

CCNP 40TH ANNUAL CONFERENCE
Preliminary Program
Four Points by Sheraton Hotel
Kingston, Ontario
June 06 - 09



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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Young Investigator Awards.

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Dear Participants:

The first Canadian College of Neuropsychopharmacology took place 40 years ago in Montreal in 1978, thanks to the vision and enthusiasm of a few neuroscientists and psychiatrists. Since then, it has travelled all over Canada (and sometimes abroad), contributed to build bridges between researchers and clinicians, and most importantly it has become a forum for learning and exchange for trainees. During these meetings, tens of prestigious awards have been given to scientists who have contributed significantly to our field. We are very proud of the work that has been done and are looking to the future with optimism.

The field of psychiatry has been faced with major changes in the last 40 years. Our knowledge of the brain, thanks to important technological advances, is progressing very fast, and many findings have transformed our understanding of the brain and behaviours. Yet, the translation of this knowledge into clinical practice in psychiatry is still slow and sometimes frustrating. However, as a community of researchers, teachers, clinicians and advocates, we have to keep the flame alive and to look into the future with enthusiasm and hope. Science is our bridge to a bright future. Science is also a bridge, among many others, to an inclusive and just society. As a first generation immigrant from a Muslim country, I am extremely proud of the values of our Canadian Society. It is inspiring to see the diversity of our community, and I am confident that the CCNP will continue to promote inclusiveness and diversity.

This 40th annual meeting in Kingston will feature an excellent program, put together by the Local Organizing Committee, chaired by Dr Roumen Milev. A hallmark of CCNP meetings has always been a balance between basic and clinical research; this year is no exception. In addition to a diversity of excellent presentations and symposia, this meeting will highlight several integrated discovery programs funded by the Ontario Brain Institute. I would like to thank the Committee for their hard work in putting an excellent program together, and I am looking forward to learning from my exchange with all of you.

This year's winners of the CCNP Awards are: Dr Paul Albert (Heinz Lehmann Award), Dr Lena Palaniyappan (Young Investigator Award), Dr Yu Tian Wang (Innovations in Neuropsychopharmacology Award) and Dr Zul Merali (CCNP Medal). My congratulations to all the winners. I also extend my congratulations to the winners of the W.G. Dewhurst awards and those selected to present their work in the Next Generation Symposium. You make us proud!

This meeting is sponsored by many local and national organizations. I would like to thank all of them, particularly Pfizer, for their continued support of the annual CCNP awards.

I am sure that we will combine learning and fun in Kingston. Looking forward to seeing all of you.

Sincerely,

Ridha Joober
CCNP President

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OVERVIEW OF EVENTS

TUESDAY JUNE 06, 2017

13:00 – 17:00 CCNP Council Meeting (British American Room)

17:00 – 21:00 Registration (Limestone Foyer)

WEDNESDAY JUNE 07, 2017

07:30 – 17:00 Registration (Limestone Foyer)

07:30 – 08:30 Breakfast (Old Stone Room)

08:30 – 09:00 Welcoming Remarks (Limestone Ballroom)
Dr. Benoit-Antoine Bacon (Provost, Queen's University) and Dr. Roumen Milev (Queen's University)

09:00 – 10:30 [Presidential Symposium](#) (Limestone Ballroom)
Dr. Georg Northoff (University of Ottawa)
What can the brain's spontaneous activity tell us about our self and its mental health

Chair: Dr. Ridha Joober (McGill University)

10:30 – 11:00 Break (Old Stone Room)

11:00 – 12:30 **Symposium 1:** *Novel perspectives on the neurobiology of bipolar disorder across the lifespan* (Limestone Ballroom)

Chair: Dr. Benjamin Goldstein (University of Toronto)
Dr. Ana Andreazza (University of Toronto)
The role of NLRP3 inflammasome in bipolar disorder

Dr. Benicio N. Frey (McMaster University)
Evidence of deficits in intracortical maturation in bipolar I disorder

Dr. Benjamin Goldstein (University of Toronto)
Neuroimaging evidence of microvascular pathology among adolescents with bipolar disorder

Dr. Flavio Kapczinski (McMaster University)
Towards a nomenclature task force on staging in bipolar disorder

12:30 – 13:30 **LUNCH/CCNP Business Meeting** (All are welcome) (Old Stone Room)

13:30 – 14:00 **CCNP Next Generation Presentation 1** (Limestone Ballroom)
Co-Chairs: Dr. Emily Hawken (Queen's University) and Dr. Hong-Yan Ren (University of Alberta)

Angélica Torres-Berrio (McGill University)

MiR-218 is a molecular switch for resilience to chronic stress

Victoria Marshe (Pharmacogenetic Research Clinic)

Unravelling genomic contributions to duloxetine and placebo response in major depressive disorder using a genome-wide approach

14:00 – 15:00 **CCNP Heinz Lehmann Award Lecture** (Limestone Ballroom)

Dr. Paul Albert (University of Ottawa)

A molecular biologist in Psychiatry: from signaling to transcription in behavior

Chair: Dr. Ridha Joober (McGill University)

15:00 – 15:30 Break (Old Stone Room)

15:30 – 17:00 **Symposium 2: Advances in brain stimulation for treating cognitive and psychiatric dysfunction** (Limestone Ball Room)

Chair: Dr. Catharine Winstanley (University of British Columbia)

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Deep-brain stimulation of the subthalamic nucleus selectively decreases risky choice in risk-preferring rats

Dr. Clement Hamani (University of Toronto)

Deep brain stimulation for obsessive-compulsive disorder and depression: evidence and lessons for improving study design

Dr. Jonathan Downar (Toronto Western Hospital)

From bench to bedside: translating rTMS research findings into clinical practice

Dr. Elise Gondard (Krembil Research Institute, Toronto Western Hospital)

Effects of DBS on memory and plasticity in Alzheimer's disease

17:00 – 17:30 Free time

17:30 – 19:30 Reception (Old Stone Room)

THURSDAY JUNE 08, 2017

07:30 – 17:00 Registration (Limestone Foyer)

07:30 – 08:30 Breakfast (Old Stone Room)

08:30 – 09:00 Welcoming Remarks – Ontario Brain Institute (Limestone Ballroom)

Dr. Tom Mikkelsen (President & Scientific Director, OBI)

09:00 – 10:30 **IDP Symposium 1: Clinical neuropsychology/neuropsychopharmacology**

Chair: Dr. Tom Mikkelsen (President & Scientific Director, OBI)

CP-NET

Dr. Jan Willem Gorter (CanChild, McMaster University)

Growing up with cerebral palsy, more than a physical disability

ONDRI

Dr. Paula McLaughlin (Western University)

Identifying cognitive and behavioural phenotypes across five distinct neurodegenerative diseases

EpLink

Dr. Mary Lou Smith (University of Toronto, Hospital for Sick Children)

Outcomes of pediatric epilepsy surgery: does neuropsychological function change over time?

POND

Dr. Evdokia Anagnostou (Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital)

Neurodevelopmental disorders: the case of lumping

10:30 – 11:00 Break (Old Stone Room)

11:00 – 12:30 **Symposium 3: Gut-brain axis** (Limestone Ballroom)

Chair: Dr. Sidney Kennedy (St. Michael's Hospital)

Dr. Jonathan Swann (Imperial College, UK)

Characterizing the functionality of the microbiome and understanding the gut-brain axis

Dr. Rochellys Heijtz (Karolinska Institutet, Sweden)

A potential new mechanism by which microbiota affect CNS function

Dr. Jane Foster (McMaster University)

Mood and microbes – the influence of microbiota on stress circuitry and behaviour

Caroline Wallace (Queen's University)

Probiotics as a novel therapeutic in a clinical sample of depressed patients

12:30 – 14:00 Lunch (Old Stone Room)

13:00 – 14:00 **CCNP Poster Session 1** (Gibraltar Room)

14:00 – 14:30 **CCNP Next Generation Presentation 2** (Limestone Ballroom)

Chair: Dr. Emily Hawken (Queen's University)

Catherine Normandeau (Queen's University)

Effects of endogenous neuropeptides in the bed nucleus stria terminalis and changes in chronic stress-induced anxiety-like behavior

Darya Naumova (McGill University)

DRD4 exon 3 genotype as predictor of symptom severity and treatment outcomes in children with ADHD: gene-treatment and gene-environment interaction study

14:30 – 15:30 **CCNP Young Investigator Award Lecture** (Limestone Ballroom)

Dr. Lena Palaniyappan (Western University)

Insights from applying systems neuroscience in psychosis

Chair: Dr. Ridha Joobar (McGill University)

15:30 – 15:45 Break (Old Stone Room)

15:45 – 17:15 **IDP Symposium 2: Reverse translation** (Limestone Ballroom)

Chair: Dr. Elizabeth Theriault (Vice President, Research & Informatics, OBI)

ONDRI

Dr. Douglas Munoz (Queen's University)

Deep phenotyping of neurodegenerative diseases: a tale of translation and reverse translation

POND

Dr. Jason Lerch (University of Toronto, Hospital for Sick Children)

Neurodevelopmental disorders: the case for splitting

CAN-BIND

Dr. Brock Schuman (St Michael's Hospital) & Dr. Juan Pablo Lopez (McGill University, Max Planck Institute of Psychiatry, Germany)

Fishing for biomarkers of depression: molecular and reverse translation insights from the CAN-BIND Program

CP-NET

Rebecca Ruddy (University of Toronto)

Sex, drugs and neural repair

17:15 – 17:45 Panel Discussion: Partnerships that Move Research Out of the Lab (Limestone Ballroom)

Moderator: Dr. Tom Mikkelsen (President & Scientific Director, OBI)

Panel Members:

Dr. Evdokia Anagnostou (Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital)

Dr. Jan Willem Gorter (CanChild, McMaster University)

Dr. Paula McLaughlin (Western University)

Dr. Mary Lou Smith (University of Toronto, Hospital for Sick Children)

Dr. Claudio Soares (Queen's University)

17:45 – 18:00 Closing Remarks – Ontario Brain Institute (Limestone Ballroom)

Dr. Elizabeth Theriault (Vice President, Research & Informatics, OBI)

18:00 – 18:30 Free time

18:30 – 19:30 Gala Dinner – Cocktails (Grandview Room, Delta Hotel, 1 Johnston Street, 5 min walk from hotel)

19:30 – 20:00 CCNP Medal Award Presentation to Dr. Zul Merali
Presenter: Dr. Ridha Joober

19:30 – 22:00 Gala Dinner (Grandview Room, Delta Hotel)

