

Cerebral blood flow and core mood symptoms in youth bipolar disorder: evidence for region-symptom specificity. ***Mikaela K. Dimick, Simina Toma, Bradley J. MacIntosh, Anahit Grigorian, Lisa Fiksenbaum, Eric A. Youngstrom, Andrew D. Robertson, Benjamin I. Goldstein*. From the Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada (Dimick, Grigorian, Fiksenbaum, Goldstein); the Department of Pharmacology, University of Toronto, Toronto, ON, Canada (Dimick, Goldstein); the Department of Psychiatry, University of Toronto, Toronto, ON, Canada (Toma, Goldstein); the Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (MacIntosh); the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (MacIntosh); the Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada (MacIntosh); the Physical Sciences Platform, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (MacIntosh); the Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA (Youngstrom); and the Schlegel-UW Research Institute for Aging, University of Waterloo, Waterloo, ON, Canada (Robertson).**

Background: Prior studies have identified mood-related differences in cerebral blood flow (CBF) among adults with bipolar disorder (BD). Here, we investigate regional CBF in relation to *DSM-5* Criterion A symptoms of depression and mania among youth with BD. **Methods:** We recruited 81 youth with BD and 75 healthy control (HC) youth aged 13–20 years. CBF was ascertained using pseudocontinuous arterial spin labelling (ASL) magnetic resonance imaging. Region of interest analyses examined the amygdala, anterior cingulate cortex (ACC) and middle frontal gyrus (MFG) as well as global grey matter CBF. The association of Criterion A depression and mania symptoms with CBF was examined dimensionally in regression analyses with continuous symptom severity scores. In addition, overall BD and HC group comparisons were conducted to give context for region of interest findings. Age and sex were included as covariates in all analyses. **Results:** In regression analyses, depressed mood inversely correlated with ACC ($\beta = -0.31$, $p_{uncorrected} = 0.004$, $p_{FDR} = 0.014$) and global CBF ($\beta = -0.27$, $p_{uncorrected} = 0.013$, $p_{FDR} = 0.046$). The same pattern and effect sizes were observed for anhedonia (ACC: $\beta = -0.33$, $p_{uncorrected} = 0.003$, $p_{FDR} = 0.014$; global: $\beta = -0.29$, $p_{uncorrected} = 0.008$, $p_{FDR} = 0.046$). Associations of depression-related irritability with lower global CBF in dimensional analyses ($\beta = -0.22$, $p_{uncorrected} = 0.04$, $p_{FDR} = 0.09$) were not significant after correction for multiple comparisons. There were no significant findings for manic symptoms. There were no significant differences in CBF between BD and HC groups after correction for multiple comparisons. **Conclusion:** Depressed mood and anhedonia are consistently associated with regional and global CBF, whereas this was not observed for depression-related irritability. Lack of findings regarding manic symptoms may reflect low between-participant differences in this outpatient sample. Longitudinal data are warranted to study mood symptoms and CBF over time.

Brain perfusion in schizophrenia-spectrum disorders: a systematic review and meta-analysis. ***Olivier Percie du Sert, Delphine Raucher-Chéné, Joshua Unrau, Claudine Gauthier, M. Mallar Chakravarty, Martin Lepage*****. From the Department of Psychiatry, McGill University, Montréal, QC, Canada (Percie du Sert, Unrau, Chakravarty, Lepage); the Cognition Santé Société Laboratory, University of Reims Champagne-Ardenne, Reims, France (Raucher-Chéné); and the Department of Physics, Concordia University, Montréal, QC, Canada (Gauthier).**