FRIDAY JUNE 09, 2017

07:30 – 12:30 Registration (Limestone Foyer)

07:30 – 08:30 Breakfast (Old Stone Room)

08:30 – 10:00 **Symposium 4:** *What brain imaging can tell us about diagnosis, treatment and mechanisms* (Limestone Ballroom)

Co-Chairs: Dr. Verner Knott (University of Ottawa) and Dr. Natalia Jaworska (McGill University)

Dr. Alexander Neumeister (University of Ottawa)
Molecular imaging provides an opportunity for evidence-based treatment developments in posttraumatic stress disorder

Dr. Natalia Jaworska (McGill University)
Neural profiles in depression – utility in response prediction

Sara de la Salle (University of Ottawa)
Electrophysiological effects of ketamine and implications of antidepressant response

Dr. Rébecca Robillard (Netherlands Institute for Neuroscience, The Netherlands)
Considering chronobiology and sleep profiles to tailor treatment strategies for mood disorders

10:00 – 10:30 **CCNP Next Generation Symposium 3** (Limestone Ballroom)

Chair: Dr. Hong-Yan Ren (University of Alberta)

Chantel Kowalchuk (Centre for Addiction and Mental Health)
Antipsychotic-induced hypothalamic inflammation as a potential mediator of metabolic side effects

Shamik Sen (Queen's University)
Evaluation of a stigma management psychoeducational and behavioural modification course for people with mood and anxiety disorders

10:30 – 11:00 Break (Old Stone Room)

11:00 – 12:30 **Symposium 5: Neurocircuitry of binge eating: alterations in reward processing**
(Limestone Ballroom)

Chair: Dr. Mary Olmstead (Queen's University)

Amanda Maracle (Queen's University)

Dopaminergic contributions in the BNST to compulsive responding for sucrose

Dr. Alfonso Abizaid (Carleton University)

A role for ghrelin receptors in the ventral tegmental area (VTA) in caloric intake in a mouse model of binge eating disorder

Dr. Iris Balodis (McMaster University)

Neuroimaging studies in binge eating disorder: linking findings with treatment outcome

Dr. Caroline Davis (York University)

The etiology of binge eating disorder from a psychobiological perspective

12:30 – 14:00 Lunch (Old Stone Room)

13:00 – 14:00 **CCNP Poster Session 2** (Gibraltar Room)

14:00 – 15:00 **CCNP Innovations in Neuropsychopharmacology Award Lecture**

(Limestone Ballroom)

Dr. Yu Tian Wang (University of British Columbia)

AMPA endocytosis in synaptic plasticity – is it a therapeutic target for improving memory?

Chair: Dr. Ridha Joober (McGill University)

15:00 – 16:30 **Symposium 6: Novel signaling mechanisms for treatment of anxiety and depression** (Limestone Ballroom)

Chair: Dr. Paul Albert (University of Ottawa)

Dr. Hsiao-Huei Chen (University of Ottawa)

Cannabinoid signaling in anxiety: anxious moments for the protein tyrosine phosphatase PTP1B

Dr. Sheena Josselyn (Hospital for Sick Kids)

Probing fear and anxiety circuits in mice

Dr. Cecilia Flores (McGill University)

MicroRNA regulation of DCC and susceptibility to depression-like behaviors in humans and mice

Dr. Paul Albert (University of Ottawa)

Novel transcriptional pathways regulating 5-HT and anxiety-depression phenotypes

16:30 Poster Awards Presentation & Closing Remarks (Limestone Ballroom)
Dr. Ridha Joober (McGill University)

Tuesday, June 06, 2017

13:00 – 17:00 CCNP Council Meeting (British American Room)

17:00 – 21:00 Registration (Limestone Foyer)

Wednesday, June 07, 2017

07:30 – 17:00 Registration (Limestone Foyer)

07:30 – 08:30 Breakfast (Old Stone Room)

08:30 – 09:00 Welcoming Remarks (Limestone Ballroom) – Dr. Roumen Milev

09:00 – 10:30 **Presidential Symposium** (Limestone Ballroom)

Dr. Georg Northoff (University of Ottawa)

What can the brain's spontaneous activity tell us about our self and its mental health?

Chair: Dr. Ridha Joobar (McGill University)

10:30 – 11:00 Break (Old Stone Room)

11:00 – 12:30 [Symposium 1](#) (Limestone Ballroom)

Novel perspectives on the neurobiology of bipolar disorder across the lifespan

Chair: Dr. Benjamin Goldstein (University of Toronto)

11:00 – 11:20 **Dr. Ana Andreazza** (University of Toronto)

The role of NLRP3 inflammasome in bipolar disorder

11:20 – 11:40 **Dr. Benicio N. Frey** (McMaster University)

Evidence of deficits in intracortical maturation in bipolar I disorder

11:40 – 12:00 **Dr. Benjamin Goldstein** (University of Toronto)

Neuroimaging evidence of microvascular pathology among adolescents with bipolar disorder

12:00 – 12:20 **Dr. Flavio Kapczinski** (McMaster University)

Towards a nomenclature task force on staging in bipolar disorder

12:20 – 12:30 **Discussion**

12:30 – 13:30 **LUNCH/CCNP Business Meeting** (All are welcome; Old Stone Room)

13:30 – 14:30 [CCNP Next Generation Presentation 1](#) (Limestone Ballroom)

Chair:

13:30 – 13:45 **Angélica Torres-Berrio** (McGill University)

MiR-218 is a molecular switch for resilience to chronic stress

13:45 – 14:00 **Victoria Marshe** (Pharmacogenetic Research Clinic)

Unravelling genomic contributions to duloxetine and placebo response in major depressive disorder using a genome-wide approach

14:00 – 15:00 [CCNP Heinz Lehmann Award Lecture](#) (Limestone Ballroom)

Dr. Paul Albert (University of Ottawa)

A molecular biologist in Psychiatry: from signaling to transcription in behavior

Chair: Dr. Ridha Joober (McGill University)

15:00 – 15:30 Break (Old Stone Room)

15:30 – 17:00 [Symposium 2](#) (Limestone Ballroom)

Advances in brain stimulation for treating cognitive and psychiatric dysfunction

Chair: Dr. Catharine Winstanley (University of British Columbia)

15:30 – 15:50 **Dr. Catharine Winstanley** (University of British Columbia)

Deep-brain stimulation of the subthalamic nucleus selectively decreases risky choice in risk-preferring rats

15:50 – 16:10 **Dr. Clement Hamani** (University of Toronto)

Deep brain stimulation for obsessive-compulsive disorder and depression: evidence and lessons for improving study design

16:10 – 16:30 **Dr. Jonathan Downar** (Toronto Western Hospital)

From bench to bedside: translating rTMS research findings into clinical practice

16:30 – 16:50 **Dr. Elise Gondard** (Krembil Research Institute, Toronto Western Hospital)

Effects of DBS on memory and plasticity in Alzheimer's disease

16:50 – 17:00 **Discussion**

17:00 – 17:30 Free Time

17:30 – 19:30 Reception (Old Stone Room)

Wednesday, June 07, 2017
Abstracts for Oral Presentations

Presidential Symposium

What can the brain's spontaneous activity tell us about our self and its mental health?

Dr. Georg Northoff, Department of Psychology, University of Ottawa, Ottawa, ON.

The self is a central core of our mental life and its abnormal changes in various psychiatric disorders. However, the neural correlates of self and its abnormal changes in psychiatric disorders remain largely unclear. I here present various lines of findings that (i) associate the self with cortical midline structures (CMS); (ii) show strong neural overlap between self-related activity and resting state in CMS; (iii) suggest strong involvement of temporal structure and stability in neural activity; and (iv) show abnormal changes in both temporal and spatial structure in resting state CMS in various psychiatric disorders. In conclusion, I demonstrate first tentative neural mechanisms underlying our sense of self and its abnormal alterations in psychiatric disorders. This sheds some novel light on the neuronal mechanisms underlying psychopathological symptoms supporting what I describe as "Spatiotemporal Psychopathology". Finally, If developed further, these could serve as biomarkers for psychiatric diagnosis and therapy.

Symposium 1 – Novel perspectives on the neurobiology of bipolar disorder across the lifespan

The role of NLRP3 inflammasome in bipolar disorder

Dr. Ana Andreazza, Departments of Psychiatry and Pharmacology, Faculty of Medicine, University of Toronto, Toronto, ON.

Dr Andreazza will show how a key component of the pathophysiology of bipolar disorder – mitochondrial dysfunction – plays a role in the development of inflammation through the NLRP3 inflammasome. Dr. Andreazza will present data demonstrating the involvement of this pathway in post-mortem brain samples and peripheral white blood cells. She will also show the genetic influence of the NLRP3 pathway for patients with bipolar disorder.

Evidence of deficits in intracortical maturation in bipolar I disorder

Dr. Benicio N. Frey, Department of Psychiatry and Behavioural Neurosciences, McMaster University; Mood Disorders Program and Women's Health Concerns Clinic, St. Joseph's Healthcare; MiNDS Neuroscience Graduate Program, McMaster University; Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, ON.

This presentation will discuss findings from a large study of intracortical myelin levels across the whole brain among 43 adults with bipolar I disorder and 67 controls, age range 17-45, based on 3T T₁-weighted images using an optimized sequence previously shown to be sensitive to myelin content in non-human primates. Intracortical myelin trajectory in healthy volunteers follows a normal and expected inverted 'U' trajectory across the age range, whereas there was no association with age and T₁-weighted signal in bipolar I disorder subjects. This study provides the first evidence of a global disruption in intracortical myelin maturation in bipolar disorder, which will be discussed in the context of implications for cognitive and emotional regulation.

Neuroimaging evidence of microvascular pathology among adolescents with bipolar disorder

Dr. Benjamin Goldstein, Departments of Psychiatry and Pharmacology, Faculty of Medicine, University of Toronto; Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre; Toronto, ON.

This presentation will discuss findings from a large neuroimaging study of 50 adolescents (13-20 years old) with bipolar disorder and 50 healthy controls, including measures of cerebral blood flow (ASL) and physiological fluctuations in white matter BOLD signal (resting state fMRI). Adolescents with bipolar disorder demonstrated elevated frontal cerebral blood flow, which was normalized following a bout of aerobic exercise in proportion with exercise-related feelings of exhaustion. Adolescents with bipolar disorder also demonstrated increased physiological fluctuations in periventricular and deep white matter regions, which were negatively correlated with global functioning. These findings, reflecting anomalous cerebral microvascular perfusion and cerebral microvascular stiffness, provide convergent evidence of microvascular pathology in a young sample in the early stages of bipolar disorder.