Background: Schizophrenia-spectrum disorders (SSD) can be studied across the continuum of psychosis from at-risk states to enduring nonaffective psychosis and represent one of the leading causes of disability worldwide. Studies of cerebral blood flow (CBF) have already provided important insights into the pathophysiology of these disorders. Recent developments in noninvasive MRI techniques such as arterial spin labelling (ASL) have allowed examination of CBF in broader clinical samples. Hence, we conducted a systematic review and meta-analysis of MRI-based perfusion studies exploring CBF across SSD. **Methods:** A systematic Ovid search was performed in Embase, MEDLINEOvid and PsycINFO. Studies eligible for inclusion involved individuals with ultra- or clinical-high risk for psychosis, first-episode psychosis or SSD; included healthy controls; involved MRI-based perfusion imaging methods; and reported CBF findings. No time span was specified for the database queries (last search: June 2021). Information related to participants, MRI techniques, CBF analyses and results were systematically extracted, reviewed and meta-analyzed. The methodological quality of each included study was assessed. **Results:** The initial Ovid search yielded 653 publications; 38 studies involving 1660 individuals were finally included in the systematic review. Eighteen studies reported significant results showing clusters of hypoperfusion mainly located in frontolimbic regions while hyperperfusion was found in subcortical structures when compared with healthy controls. The meta-analysis conducted on 17 studies involving 622 patients with SSD confirmed the robustness of the hypoperfusion in the left middle frontal gyrus and anterior cingulate. Interestingly, regional hypo- and hyperperfusions seem to be associated with negative and positive symptoms, respectively. **Conclusion:** In line with the dysconnectivity hypothesis of SSD, this updated review of the literature supports the implication of hemodynamic correlates in the pathophysiology of psychotic symptoms and disorders, including regional cortical hypoperfusions and subcortical hyperperfusion.

Sex differences in the conditioned enhancing effects of morphine as an occasion setter on morphine self-administration. ***Allyson K. Andrade, Adiia P. Stone, Briana Renda, Rita El Azali, Jessica M. Karlovcec, Jennifer E. Murray*****. From the Department of Psychology, University of Guelph, Guelph, ON, Canada (Andrade, Renda, El Azali, Murray); the Collaborative Neurosciences Graduate Program, University of Guelph, Guelph, ON, Canada (Andrade, Renda, Murray); and the Department of Molecular and Cellular Biology, University of Guelph, ON, Canada (Stone, Karlovcec).**

Background: The internally perceived (i.e., interoceptive) effects of opioids have been found to play a role in the development and maintenance of opioid use disorder, though that work has not been investigated from the perspective of potential sex differences. The present study investigated whether the nature of a learned experience involving the interoceptive cues elicited by morphine could differentially alter the motivational value of that morphine stimulus in male and female rats. **Methods:** Male and female Sprague Dawley rats were assigned to feature positive (FP), feature negative (FN), or pseudoconditioning (FX) groups and received daily intermixed morphine or saline injections 15 minutes before 20-minute sessions with 8 15-second white noise (WN) presentations. For FP-assigned rats, on morphine sessions, each WN was followed by 4-second access to sucrose; on saline sessions, WN was presented but sucrose was withheld. The FN-assigned rats learned the reverse contingency; sucrose followed WN on saline sessions. Rats assigned to FX-training learned that neither morphine nor saline was

indicative of any conditioned stimulus–unconditioned stimulus associability. After stable discrimination in FP and FN groups, rats were implanted with jugular catheters and learned to lever press for intravenous self-administration of morphine on a fixed ratio 1 schedule of reinforcement that increased to progressive ratio schedules of reinforcement. After 5 extinction sessions and 1 reinstatement session, a retention assessment with WN was conducted to determine whether rats maintained the Pavlovian discrimination. **Results:** The nature of the learned association with a morphine stimulus altered the value of the drug differently in male and female rats. The FN-assigned females administered more morphine than the FP. However, males in the FP group showed greater motivation for morphine than with FN-assigned males. **Conclusion:** Sex plays an essential role in how the interoceptive cues elicited by an opioid agonist (morphine) become associated with other stimuli to guide reward-seeking behaviours.