Towards a nomenclature task force on staging in bipolar disorder

Dr. Flavio Kapczinski, Department of Psychiatry, Faculty of Medicine, McMaster University, Hamilton, ON.

The concept of staging, relevant to disorders that progress from prodromal phases to symptomatic full blown syndromes, has developed rapidly in the field of bipolar disorder. There are subsets ranging from patients who present an episodic disorder with good functioning in between episodes who are often lithium-responsive, to patients who present with a highly symptomatic inter-episodic period including high levels of anxiety, substance abuse and functional impairment. The main debate in the field is whether episodes and illness progression give rise to more complicated presentations over time or course of illness is related to clinical subtypes and heterogeneity. This presentation will summarize the current debate in this area in the light of available evidence.

CCNP Next Generation Presentation 1

MiR-218 Is a Molecular Switch for Resilience to Chronic Stress

Angélica Torres-Berrío, PhD (C), Integrated Program in Neuroscience, McGill University, Montréal, Québec, Canada. Dominique Nouel, PhD, Douglas Mental Health University Institute, Montréal, Québec, Canada. Santiago Cuesta, PhD, Department of Psychiatry, McGill University, Montréal, Québec, Canada. Gustavo Turecki, MD, PhD, Department of Psychiatry, McGill University, Montréal, Québec, Canada. Eric J. Nestler, MD, PhD, Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY USA. Cecilia Flores, PhD, Department of Psychiatry, McGill University, Montréal, QC.

Introduction: We recently identified miR-218 as repressor of the guidance cue receptor gene DCC (Deleted in colorectal cancer). Indeed, low miR-218, but exaggerated DCC, expression in the prefrontal cortex (PFC) are consistent traits of human depression, and stress-induced depression-like behaviors in mice. Remarkably, miR-218 can be measured in blood, suggesting its potential role as novel biomarker of vulnerability to depression.

Methods: Here we used C57BL/6 mice, viral-mediated gene transfer, and quantitative-PCR to assess whether (1) direct manipulation of miR-218 in the PFC determines resilience or susceptibility to chronic social defeat stress (CSDS), (2) miR-218 expression in blood correlates with depression-like behaviors, and (3) variations in blood expression of miR-218 depends on

changes in levels of miR-218 in PFC.

Results: We report that miR-218 is expressed by pyramidal neurons in the mouse PFC. We then find that overexpression of miR-218 selectively in PFC pyramidal neurons prior to CSDS promotes resilience to stress by reducing social avoidance. Conversely, blocking the function of miR-218 in the PFC before a single social defeat exposure induces susceptibility to stress. We also find that expression of miR-218 in blood correlates with depression-like behaviors and that susceptible, but not control or resilient, mice exhibit low levels of miR-218 in blood. Most importantly, we demonstrate that changes in blood expression of miR-218 resemble the ones observed in the PFC.

Conclusion: Our results reveal that miR-218 in the PFC functions as a molecular switch that determines resilience or susceptibility to chronic stress. Remarkably, stress-induced variations in PFC levels of miR-218 can be readily detected in blood. We are currently assessing whether miR-218 levels in both PFC and blood change in response to antidepressant treatment. We propose that blood expression of miR-218 might function as potential biomarker of vulnerability to stress and predict the outcome of therapeutic or pharmacological interventions.

miR-218: a key target for the alterations in dopamine development induced by abused doses of amphetamine in adolescence

Unravelling genomic contributions to duloxetine and placebo response in major depressive disorder using a genome-wide approach

Victoria S. Marshe, HBSc (^{1, 2}); Malgorzata Maciukiewicz, PhD (¹); Arun K. Tiwari, PhD (^{1, 3}); Trehani M. Fonseka, MSc (^{1, 4, 5}); Natalie Freeman, MSc (¹); Susan Rotzinger, PhD (^{3, 4}); Jane A. Foster, PhD (^{4, 6}); James L. Kennedy, MD MSc (^{1, 2, 3}); Sidney H. Kennedy, MD (^{3, 4, 5}); Daniel J. Mueller, MD PhD (^{1, 2, 3}) (¹) Pharmacogenetic Research Clinic, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada (²) Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada (³) Department of Psychiatry, University of Toronto, Toronto, ON, Canada (⁴) University Health Network, Toronto, ON, Canada (⁵) Department of Psychiatry, St. Michael's Hospital, Toronto, ON, Canada (⁶) Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, ON.

Background: Genomic analyses may identify markers associated with antidepressant response and unravel novel pathways for drug discovery. We utilized a hypothesis-free, genome-wide approach to investigate genetic contribution to antidepressant (i.e., duloxetine) and placebo response for patients with major depressive disorder (MDD), followed by construction of preliminary, predictive machine learning (ML) models.

Methods: We performed a GWAS in MDD patients treated with duloxetine (N=186) or placebo (N=205) for up to 8 weeks. Individuals were genotyped using the Illumina PsychChip, followed by imputation, resulting >2 million variants per individual under standard quality control. We investigated percentage change of MADRS score corrected for baseline depression severity, length of treatment and cohort. We also constructed preliminary ML models using the best genetic and clinical predictors using LASSO regression for response (>50% of MADRS decrease). Subsequently, we utilized classification-regression trees (CRT) and support vector machines (SVM) to construct models, using ten-fold, repeated cross-validation.

Results: For duloxetine response, we observed top hits ($p < 10^{-6}$) on chromosomes 1, 7 and 19 implicating previously under-investigated intergenic variants. For placebo response, there was a significant hit on chromosome 3 ($p = 1.87 \times 10^{-9}$) located 150kb from STAC1, implicated in neuron-specific signal transduction expressed in nociceptive neurons. Carriers of the C/C genotype improved on average by 49.6% of MADRS score while non-carriers improved clinically significantly worse by 23.9%. Furthermore, there was a suggestive association ($p < 10^{-6}$) within a marker located in the TPO gene involved in thyroid functioning. None of the top variants replicated between duloxetine and placebo samples. Preliminary ML models achieved an accuracy of 63.43% for CRT and 78.93% for SVM when predicting response to duloxetine.

Conclusions: Our data provide new insights into genetic pathways implicated in response to antidepressants and placebo, rejecting the notion that similar pathways are involved. Replication studies in comparable samples including IRLGRey, CAN-BIND-I and STAR*D are pending.

CCNP Heinz Lehmann Award Lecture

A molecular biologist in Psychiatry: from signaling to transcription in behavior

Dr. Paul Albert, Ottawa Hospital Research Institute, UOttawa Brain and Mind Research Institute
451 Smyth Road, Ottawa, ON.

Having cloned and characterized 5-HT_{1A} receptor gene (HTR1A) expression and signaling, in a reductionist, hypothesis-driven approach we focused on its transcriptional regulation, given the chronic nature of mental illness and its treatment. Altered activity of serotonin (5-HT) is implicated in anxiety and depression and the 5-HT_{1A} receptor is a dual regulator of 5-HT activity, both as an autoreceptor inhibiting 5-HT neurons, and as a post-synaptic heteroreceptor implicated in anxiety and depression. We hypothesized that de-repression of 5-HT_{1A} autoreceptors could predispose to depression and confer resistance to antidepressants. In ground-breaking studies, we associated a novel HTR1A promoter polymorphism rs6295 with depression, suicide and reduced response to antidepressants. Since rs6295 is within a 26-bp palindrome, we used this DNA element to clone Deaf1/NUDR and Hes as allele-specific HTR1A repressors, as well as a separate repressor, Freud-1/CC2D1A. We have shown that in mouse models, knockout of these repressors induces 5-HT_{1A} autoreceptors, reduces 5-HT and results in a treatment-resistant anxiety-depression phenotype. Recently we found that human PFC 5-HT_{1A} expression is also allele-dependent, and this dependence is lost in depressed subjects, suggesting that dys-regulation of Deaf1 function may underlie some forms of depression. Our Deaf1 and Freud-1 knockout mice provide new models of treatment-resistant anxiety-depression and adaptive compensatory changes that correspond with clinical studies. Together, they implicate transcriptional dys-regulation in depression and anxiety, and in response to antidepressants, providing new biomarkers and drug targets to re-establish normal 5-HT function and behavior and a transcriptional framework to identify underlying regulatory mechanisms that lead to mental illness.

Supported by CIHR, OMHF, CPSR

Symposium 2 - Advances in brain stimulation for treating cognitive and psychiatric dysfunction

Deep-brain stimulation of the subthalamic nucleus selectively decreases risky choice in risk-preferring rats

Dr. Catharine Winstanley, Department of Psychology, University of British Columbia, Vancouver, BC.

STN-DBS may constitute a relatively safe and effective alternative to pharmacotherapy, not just for Parkinson's Disease, but for disorders of addiction and compulsion in which decision making is compromised. However, concern remains over whether this manipulation may itself trigger impulse control deficits or risky decision making, as may be predicted from rodent lesion data. Here, we directly test this hypothesis, and evaluate the effects of STN-DBS in rats performing a rodent gambling paradigm based on the Iowa Gambling Task used clinically. Far from inducing

impulsivity or exacerbating risky choice, STN-DBS selectively improved decision making in animals exhibiting a risk-preferring strategy at baseline. These data suggest that STN-DBS may be beneficial in the treatment of psychiatric, rather than solely neurological, conditions.

Deep brain stimulation for obsessive-compulsive disorder and depression: evidence and lessons for improving study design

Dr. Clement Hamani, Division of Neurosurgery, University of Toronto, Centre for Addiction and Mental Health, Toronto, ON.

Deep brain stimulation (DBS) is currently being investigated for numerous psychiatric conditions, including obsessive-compulsive disorder (OCD) and depression. We will review current evidence supporting this therapy in both disorders and briefly describe the guidelines of the American Society for Stereotactic and Functional Neurosurgery for the use of DBS in OCD. Caveats of current studies and steps needed to implement this therapy will be discussed.

From bench to bedside: translating rTMS research findings into clinical practice

Dr. Jonathan Downar, Department of Psychiatry, Toronto Western Hospital, Toronto, ON.

rTMS is emerging into routine clinical use as a treatment for medication-resistant depression and other psychiatric illnesses. Current research efforts seek to optimize the parameters of treatment in order to enhance efficacy, accelerate treatment courses, enhance treatment capacity, and reduce cost. Here we review a series of recent translational advances that are improving the clinical utility of rTMS, including shorter protocols (e.g., 3 min theta-burst stimulation), accelerated courses (multiple daily sessions), novel stimulation targets (including dorsomedial prefrontal and orbitofrontal cortex), and improved characterization of neutrally-defined patient subtypes within the conventional diagnostic categories of psychiatry.

Effects of DBS on memory and plasticity in Alzheimer's disease

Dr. Elise Gondard, Krembil Research Institute, Toronto Western Hospital, Toronto, ON.

The potential beneficial effects of DBS for memory enhancement in rodents and humans has been reported, including potential implications for therapeutic applications. Fornix DBS is being evaluated as a therapy to improve cognitive function in patients with Alzheimer's disease. Preclinical studies are currently being conducted to test the effects of stimulation. We have shown that one hour of fornix DBS in rats can trigger hippocampal activity and rapidly modulate the expression of neurotrophic factors and markers of synaptic plasticity known to play key roles in memory processing. Moreover, we showed that chronic DBS can enhance spatial memory in a transgenic mouse model of Alzheimer's disease.

Thursday, June 08, 2017

07:30 – 17:00 Registration (Limestone Foyer)

07:30 – 08:30 Breakfast (Old Stone Room)

08:30 – 09:00 Welcoming Remarks – Ontario Brain Institute (Limestone Ballroom)
Dr. Tom Mikkelsen (President & Scientific Director, OBI)

09:00 – 10:30 [IDP Symposium 1](#) (Limestone Ballroom)

Clinical Neuropsychology/neuropsychopharmacology

Chair: Dr. Tom Mikkelsen (President & Scientific Director, OBI)

09:00 – 09:20 **CP-NET**

Dr. Jan Willem Gorter (CanChild, McMaster University)
Growing up with cerebral palsy, more than a physical disability

09:20 – 09:40 **ONDRI**

Dr. Paula McLaughlin (Western University)
Identifying cognitive and behavioural phenotypes across five distinct neurodegenerative diseases

09:40 – 10:00 **EpLink**

Dr. Mary Lou Smith (University of Toronto, Hospital for Sick Children)
Outcomes of pediatric epilepsy surgery: does neuropsychological function change over time?

10:00 – 10:20 **POND**

Dr. Evdokia Anagnostou (Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital)
Neurodevelopmental disorders: the case of lumping

10:20 – 10:30 **Discussion**

10:30 – 11:00 Break (Old Stone Room)

11:00 – 12:30 [Symposium 3](#) (Limestone Ballroom)

Gut-brain axis

Chair: Dr. Sidney Kennedy (St. Michael's Hospital)

- 11:00 – 11:20 **Dr. Jonathan Swann** (Imperial College, UK)
Characterizing the functionality of the microbiome and understanding the gut-brain axis
- 11:20 – 11:40 **Dr. Rochellys Heijtz** (Karolinska Institutet, Sweden)
A potential new mechanism by which microbiota affect CNS function
- 11:40 – 12:00 **Dr. Jane Foster** (McMaster University)
Mood and microbes – the influence of microbiota on stress circuitry and behavior
- 12:00 – 12:20 **Caroline Wallace** (Queen's University)
Probiotics as a novel therapeutic in a clinical sample of depressed patients
- 12:20 – 12:30 **Discussion**
-

12:30 – 14:00 Lunch (Old Stone Room)

13:00 – 14:00 [CCNP Poster Session 1](#) (Gibraltar Room)

14:00 – 14:30 [CCNP Next Generation Presentation 2](#) (Limestone Ballroom)

Chair:

- 14:00 – 14:15 **Catherine Normandeau** (Queen's University)
Effects of endogenous neuropeptides in the bed nucleus stria terminalis and changes in chronic stress-induced anxiety-like behavior
- 14:15 – 14:30 **Darya Naumova** (McGill University)
DRD4 exon 3 genotype as predictor of symptom severity and treatment outcomes in children with ADHD: gene-treatment and gene-environment interaction study
-

14:30 – 15:30 [CCNP Young Investigator Award Lecture](#) (Limestone Ballroom)
Dr. Lena Palaniyappan (Western University)
Insights from applying systems neuroscience in psychosis

15:30 – 15:45 Break (Windsor Foyer)

15:45 – 17:15 [IDP Symposium 2](#) (Limestone Ballroom)

Reverse translation

Chair: Dr. Elizabeth Theriault (Vice President, Research & Informatics, OBI)

15:45 – 16:05 **ONDRI**

Dr. Douglas Munoz (Queen's University)

Deep phenotyping of neurodegenerative diseases: a tale of translation and reverse translation

16:05 – 16:25 **POND**

Dr. Jason Lerch (University of Toronto, Hospital for Sick Children)

Neurodevelopmental disorders: the case for splitting

16:25 – 16:45 **CAN-BIND**

Dr. Brock Schuman (St. Michael's Hospital) & **Dr. Juan Pablo Lopez** (McGill University, Max Planck Institute of Psychiatry, Germany)

Fishing for biomarkers of depression: molecular and reverse translation insights from the CAN-BIND program

16:45 – 17:05 **CP-NET**

Rebecca Ruddy (University of Toronto)

Sex, drugs and neural repair

17:05 – 17:15 **Discussion**

17:15 – 17:45 **Panel Discussion: partnerships that move research out of the lab** (Limestone Ballroom)

Moderator: Dr. Tom Mikkelsen (President & Scientific Director, OBI)

17:45 – 18:00 **Closing Remarks – Ontario Brain Institute** (Limestone Ballroom)

Dr. Tom Mikkelsen (President & Scientific Director, OBI) & Dr. Elizabeth Theriault (Vice President, Research & Informatics, OBI)

18:00 – 18:30 Free time

18:30 – 19:30 Gala Dinner – Cocktails (Grandview Room, Delta Hotel, 1 Johnston Street, 5 min. walk from hotel)

19:30 – 22:00 Gala Dinner (Grandview Room, Delta Hotel)

Thursday, June 08, 2017
Abstracts for Oral Presentations

IDP Symposium 1 – Clinical neuropsychology/neuropsychopharmacology

CP-NET

Growing up with cerebral palsy, more than a physical disability

Dr. Jan Willem Gorter, CanChild Centre for Childhood Disability Research, Department of Pediatrics, McMaster University, Hamilton, ON.

Cerebral palsy is defined as a disorder of movement or posture due to an injury to the developing brain before, during or shortly after birth. Most brain research in CP has focused primarily on changes that may occur in the brain during early development. Little is known about the brain changes that may occur as the child with CP matures into adolescence and into young adulthood. What we know suggests that individuals who grow up with CP lead complicated lives. These adolescents and young adults (AYA) have aspirations similar to those of peers without CP, but face challenges to physical and mental health, and wellness. In addition to motor impairments, AYA with CP may be affected by chronic pain, fatigue and depressive symptoms, are more likely to engage in passive solitary activities, and experience a decreased sense of belonging.

In the ongoing Ontario Brain Institute funded MyStory project as part of the CP-NET research program, we heard from young people with CP that they struggle with their identity. In this presentation, preliminary findings will be presented from our survey (n=77) on anxiety and depression levels, as well as findings of two feasibility studies examining brain function in adolescents and adults with cerebral palsy (age 16-30 years). Our brain imaging studies in CP show that we can image the brain in adults with CP (using both fMRI and EEG). Early results from our EEG study (n=8) indicate a wide range of reaction times to our selective attention task, which may be correlated with CP severity levels suggesting difficulties in selectively paying attention to what is required and ignoring distractors. We have collected cognitive data requiring motor responses in the fMRI scanner from 9 young people with CP.

ONDRI

Identifying cognitive and behavioural phenotypes across five distinct neurodegenerative diseases

Dr. Paula McLaughlin, Schulich School of Medicine and Dentistry, Western University, London, ON.

The Ontario Neurodegenerative Disease Research Initiative (ONDRI; Farhan, Bartha et al., 2016) is an integrative, multidisciplinary longitudinal research program funded by the Ontario Brain Institute to investigate five distinct neurodegenerative diseases. These include Alzheimer's disease and mild cognitive impairment, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, Parkinson's disease, and vascular cognitive impairment. The overarching goals of this research program are to identify and characterize the phenotypic profiles associated with neurodegenerative diseases, and to determine which biological and behavioural features are most sensitive to early detection and disease progression. In collaboration with 13 research institutions and academic centres across Ontario, deep phenotyping is achieved through comprehensive platform assessments that are completed at baseline and annually, up to 3 years. The ONDRI platform assessments include neuropsychological testing; neuroanatomical, microstructural, and functional imaging measures; genetic mutations and common genetic susceptibility indices (Farhan, Dilliot et al., 2016); eye-tracking; retinal nerve fiber layer thickness; and balance and gait testing (Montero-Odasso, et al., submitted). In the neuropsychology assessment platform,

cognition and behaviour are assessed using techniques that merge cognitive neuroscience with clinical neuropsychology and speech-language pathology. This comprehensive protocol provides measures of attention, processing speed, speech production, language, memory, executive skills, visuoperceptual abilities, and intellectual functioning, as well as neuropsychiatric symptoms, metacognition, social cognition, and daily functioning. Over 500 participants have completed their baseline ONDRI assessments, with preliminary results from the neuropsychology platform showing discrete cognitive and behavioural profiles. These preliminary results and the implication of these findings, as well as future directions of ONDRI will be discussed.

EpLink

Outcomes of pediatric epilepsy surgery: does neuropsychological function change over time?

Dr. Mary Lou Smith, Department of Psychology, University of Toronto Mississauga
Senior Associate Scientist, Neurosciences and Mental Health Program, Hospital for Sick Children, Mississauga, ON.

Introduction: Children with epilepsy are at increased risk for cognitive and behavioural dysfunction, and greater severity of deficits is associated with longer duration of epilepsy disorder and earlier age of onset. It has been hoped that improved seizure control from epilepsy surgery in children would lead to improved cognitive and psychosocial functioning. The rationale for such hope rested on three assumptions: that seizures interfere with brain functioning and their elimination will increase the likelihood of achieving optimal cognitive and psychological attainments; that the cognitive and psychosocial sequelae of epilepsy may not be as entrenched in childhood as they would be later in life, and earlier intervention is a form of prevention; and, that the capacity for plasticity in the young brain will allow for restitution or reorganization to support further development. Therefore, in evaluating the outcome of surgery, an important question is whether surgery has altered the course of development as it would have unfolded had the child continued to have seizures.