Establishing oral morphine self-administration in male and female rats. ***Allyson K. Andrade, M. Lupita Reyes, Adiia P. Stone, Ava Rae Noon, Jennifer E. Murray*****. From the Department of Psychology, University of Guelph, Guelph, ON, Canada (Andrade, Reyes, Murray); the Collaborative Neurosciences Graduate Program, University of Guelph, Guelph, ON, Canada (Andrade, Murray); and the Department of Molecular and Cellular Biology, University of Guelph, Guelph, ON, Canada (Stone, Noon).**

Background: The misuse of opioids has reached an epidemic level, and the rate of opioid and psychostimulant couse is steadily increasing. Preclinical literature regarding sex differences in opioid misuse is scarce, with most preclinical studies assessing only males. Further, even fewer studies have used oral morphine, despite it being the most common route of administration in the human population. The purpose of our study was to establish reliable oral morphine self-administration in a time-limited operant model, similar to that used for intravenous research. **Methods:** Male and female rats were initially trained in 1-hour sessions to lever press in operant chambers for 10-second oral access to 0.1 mL of 0.5 mg/mL morphine in 20% sucrose solution. To reduce the first-pass effect, the solution also contained 10% grapefruit juice. Following 10 sessions of stable intake, sucrose was faded to 10% for 5 sessions, then 5% for 5 sessions, and then they stabilized intake on 0% sucrose for 10 sessions. Grapefruit juice remained at the same concentration throughout. Dose and drug generalization procedures are currently underway wherein rats are being challenged with intraperitoneal pretreatment of varying doses of morphine, fentanyl, naloxone and methamphetamine to determine their effect on oral morphine self-administration. **Results:** Male and female rats readily self-administered the morphine, and though shifts in sucrose concentration were noticed by temporary dips in intake, rats quickly recovered and continued intake. We anticipate systemic administration of opioid agonists at high doses will reduce motivation to self-administer oral morphine in both sexes; however, this is not expected at low and moderate doses. Conversely, we expect that administration of opioid antagonist and psychostimulants will increase self-administration, and this effect will be more pronounced in females than males. **Conclusion:** We have established stable oral intake of morphine in a brief operant access task using a sucrose fading procedure.

Transcriptome profiling of the brain's reward circuitry in heroin self-administration identifies a ventral hippocampus gene network related to relapse susceptibility. ***Caleb J. Browne, Rita Futamura, Aarthi Ramakrishnan, Xianxiao Zhou, Angélica Minier-Toribio, Freddyson Martínez-Rivera, Molly Estill, Arthur Godino, Angélica Torres-Berrío, Eric M. Parise, Ashley M. Cunningham, Peter J. Hamilton, Deena M. Walker, Bin Zhang, Yasmin L. Hurd, Li Shen, Eric J. Nestler*****. From the Nash Family Department of Neuroscience and Friedman Brain Institute (Browne, Futamura, Ramakrishnan, Minier-Toribio, Martínez-Rivera, Estill, Gordino, Torres-Berrío, Parise, Cunningham, Hamilton, Walker, Shen); the Department of Genetics and Genomic Sciences and the Icahn Institute for Data Science and Genomic Technology, New York, NY, USA (Zhou, Zhang); and the Department of Psychiatry, and the Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Hurd, Nesstler).**

Background: Opioid addiction exacts a devastating toll on individuals, their families, and the health care system. Treatment is made exceptionally difficult by prolonged susceptibility for relapse into compulsive drug-seeking and taking, often triggered by re-exposure to drug-associated cues or the drug itself. Lasting relapse susceptibility may be mediated by persistent changes in gene expression throughout interconnected reward-processing regions of the brain. However, few studies have performed transcriptome-wide analyses across brain reward regions following volitional opioid intake. **Methods:** Here, we combine heroin self-administration in mice, RNA sequencing (RNA-seq), and advanced bioinformatics approaches to identify novel genes and gene networks throughout the reward circuitry regulated by opioid intake and drug-seeking. Mice underwent a 15-day intravenous heroin (or saline) self-administration paradigm, and subsequently underwent 30 days of home cage forced abstinence. After this period, mice received either a saline or heroin injection and were placed back into self-administration chambers to measure context-induced and drug-primed reinstatement of heroin-seeking and euthanized 2 hours later. RNA-seq was conducted on 6 key reward-processing brain regions: medial prefrontal cortex, nucleus accumbens, dorsal striatum, basolateral amygdala, ventral hippocampus and ventral tegmental area. **Results:** Bioinformatic analysis of this rich data set has uncovered numerous patterns of differential gene expression in a region- and condition-dependent manner. Employing multiscale embedded gene coexpression network analysis (MEGENA), we identified a key gene network in the ventral hippocampus specifically associated with context- and drug-induced heroin-seeking. Strikingly, this network consists of

several genes responsible for various epigenetic modifications that may mediate long-term changes in ventral hippocampal function. **Conclusion:** These results show that heroin abuse causes broad patterns of transcriptional regulation across the reward system. The ventral hippocampus emerged as a potential key regulator of relapse to heroin-seeking, and identification of a unique gene network enriched with epigenetic modifiers points to potential mechanisms of long-term dysfunction underlying relapse susceptibility.

Investigating the interaction between the human gut microbiome and clozapine therapy in schizophrenia. *Jonathan C.W. Liu, Ilona Gorbovskaya, Elena F. Verdu, Premysl Bercik, Giada De Palma, Margaret K. Hahn, Daniel J. Müller*. **From the Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada (Liu, Gorbovskaya, Müller); the Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada (Liu, Müller); the Farncombe Family Digestive Health Research Institute, Department of Medicine, McMaster University, Hamilton, ON, Canada (Verdu, Bercik, De Palma); the Complex Mental Illness Program, Centre for Addiction and Mental Health, Toronto, ON, Canada (Hahn); the Department of Psychiatry, University of Toronto, Toronto, ON, Canada (Hahn, Müller); and the Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada (Müller).**

Background: The gut microbiome (GMB) plays an important role in developmental processes and has been implicated in the etiology of psychiatric disorders. However, the relationship between the GMB and schizophrenia remains unclear. We aim to elucidate the role of the GMB in schizophrenia and clozapine-induced metabolic adverse effects. Clozapine is the first-line medication for treatment-resistant schizophrenia; however, it is inducing metabolic abnormalities and significant weight gain in more than 30% of patients. **Methods:** We developed a cross-sectional study that included 25 patients with schizophrenia who have been treated with clozapine for a minimum of 6 months and 25 matched healthy controls. Participants provided a saliva sample, stool sample, blood sample, anthropometric measures, and underwent detailed clinical assessments. Stool samples were analyzed through amplification of the V3 region of the 16S rRNA. To elucidate the direct effects of clozapine on the GMB, we propose a longitudinal study that will include 25 patients with schizophrenia who are starting clozapine therapy. Participants will come in for 3 visits: before starting clozapine, and 3 weeks and 6 weeks after starting clozapine. Similar to our initial study, participants will undergo a detailed assessment and provide biosamples. **Results:** Preliminary GMB cross-sectional analysis showed that patients with schizophrenia had a lower α diversity (abundance and evenness) of microbial bacteria. Patients with schizophrenia also presented with a different GMB profile (β diversity). **Conclusion:** These preliminary findings suggest significant differences within the GMB of patients and healthy controls. However, the direct effects of antipsychotics on the GMB remain unknown. Our findings of a difference in α and β diversity in patients with schizophrenia are consistent with most studies in the literature. However, we were unable to detect any changes in relative abundances when looking at various taxonomic groups. This could be because of our smaller samples size, therefore making it difficult to detect significant changes.