Methods: In this talk I review my research on the long-term neuropsychological outcomes of pediatric epilepsy surgery, with emphasis on intellectual and memory function. Participants were followed 4-11 years after surgery, and their performance was compared with individuals with childhood-onset epilepsy who did not undergo surgery. Results: There were minimal changes associated with seizure freedom at the time of follow-up.

Conclusions: The results suggest that the effects of plasticity are limited, and that major changes in cognition after pediatric epilepsy surgery should not be anticipated.

POND

Neurodevelopmental disorders: the case of lumping

Dr. Evdokia Anagnostou, Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital

Neurodevelopmental disorders are prevalent, persistent, impairing and costly. Family and twin studies clearly implicate genetic risks in neurodevelopmental disorders and clinical studies indicate that these disorders are characterized by atypical features in neural structure, function, and physiology as well as cognition, language, emotion regulation and behavior.

Although the field has made significant gains, our ability to change long term outcomes remains limited. The development of novel treatments for neurodevelopmental disorders has been hampered by a number of key factors, including our limited understanding of the biological mechanisms underlying these disorders, limiting our choice of molecular targets, the lack of specificity of emerging biological mechanisms to any single diagnostic entity, and the lack of biomarkers and specific phenotypes to stratify patients into more homogeneous subgroups than groupings predicted by existing nosological categories.

To address these gaps, we have created the Province of Ontario Neurodevelopmental Disorders (POND) Network, an integrated discovery system to perform biomedical research studies aimed at understanding the biology of ASD, ADHD, ID, OCD, and rare neurodevelopmental disorders. Within POND we discover that which is shared and that which is unique to these disorders. This presentation will focus on lessons learned about what is shared from genomic and imaging work and will highlight early insights from the first clinical trials.

Symposium 3 – Gut-brain axis

Characterizing the functionality of the microbiome and understanding the gut-brain axis

Dr. Jonathan Swann, Imperial College, UK.

Metabolic phenotyping (metabonomics/metabolomics) allows the biochemical output of the microbiome and its biomolecular interactions with the host to be measured. Integrating metabonomics with other systems biology approaches, such as metataxonomics and host transcriptomics, enables a high-resolution overview of the multicomponent supra-organism and a deeper understanding of the gut microbial role in health and disease. One area of great interest is the gut-brain axis and the application of such approaches is helping to illuminate the metabolic exchange that occurs through these complex communication networks. This presentation will show metabolic changes in depressed individuals and healthy individuals.

A potential new mechanism by which microbiota affect CNS function

Dr. Rochellys Heijtz, Department of Neuroscience, Karolinska Institutet, Retzius väg 8, 171 77 Stockholm, Sweden.

Recent animal studies from our laboratory and other groups have revealed that the gut microbiota has much wider effects on host physiology and development than originally believed, including the early-life programming of brain circuits involved in the control of emotions, motor activity, and social behavior. However, the cellular and molecular mechanisms mediating interactions between the gut microbiota and the developing brain remain poorly understood. Recently, we discovered that fragments of bacterial peptidoglycan (PGN; a major component of the bacterial cell wall) derived from gut microbiota can cross the blood brain barrier under normal conditions and influence the developing brain via activation of pattern recognition receptors (PRRs). Using various expression-profiling techniques, we showed that two families of PRRs that specifically detect PGN fragments (PGN recognition proteins and NOD-like receptors) are highly expressed in the developing brain during critical windows of postnatal development. In addition, we demonstrated that the expression of several of these PGN-sensing molecules are sensitive to manipulation of the gut microbiota (germ-free conditions and antibiotic exposure in early life). Finally, we demonstrated that the absence of PGN recognition protein 2 leads to alterations in the expression of the autism risk gene *c-Met*, and sex-dependent changes in social behavior in juvenile mice. These findings suggest that the central activation of PRRs by microbial products could be one of the signaling pathways mediating the communication between the gut microbiota and the developing brain.

Mood and microbes – the influence of microbiota on stress circuitry and behaviour

Dr. Jane Foster, Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON.

Introduction: Excitement has been generated in mental health research by recent findings from animal and clinical studies demonstrating an important role for gut microbiota in brain function and behaviour. Scientists have established a link between gut bacteria and anxiety-like behaviours in animal models and with emotional brain regions in healthy people. Work to date by our group and others suggest that microbiota influence brain structure, gene expression of stress-related and plasticity-related genes, stress-reactivity, and behaviour. Our initial results revealed that germ-free mice showed reduced anxiety-like behaviour in the elevated plus maze, a well-established behavioural test that examines approach and avoidance behaviour in mice, in comparison to specific pathogen free mice. The low anxiety-like behavioural phenotype observed in germ-free mice was accompanied by long-term changes in plasticity-related genes in the hippocampus and amygdala.

Methods: Using different mouse strains that show natural differences in anxiety-related behaviour, we have examined the link between microbiota and behaviour. Bacterial community profiling of 16SrRNA gene was carried out using a modified bar coded Illumina sequencing method in the McMaster Genome Center in male and female Balb/C, C57Bl/6, and FVB mice.

Results: Strain-specific differences in microbiota diversity were observed with reduced alpha diversity in Balb/C mice compared to C57Bl/6 and FVB. Beta diversity analysis revealed strain-specific differences in microbiota composition; principal coordinates analysis (PCoA) showed 3 distinct clusters separated by strain. The taxonomic profile of the microbiota showed significant strain differences in relative abundance of clinically commensals such as *Bifidobacterium*, *Lactobacillus*, *Alistipes*, and *Prevotella*. We also examined whole brain structure using high resolution ex vivo magnetic resonance imaging to determine the association of microbiota and brain structure in different strains of mice. Initial analysis of several significant strain differences in normalized brain volume in several key brain regions implicated in stress-related behaviour.

Conclusion: Our results show that microbiota and host genetics influence behaviour and brain structure - deciphering the molecular mechanisms involved is necessary to advance the use of microbiota-targeted therapies for use in clinical populations.

Probiotics as a novel therapeutic in a clinical sample of depressed patients

Caroline Wallace, Centre for Neuroscience Studies, Queen's University, Kingston, ON.

Preclinical and clinical studies have shown that consuming probiotics can improve mood, anxiety, and cognition, as well as alter brain activity in both rodents and healthy humans. It is hypothesized that these outcomes may be driven by probiotics reducing overall levels of inflammatory markers, as well as by indirectly increasing serotonin availability. This talk will focus on preliminary findings from our recent open-label, 8-week pilot study assessing the effects of a probiotic supplement containing *Lactobacillus helveticus* and *Bifidobacterium longum* (Probio'Stick, Lallemand Health Solutions) on symptoms of depression including mood, anhedonia, anxiety, and sleep quality in treatment-naïve patients. Plans outlining our double-blind randomized placebo-controlled expansion study, which will collect clinical, sleep, neuroimaging, and molecular data from a similar patient population consuming Probio'Stick, will also be discussed.

CCNP Next Generation Presentation 2**Effects of endogenous neuropeptides in the bed nucleus stria terminalis and changes in chronic stress-induced anxiety-like behaviour**

Catherine P. Normandeau, Ana Paula Ventura Silva, Emily R. Hawken, Staci Angelis, Calvin Sjaarda, Xudong Liu, José Miguel Pêgo, Éric C. Dumont

Chronic stress is a major cause of anxiety disorders that can be reliably modeled pre-clinically. Stress-mediated deregulation of the bed nucleus of the stria terminalis (BNST) is strongly associated with anxiety-like behaviours. We hypothesized that chronic stress alters neuropeptidergic modulation of BNST synaptic transmission that can precipitate anxiety disorders. Uncovering these changes may provide much needed insight into alternative therapeutic targets for this mental health illness. We use brain slice neurophysiology and behavioural pharmacology to compare the role of locally released neuropeptides on synaptic transmission in the oval (ov) BNST of non-stressed (NS) or chronic unpredictably stressed (CUS) rats. We found that post-synaptic depolarization induced the release of vesicular neurotensin (NT) and corticotrophin releasing factor (CRF) which co-acted to increase ovBNST inhibitory synaptic transmission in 59% of recorded neurons. CUS bolstered this potentiation (100% of recorded neurons) through an enhanced contribution of NT over CRF. In contrast, locally-released opioid neuropeptides decreased ovBNST excitatory synaptic transmission regardless of stress. Consistent with CUS-induced enhanced contribution of the modulatory effects of NT, blockade of ovBNST neurotensin receptor 1 and 2 (NTR1/2) completely abolished stress-induced anxiety-like behaviours in the elevated plus maze paradigm. Our data highlights NT as a key link of chronic stress-induced anxiety behaviours. This is a novel finding as up until now, NT has been largely overlooked.

DRD4 exon 3 genotype as predictor of symptom severity and treatment outcomes in children with ADHD: gene-treatment and gene-environment interaction study

Darya Naumova (^{1,2}), BSc; Sarojini M. Sengupta ^{2,3}, PhD; Natalie Grizenko (^{2,3}), MD; and Ridha Joobar (^{1,2,3}), MD PhD. (¹) Department of Human Genetics, McGill University, Montreal, Quebec, Canada (²) Douglas Mental Health University Institute, Montreal, Quebec, Canada (³) Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Both genetic and environmental factors have been implicated in the etiology of ADHD, but there is a need for further characterisation of the risk factors. This study presents a comprehensive analysis of the role of dopamine receptor 4 (DRD4) gene polymorphism in childhood ADHD. First, we examine the effect of DRD4 exon 3 genotype on response to methylphenidate (MPH). Second, we explore an interaction between the genotype and exposure to maternal stress during pregnancy and their effect on symptom severity in children with ADHD.

Methods: Children (ages 6-13) were recruited from an ongoing 2-week, placebo-controlled, double blind, crossover trial at the Douglas Institute (Montreal, QC). Response to MPH was evaluated by parents and teachers using Conner's Global Index; information on symptom severity was extracted from Child Behavioral Checklist (CBCL) questionnaire completed by the parents; stress during pregnancy was classified into low (no and mild) and high (moderate, severe and extreme). DNA samples were collected and extracted from 404 subjects. Subject were divided into three genotype groups: homozygotes for short alleles, homozygotes for long alleles, and heterozygotes for both.

Result: There was a significant interaction between DRD4 genotype and treatment course ($p=.037$, effect size of 0.013). Homozygotes for long allele had a better response to placebo, and lower symptomatology at both placebo and active medication weeks, as evaluated by parents. There was a significant effect of gene-by-environment interaction ($p=.003$, effect size of 0.030) on overall CBCL score.