Inhibition of noradrenergic and corticotrophin-releasing factor systems block enhancement of memory consolidation by heroin withdrawal and conditioned heroin withdrawal. *Nana Baidoo, Francesco Leri*. **From the Department of Psychology and the Collaborative Neuroscience Program Guelph, ON, Canada.**

Background: It is well established that opioid withdrawal can be associated with environmental stimuli through classical conditioning to produce conditioned withdrawal. We have recently found that conditioned withdrawal has significant cognitive effects as, similarly to acute precipitated withdrawal, it enhances consolidation of memory. The aim of the current study was to explore the role of noradrenaline and corticotrophin-releasing factor (CRF) in memory modulation induced by unconditioned and conditioned heroin withdrawal. **Methods:** Male Sprague Dawley rats were implanted with osmotic mini-pumps releasing 3.5 mg/kg/d heroin and received injections of 3 mg/kg naloxone preceded by 0.1–0.6 mg/kg lofexidine (α-2 adrenergic agonist) or 10–20 mg/kg antalarmin (CRF 1 receptor antagonist) immediately after the sample phase of a spontaneous object recognition memory task. To produce conditioned withdrawal, a contextual conditioning procedure was used whereby heroin-exposed rats were confined for 2 hours in a context (CS+) following injections of 3 mg/kg naloxone and in another context (CS–) following vehicle injections. Seven days after removal of mini-pumps, the effects of immediate exposure to the CS+ (or CS–) preceded by 0.6 mg/kg lofexidine or 20 mg/kg antalarmin were tested. **Results:** We found that both lofexidine and antalarmin blocked the enhancement of object memory consolidation by posttraining naloxone-precipitated withdrawal and by conditioned withdrawal. **Conclusion:** These experiments suggest that pharmacological and psychological withdrawal have significant effects on memory storage by activating noradrenergic and CRF systems.

Translatomic database of cortical astroglia across mouse postnatal development reveals sex differences in developmental patterns. *Gareth M. Rurak, Stephanie Simard, Moises Freitas-Andrate, Baptiste Lacoste, François Charih, Amanda Van Geel, John Stead, Barbara Woodside, James R. Green, Gianfilippo Coppola, Natalina Salmaso*. **From the Department of Neuroscience, Carleton University, Ottawa, ON, Canada (Rurak, Simard, Van Geel, Stead, Woodside, Salmaso); the Child Study Center, Yale University, New Haven, CT, USA (Coppola, Salmaso); the Department of Psychology, Concordia University, Montréal, QC, Canada**

(Woodside); the Department of Systems and Computer Engineering, Carleton University, Ottawa, ON, Canada (Charih, Green); the Neuroscience Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada (Freitas-Andrate, Lacoste); the Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada (Freitas-Andrate, Lacoste); and the Brain and Mind Research Institute, University of Ottawa, Ottawa, ON, Canada (Freitas-Andrate, Lacoste)

Background: Astroglial cells are emerging as key players in the development and homeostatic maintenance of neurons and neuronal networks. Astroglial cell functions are critical to neuronal migration and maturation, myelination, and synapse dynamics; however, little is known about astroglial phenotypic changes over development. Furthermore, astroglial cells express steroid hormone receptors and show rapid responses to hormonal manipulations; however, despite important sex differences in telencephalic regions such as the cortex and hippocampus, few studies have examined sex differences in astroglial cells in telencephalic development. **Methods:** To phenotype cortical astroglial cells across postnatal development while considering potential sex differences, we used translating ribosome affinity purification together with RNA sequencing (TRAPseq), fluorescent in situ hybridization (FISH), and immunohistochemistry to phenotype the entire astroglial translatome in males and females at key developmental time points: P1, P4, P7, P14, P35 and in adulthood. **Results:** Overall, we found 2 distinct astroglial phenotypes between early (P1–P7) and late development (P14–adult), independent of sex. The astroglial translatome also showed significant sex differences in gene expression patterns over development, with peak sex differences observed at P7. At least part of the sex differences observed at P7 appear to be due to males reaching a more mature astroglial phenotype earlier than females. Many astroglial cell subtypes show gene expression overlap with neurologic and neurodegenerative disorders. **Conclusion:** We have developed an open-access, user-friendly, searchable database of the cortical astroglial cell translatome across postnatal development and between sexes. These data clearly delineate and phenotype astroglia across development and identify sex differences in astroglial developmental programs. Importantly, these developmental sex differences could have an impact on the construction and maintenance of neuronal networks and potential developmental windows of vulnerability to neurologic and psychiatric disease.