Conclusion: According to the parents, children homozygous for long DRD4 exon 3 allele should better response to MPH. In addition, an interaction between genotype and high stress during pregnancy resulted in significantly higher CBCL scores, reflecting more behavioral problems in these children. The results suggest DRD4 genotype could be used to predict the strength of treatment and clinical outcomes in children with ADHD.

CCNP Young Investigator Award Lecture

Insights from applying systems neuroscience in psychosis

Dr. Lena Palaniyappan, Western University

A striking feature of psychosis is the heterogeneity of its presentation. Psychosis-like experiences occur in the general population, often without notable functional consequences; in psychiatric clinics, the course of psychosis varies from being a single, time-limited episode on one end of the spectrum to a tenacious illness on the other extreme, with a wide range of variable trajectories. Even among patients with schizophrenia, who are diagnosed on the basis of persistent deterioration, marked variation is present in response to treatment, frequency of relapses and degree of eventual recovery. In this review, I make an attempt to link several existing notions on the biology of psychosis with the variant clinical trajectories using the perspective of Systems Neuroscience. To this end, I first briefly review the concept of symptom resolution in psychosis and the evidence linking psychosis in general, and schizophrenia in particular, to cellular and systems level brain connectivity. Existing ideas about the role of brain development, degeneration and plasticity will be invoked to show how the concept of brain network-level homeostasis can give an account of the varied course of psychosis. I also argue that resolution of psychotic symptoms requires intact homeostatic processes, which when aberrant, inhibit a fuller recovery. My aim is to put forward a thesis that could be invoked during the clinical dialogue with a concerned carer wondering why his/her loved one is presenting so differently from another patient attending the same treatment program.

IDP Symposium 2 – Reverse translation

ONDRI

Deep phenotyping of neurodegenerative diseases: a tale of translation and reverse translation

Dr. Douglas Munoz, Centre for Neuroscience Studies, Queen's University, Kingston, ON.

The Ontario Neurodegenerative Disease Research Initiative (ONDRI) is a provincial collaboration studying dementia and how to improve the diagnosis and treatment of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, and vascular cognitive impairment resulting from stroke. Patients are being recruited into a multidisciplinary study designed to produce deep phenotyping of disease processes using platforms that include genetics, neuroimaging, neuropsychological testing, eye tracking, retinal imaging, and analysis of gait and balance. This approach is providing unprecedented detail of neurodegenerative processes within ONDRI. In parallel, monkey models of neurodegenerative diseases are being developed and validated against the ONDRI dataset. Specifically, animal models are validated with molecular biomarkers, neuroimaging, neuropsychological testing, and eye tracking. This translation – reverse translation approach is

critical for future development of therapeutics that can translate effectively to human use. Supported by OBI, CIHR and Brain Canada.

POND

Neurodevelopmental disorders: the case for splitting

Dr. Jason Lerch, University of Toronto, Hospital for Sick Children

Identifying the boundaries of disorders is an important challenge: a good case can be made for grouping multiple childhood mental health disorders into a single, larger group of neurodevelopmental disorders. Conversely, one can argue that the existing disorders, such as autism, need to be split into separate, smaller categories. I will use a mix of genetic and brain imaging data in human populations and mouse models to make the case for splitting. In particular, I will argue that rare mutations are driving important aspects of the phenotype, with different mutations associated with different phenotypic signatures. I will conclude with preliminary attempts to group autism related mutations into a smaller set of core phenotypes.

CAN-BIND

Fishing for biomarkers of depression: molecular and reverse translation insights from the CAN-BIND program

Dr. Brock Schuman, Keenan Research Centre for Biomedical Science of St. Michael's Hospital, Toronto, ON and Dr. Juan Pablo Lopez, McGill Group for Suicide Studies, McGill University, Montreal, Quebec, Canada; Max Planck Institute of Psychiatry, Munich, Bavaria, Germany

Introduction: Antidepressants (ADs) are the most common treatment for major depressive disorder (MDD). However, only about 30% of patients experience adequate response after a single AD trial, and this variability remains poorly understood. Here, we investigated microRNAs (miRNAs) as biomarkers of AD response, and their applicability for reverse translation and high-throughput drug discovery in zebrafish.

Methods: MiRNAs were identified using small RNA-sequencing in paired samples from MDD patients enrolled in a large, randomized placebo-controlled trial of duloxetine collected before and eight weeks after treatment. Validated miRNAs were further explored in both zebrafish embryos and adults subjected to a novel behavioural paradigm, which was validated with 7 clinically used antidepressants.

Results: Our results revealed differential expression of miR-146a-5p, miR-146b-5p, miR-425-3p and miR-24-3p according to treatment response. These results were replicated in two independent clinical trials of MDD, a well-characterized animal model of depression, and post-mortem human brains. Using a combination of bioinformatics, mRNA studies and functional in vitro experiments, we showed significant dysregulation of genes involved in MAPK/Wnt signaling pathways. Furthermore, these results were conserved in zebrafish.

Conclusions: Together, our results indicate that these miRNAs are consistent markers of treatment response and regulators of the MAPK/Wnt systems and may be exploited for high-throughput drug screening with zebrafish embryos. Our zebrafish behavioural model is applicable to both male and female animals, and can differentiate depression-like symptoms from anxiety.

CP-NET

Sex, drugs and neural repair

Rebecca M. Ruddy¹, Kelsey Adams¹, Daniel Derkach¹ and Cindi M. Morshead²
Institute of Medical Science¹, Division of Anatomy, Department of Surgery², University of Toronto, Toronto, Ontario, Canada.

Metformin, a drug typically used to treat type II diabetes, has been shown to promote neurogenesis and represents a promising repair strategy following brain injury. Metformin

treatment leads to the expansion of the neural precursor cell (NPC) pool, enhanced neurogenesis and oligogenesis, and functional motor recovery in a rodent model of cerebral palsy (hypoxic-ischemic insult). More recently, we have demonstrated that the hypoxic-ischemic insult also leads to cognitive impairments and we explored the potential for metformin treatment to rescue this impairment. Interestingly, our findings revealed that chronic post-injury metformin treatment led to the rescue of cognitive deficits in females, but not males. This striking observation has led us to consider the role of the NPC microenvironment (the niche) in regulating metformin's effects on NPCs and neural repair. We investigated how the factors of age, sex and brain region modulate the response of NPCs to metformin in the intact and injured brain. We performed a number of in vitro and in vivo assays and found that the NPC niche through age, and across brain regions and sex, have significant impact on NPC activation. Taken together, these findings reveal that the stem cell niche plays a crucial role in the regulation of the NPC response to metformin, and that metformin treatment has the potential to differentially rescue cognitive function following brain injury.

*Poster Session I – Thursday, June 08, 2017
13:00 – 14:00 – Gibraltar Room*

1. The role of serotonergic genes in influencing suicide attempt and suicidal ideation in patients with major depression

Ali Bani-Fatemi, Vincenzo De Luca, Eric Lenze, James L. Kennedy, Charles F. Reynolds, Benoit H. Mulsant

Background: Familial, adoption, and twin studies suggest that suicidal behavior is genetic and heritable. However, suicidal ideation does not seem to be linked to a family history of suicidal ideation as clearly as suicide attempt. On the other hand, a family history of a suicide attempt predicts a higher frequency of suicidal ideation. Unfortunately, the majority of findings drawn from the candidate gene studies in suicidal behavior are inconsistent. The proposed project was aimed to identify the genetic variants in the selected serotonin genes that are related to suicide attempt and suicidal ideation.

Methods: Genomic DNA was extracted from 466 older adult patients with a diagnosis of Major Depressive Disorder (MDD). Twenty-one polymorphisms located in eight serotonin genes were genotyped using Taqman Array. Suicide attempt was assessed using a Suicide History Questionnaire and suicidal ideation was assessed by the Suicide Ideation Scale. The genetic variants of each gene were compared between suicide attempters and non-attempters and also between patients with and without suicidal ideation using Pearson chi-square.

Results: We found that the 5HTT-VNTR in intron 2 of 5HTT, and the short and G allele (rs25531) of HTTLPR is significantly associated with suicide attempt. However, these variants were not significantly associated with suicidal ideation.

Discussion: This study suggests that the G allele in the HTTLPR region should be considered as a single marker in the studies aimed to find genetic predictors for suicide attempt. Future studies should aim to identify variants associated with suicidal ideation in MDD.

2. Clinical utility of a short resting state MRI scan in differentiating bipolar from unipolar depression

Mingli Li¹²³ MD, Tushar Das⁴⁵⁶ PhD, Wei Deng¹²³ MD, Qiang Wang¹²³ MD, Yinfei Li¹²³ MD, Liansheng Zhao¹²³ PhD, Xiaohong Ma¹²³ MD, Yingcheng Wang¹²³, Hua Yu¹²³ MD, Xiaojing Li¹²³ MD, Yajing Meng¹²³ MD, Lena Palaniyappan^{456**} MD&PhD, Tao Li^{123**} MD&PhD ¹Mental Health Center, West China Hospital of Sichuan University, Chengdu, P R China ²State Key Laboratory of Biotherapy, Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, P R China ³West China Brain Research Center, West China Hospital of Sichuan University, Chengdu, P R China ⁴Robarts Research Institute & The Brain and Mind Institute, University of Western Ontario, London, Ontario, Canada ⁵Department of Psychiatry, University of Western Ontario, London, Ontario, Canada ⁶Lawson Health Research Institute, London, Ontario, Canada. Corresponding authors: **Dr Tao Li, Mental Health Center, West China Hospital, Sichuan University, Chengdu, Sichuan, P R China; Email: litaohx@scu.edu.cn, Tel: +86-28-8⁵⁴²³⁵6¹, Fax: +86-28-8⁵⁴²²⁶3². Or Dr Lena Palaniyappan, Prevention & Early Intervention Program for Psychoses (PEPP), A²⁻⁶36, LHSC-VH, 800 Commissioners Road, London, Ontario N6A ⁵W9, Canada, Ph: (⁵¹⁹) 68⁵-8⁵⁰⁰ ext. ⁵⁸⁰5⁴ Email: lpalaniy@uwo.ca

Objective: Depression in bipolar disorder (BipD) requires a distinct therapeutic approach from unipolar major depressive disorder (UniD); but to date no reliable methods could separate these two. The aim of this study is to establish the clinical validity and utility of a non-invasive functional MRI-based method to classify BipD from UniD.

Method: The degree of connectivity (degree centrality or DC) of every small unit (voxel) with every other unit of the brain was estimated in 22 patients with BipD and 22 age, gender and depressive

severity matched patients with UniD and 22 healthy controls. Pattern classification analysis was carried out using a support vector machine (SVM) approach.

Results: DC pattern from 6-minutes resting fMRI discriminated BipD from UniD with an accuracy of 86% and diagnostic odds ratio of 9.6. DC was reduced in the left insula and increased in bilateral precuneus in BipD when compared to UniD. In this sample with a high degree of uncertainty (50% prior probability), positive predictive value of the DC test was 79%.

Conclusion: DC maps are potential candidate measures to separate bipolar depression from unipolar depression. Test performance reported here requires further pragmatic evaluation in regular clinical practice.

3. Antipsychotic-induced hypothalamic inflammation as a potential mediator of metabolic side effects

Chantel Kowalchuk, BSc a, b, Denise Belsham, PhD c, d, Gary J. Remington MD, PhD, FRCPC a, b, e, Margaret K. Hahn, MD, PhD, FRCPC a, b, e a Centre for Addiction and Mental Health, Toronto, Ontario, Canada b Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada c Department of Physiology, University of Toronto, Toronto, Ontario, Canada. d Departments of Medicine and Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada. e Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Introduction: Antipsychotics (AP)s are the cornerstone treatment for schizophrenia but cause serious metabolic dysregulation. The hypothalamus is the primary brain region responsible for energy regulation, and inflammation in this region has been implicated in impaired energy homeostasis resulting in insulin resistance and weight gain. Thus, hypothalamic inflammation could be involved in the metabolic disturbances seen with AP use.

Methods: The rat hypothalamic cell line, rHypoE-19, was treated with 100uM of olanzapine. Quantitative real-time PCR was performed to determine changes in the mRNA expression of tumor necrosis factor (TNF- α), interleukin (IL)-6, and brain derived neurotrophic factor (BDNF), and western blot was used to detect changes in the activation of the insulin signaling pathway (IRS-AKT-GS3K), and components of the MAPK pathway (ERK1/2 and JNK), the latter which are linked to inflammation.

Results: There was a significant increase in BDNF and TNF- α expression with olanzapine treatment versus the control. There was a trend toward an increase in IL-6 expression with olanzapine treatment, but it was not significant. Olanzapine also significantly increased activation of ERK1/2, with a trend towards an increase in JNK.

Conclusions: Olanzapine increased the expression of TNF- α , and activated the MAPK pathway, suggesting that olanzapine can induce hypothalamic inflammation. Olanzapine also increased BDNF; this may potentially be therapeutic as decreases in BDNF have been linked to the underlying etiology of schizophrenia. Our findings suggestive of olanzapine-induced hypothalamic neuroinflammation may link to AP-induced metabolic dysfunction, while also suggesting a potential therapeutic mechanism through upregulation of BDNF.

4. The gut microbiome in schizophrenia and antipsychotic induced metabolic dysfunction

Kanji S¹, **Gorbovskaia I**¹, **Fonseka TM**¹, **Marshe VS**^{1,2}, **MacKenzie N**⁵, **Hahn M**^{3,4}, **Müller DJ**^{1,3,1}. Pharmacogenetics Research Clinic, Centre for Addiction and Mental Health, Toronto ON, Canada ². Institute of Medical Science, University of Toronto, Toronto, ON, Canada ³. Department of Psychiatry, University of Toronto, Toronto, ON, Canada ⁴. Complex Mental Illness, Centre for Addiction and Mental Health ²⁵⁰ College Street, Toronto ON, Canada, M^{5T} 1R8

Introduction: Antipsychotic (AP) medications are the cornerstone of treatment for schizophrenia (SCZ), with off-label prescription rapidly increasing. However, APs have been associated with metabolic side effects. Although several mechanisms have been proposed, the gut microbiome

(GMB) is a potential mediator of AP induced metabolic effects due to its role in metabolic regulation, as well as emerging evidence demonstrating a shift in the microbiome of AP treated animals and humans.

Purpose & Objectives: The purpose of the current study is to 1) Investigate the GMB in SCZ patients and healthy individuals. 2) To examine the influence of AP treatment on GMB and metabolic disturbances.

Methods: Three groups of 25 participants will be recruited. Group A: Long term clozapine (CLZ) treated patients (minimum 6 months). Group B: Healthy controls matched with Group A for BMI, age, sex and smoking status. Group C: Treatment naive SCZ patients starting an AP or newly switching to CLZ. Groups A and B will be assessed once (week 0) whereas Group C will be assessed prospectively at weeks 0, 3 and 12. Stool samples, anthropometric and metabolic indices will be collected at each time point. PROGRESS: To date, more than 50 patients have been screened, 14 enrolled (13 patients in group A, 1 control in group B, 2 in group C) and 13 have completed the study.

Conclusion: To our knowledge, this is the first study assessing GMB in adult schizophrenic patients. Our pilot study proves feasibility regarding recruitment and has potential to help unravel the role of GMB in SCZ and outcome to antipsychotic medications.

5. Using an emotional saccade task to establish behavioural biomarkers in attention-deficit hyperactivity disorder and bipolar disorder

Rachel Yep, MSc ⁽¹⁾, Donald C. Brien, MSc ⁽¹⁾, Brian C. Coe, PhD ⁽¹⁾, Alina Marin, MD, PhD ⁽²⁾, Douglas P. Munoz, PhD ^(1,3) ⁽¹⁾ Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada, ⁽²⁾ Department of Psychiatry, Hotel Dieu Hospital, Kingston, Ontario, Canada, ⁽³⁾ Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada

Introduction: Despite distinct differences in age of onset and core symptoms, attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) share cognitive and emotional processing deficits that can make differential diagnoses difficult. In order to better characterize these two disorders, we compared ADHD and BD performance on a saccade paradigm designed to probe both executive functioning and emotional processing. We hypothesize that patient groups will be differentiated from controls on the basis of executive functioning performance, and that patient groups will be differentiated from one another on the basis of emotional processing performance.

Methods: Healthy controls, ADHD, and BD participants performed an interleaved pro/antisaccade task (look towards vs. look away from a visual target, respectively) in which the gender of emotional faces (happy, sad, fearful, angry, neutral) acted as the directional cue to perform either the pro or antisaccade. Saccade behavior, including saccadic reaction time and direction error percentage, was compared between pro/antisaccade trials, face stimuli, and participant groups.

Results: Saccadic reaction time and direction error performance was significantly worse on antisaccade trials compared to prosaccade trials, with ADHD and BD groups making more direction errors than controls on antisaccade trials. The presentation of emotional face stimuli, particularly negatively valenced and neutral faces, differentially affected the behavioural performance of ADHD and BD groups.

Conclusion: Performance on this saccade paradigm is capable of identifying subtle differences between ADHD and BD that traditional clinical assessments may not be sensitive enough to capture. The findings presented here suggest that executive dysfunction is a key deficit in both patient groups, and that it is differentially impaired when recruitment of emotional processing systems is also required. Further characterization of how these processing systems interact in ADHD and BD could be used to develop psychiatric endophenotypes to help improve diagnoses.

6. Changes in beta-actin and beta-tubulin immunodetection in Alzheimer disease brain samples suggest region- and sex-dependent mechanisms in disease progression

Jennifer N.K. Nyarko, Ph.D; Maa O. Quartey, Ph.D; Ryan M. Heistad; Paul R. Pennington; Darrell D. Mousseau, Ph.D. Department of Psychiatry, University of Saskatchewan, Saskatoon, SK, Canada

Introduction: Changes in the cytoskeleton (beta-tubulin, beta-actin etc) cause cells to lose their structure and connectivity with neighbouring cells. In the Alzheimer disease (AD) brain, it is abnormal phosphorylation of the Tau protein (associated with the hallmark 'neurofibrillary tangle') that is thought to trigger much of this structural change, and disease progression is thought to follow a temporal pattern, i.e. neurofibrillary pathology appears in hippocampus first, then in cortex.

Methods: We used standard western blotting to examine the expression of beta-tubulin, beta-actin, and phosphoSer396-Tau (pS396-Tau: associated with the paired helical filament conformation that precedes the formation of the neurofibrillary tangle) in autopsied AD (early-onset: EOAD; late-onset: LOAD) cortical and corresponding hippocampal samples.

Results: Levels of pS396-Tau were comparable between cortical and hippocampal samples, and were primarily increased in the EOAD samples, regardless of the sex of the donor. The levels of beta-tubulin were decreased only in hippocampal AD samples (regardless of sex). In contrast, levels of beta-actin were decreased in both cortical and hippocampal EOAD and LOAD samples, but only in females. Any decrease in beta-actin immunodetection in males was limited to EOAD samples. A gnuplot of these data reveals a proportionally greater change in beta-actin in female AD cortex, whereas in males with LOAD the change is proportionally skewed towards a loss of beta-tubulin in the hippocampus. The changes in beta-tubulin align with signaling changes (i.e. cofilin, LIMK1, but not GSK-3beta), whereas the decrease in beta-actin align with diminished beta-ACTIN mRNA expression.

Conclusion: The loss of beta-actin and beta-tubulin in AD samples are far more consistent than the aberrant phosphorylation of Tau protein. While a loss of either beta-actin or beta-tubulin would alter connectivity and ultimately a cognitive phenotype, different mechanisms appear to be involved which could explain the sex-dependent risks and differences in AD progression.

7. Statins and cognition in late-life bipolar disorder

Soham Rej MD, MSc^{1,2,3}, Sarah Waters Schulte BSc^{1,2}, Tarek K Rajji MD^{1,2}, Ariel G Gildengers MD⁴, Saeid Noohi BSc^{3,5}, Dielle Miranda MA^{1,2}, Mahesh Menon PhD⁶, Meryl A Butters PhD⁴, Benoit H Mulsant MD, MS^{1,2,1} Department of Psychiatry, University of Toronto, Toronto, ON, Canada² Department of Psychiatry, Centre for Addiction and Mental Health, Toronto, ON, Canada³ Department of Psychiatry, Jewish General Hospital, McGill University, Montreal, QC, Canada⁴ Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA⁵ Faculty of Medicine, Columbia University, New York City, NY, USA⁶ Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

Introduction: Recent data suggests that statins have positive effects on cognition in older adults. Studies in patients with mood disorders have found contradicting positive and negative effects of statins on mood and cognition, with limited data in bipolar disorder (BD). The objective of this study was to assess the association between statin use and cognition in older adults with BD.

Methods: In a cross-sectional sample of 143 euthymic participants with BD, statin users (n=48) and non-users (n=95) were compared for cognitive outcomes: Global and cognitive domain Z-scores were calculated from detailed neuropsychological batteries using normative data from healthy comparators (n=87).

Results: Statin users did not differ from non-users on global (-0.60 [+/-0.69] vs. -0.49 [+/-0.68], t[127]= 0.80, p=0.42) or individual cognitive domains Z-score.

Conclusion: In older patients with BD, statin use is not independently associated with cognitive impairment. This suggests that in older BD patients, the cognitive dysfunction associated with BD trumps the potential cognitive benefit that is associated with statins in older adults without a

psychiatric disorder. Further, statins don't seem to exacerbate this dysfunction. Future longitudinal studies are needed to confirm these findings.

8. Evaluating changes in factors associated with suicidal thinking using the suicide ideation and behavior assessment tool (sibat)

Larry Alphs¹, Carla M. Canuso², David Williamson¹, Rosanne Lane², Marsha Wilcox² ¹ Janssen Scientific Affairs, LLC, Titusville NJ, USA ² Janssen Research and Development LLC, Titusville, NJ, USA

Objective: A promising new instrument, the Suicide Ideation and Behavior Assessment Tool (SIBAT), combines patient report, patient performance on an implicit association task, and clinician judgment in a flexible, module-based format. Our recent clinical trial of intranasal esketamine in patients with major depressive disorder (MDD) at imminent risk of suicide allowed us to examine how patients' characterization of their thinking on these factors changes as a function of treatment.

Methods: A factor analysis of baseline data was performed on the "My Thinking" module of the SIBAT. This module assesses current suicidal thinking. A 7-factor solution was considered conceptually optimal. Subscales based on these factors were derived and named as follows: 1) Suicidality, 2) Hopelessness, 3) Protective Beliefs, 4) Worry and Guilt, 5) Orientation to Others, 6) Psychosis, and 7) Greater Purpose. Patients treated with esketamine plus standard of care (SoC) or placebo plus SoC were reassessed at 4 and 24 hours following treatment initiation with blinded assessments on the SIBAT. Total scores for each of the 7 component subscales were calculated and change from baseline to 4 and 24 hours calculated.

Results: Sixty-six individuals (55% between the ages of 18-34; 53% white) were randomized to receive esketamine plus SoC (n = 35) and placebo plus SoC (n = 31). Results characterize the changes seen across the identified subscales of the suicide thinking module from baseline to 4 hours and 24 hours posttreatment.

Conclusions: The SIBAT allowed comparison of standard and experimental treatment effect on suicidal thinking.

9. The role of the paraventricular nucleus of the thalamus in the augmentation of heroin seeking induced by chronic food restriction

Alexandra Chisholm, BAH, Department of Psychology, Concordia University, QC, Canada Damaris Rizzo, Department of Psychology, Concordia University, QC, Canada Natasha Gonzalez, Department of Psychology, Concordia University, QC, Canada Christina McAnulty, Department of Psychology, Concordia University, QC, Canada Emilie Fortin, Department of Psychology, Concordia University, QC, Canada Dr. Uri Shalev, PhD, Department of Psychology, Concordia University, QC, Canada

Introduction: Drug addiction is a chronic disorder that is characterized by compulsive drug seeking and involves switching between periods of drug abstinence and relapse. In both human and animal models of addiction chronic food restriction has been shown to increase rates of relapse. Our laboratory has demonstrated a robust increase in drug seeking following a period of withdrawal in chronically food-restricted rats. However, the neural mechanisms that mediate this effect have not been elucidated. The paraventricular thalamus (PVT) appears to be a promising candidate to investigate. The PVT is uniquely placed to contribute to both homeostatic control and drug seeking systems. Thus, the objective of the current study was to examine the effect of PVT inactivation on heroin seeking under food restriction conditions.

Methods: Male Long Evans rats were trained to self-administer heroin over the course of 10 days (0.1 mg/kg/infusion; i.v.). Following training, rats were removed from the operant conditioning chambers and experienced drug withdrawal for 16 days. Over the withdrawal period, rats were exposed to a mild food restriction (90% of end of training body weight) or were given unrestricted

access to food. On the 14th and 16th day of the withdrawal period, two drug-seeking tests were conducted in which rats were injected intra-PVT with either baclofen-muscimol (0.3/0.03 nmol) or vehicle, 5-10 minutes prior to test. PVT placement was verified histologically.

Results: All rats reliably learned to self-administer heroin. As expected, food-restricted rats demonstrated robust heroin seeking during the heroin-seeking test in comparison to sated rats. However, PVT inactivation did not alter heroin seeking regardless of the feeding condition.

Conclusions: These results suggest that PVT activity does not play a role in heroin seeking following prolonged withdrawal. Thus, PVT activity may not modulate the augmentation of heroin seeking following chronic food restriction.

10. PerSEVERe: a study of esketamine for the rapid reduction of the symptoms of major depressive disorder, including suicidal ideation, in patients assessed to be at imminent risk for suicide

Carla M. Canuso*, Jaskaran B. Singh, Maggie Fedgchin, Larry Alphs, Rosanne Lane, Pilar Lim, Christine Pinter, Hussein Manji, Wayne Drevets Neuroscience, Janssen Research & Development, Titusville, NJ, USA

Introduction: Major depressive disorder (MDD) is associated with an elevated rate of mortality, primarily due to suicide; risk of suicide in those with MDD is about 20 times that of the general population, with over half of all suicides occurring in depressed individuals. Preliminary studies of ketamine suggest it may have a rapid effect in significantly reducing suicidal ideation (SI) in patients with MDD. The objective of this study is to evaluate the efficacy of intranasal esketamine compared with intranasal placebo in reducing the symptoms of MDD, including SI.

Methods: PerSEVERe is a 12-week, randomized, double-blind, placebo-controlled, multicenter Phase 2 study of intranasal esketamine or placebo plus standard antidepressant medication in 68 adult patients with MDD who are assessed to be at imminent risk for suicide. The primary objective is to evaluate the efficacy of intranasal esketamine 84 mg compared with intranasal placebo in reducing the symptoms of MDD, including SI, as measured by the change from baseline on the MADRS total score at 4 hours post-dose on Day 1. Secondary efficacy objectives include the clinician's assessment of suicide risk as measured by the Suicide Ideation and Behavior Assessment Tool, and the patient's report of the severity in SI as measured by the Beck Scale for Suicide Ideation. Safety objectives include the assessment of transient perceptual changes, sedation, nasal tolerability, vital signs and suicidal thinking and behavior. Given the vulnerability of the patient population, the study was conducted in the context of standard clinical care, with all patients receiving initial in-patient hospitalization.

Results: Preliminary efficacy and safety results from the double-blind treatment phase will be presented.

Conclusion: PerSEVERe is the first multi-center placebo-controlled study of a potential rapidly acting antidepressant in patients with MDD who are assessed to be at imminent risk for suicide.

11. Intranasal esketamine in treatment resistant depression - a double-blind, randomized, efficacy and dose response study

Ella J. Daly¹, Jaskaran B. Singh^{1*}, Maggie Fedgchin¹, Kimberly Cooper¹, Pilar Lim¹, Caroline Melman², Hussein Manji¹, Luc Van Nueten¹, Richard C. Shelton³, Michael E. Thase⁴, Maha Ahmad⁵, Geert De Bruecker⁶, Wayne C. Drevets¹ Janssen Research & Development; ²Janssen-Cilag B.V., Netherlands; ³The University of Alabama at Birmingham, USA; ⁴University of Pennsylvania School of Medicine, USA; ⁵Clinilabs, Inc., USA; ⁶Psychiatric Hospital, Belgium

Introduction: Over one-third of patients with major depressive disorder (MDD) do not respond to currently available antidepressant therapies, and new therapies are warranted. This study assessed the efficacy, dose response, and safety of intranasal esketamine in patients with treatment resistant depression (TRD).

Methods: In this double-blind study, 67 participants with TRD received intranasal study medication twice weekly in two 1-week periods: in Period 1 participants were randomized [3:1:1:1] to placebo, esketamine 28, 56, or 84 mg twice-weekly; in Period 2 placebo-treated participants with moderate-to-severe symptoms were re-randomized [1:1:1:1] to one of the four treatment arms; those with mild symptoms stayed on placebo. The primary efficacy endpoint was change from baseline to day 8 (each period) in Montgomery-Asberg Depression Rating Scale (MADRS) total score. The double-blind treatment phase was followed by an up to 9-week open-label phase during which dosing frequency was reduced initially from twice weekly to weekly, and subsequently to every other week.

Results: Mean change in MADRS total score (both periods combined) in all 3 esketamine groups was superior to placebo (esketamine 28 mg: $p=0.021$, 56 mg: $p=0.001$, 84 mg: $p<0.001$), with a significant ($p<0.001$) ascending dose-response relationship. Improvement in depressive symptoms appeared to be sustained despite reduced frequency of dosing in the open-label period. The most common adverse events were dizziness, headache, and dissociation.

Conclusions: All three doses of intranasal esketamine were efficacious in treating TRD and were generally well tolerated. There was evidence of more robust efficacy at the higher doses and response to 56 mg and 84 mg doses appeared better sustained across the DB treatment period; the 28 mg dose had a less durable effect. Data suggests that efficacy was sustained over the OL phase, with a reduced frequency of intranasal treatment dosing.

12. Monoamine oxidase-A (MAO-A) and MAO-B catalytic activities do not reflect the expression of their respective proteins in autopsied human control and Alzheimer brain samples: implications for interpretation of the role of MAOs in neuropathology

Maa O. Quartey, PhD; Jennifer N.K. Nyarko, PhD; Paul R. Pennington; Ryan M. Heistad; Glen B. Baker, PhD; Darrell D. Mousseau, PhD MOQ, JNN, RMH, PRP, DDM: Department of Psychiatry, University of Saskatchewan, Saskatoon, SK GBB: Department of Psychiatry, University of Alberta, Edmonton, AB

Introduction: Monoamine oxidase-A (MAO-A) and MAO-B regulate neurotransmission by degrading biogenic amine neurotransmitters such as serotonin and dopamine. Changes in MAO function are thought to contribute to a range of brain pathologies, including depression and Alzheimer disease (AD).

Methods: We analyzed autopsied AD (early-onset: EOAD; late-onset: LOAD) cortical and corresponding hippocampal samples for MAO-A/B mRNA and protein expression, and catalytic activity. We also measured levels of major acid metabolites of serotonin and dopamine, i.e. 5-hydroxyindoleacetic acid, homovanillic acid, and dihydroxyphenylacetic acid.

Results: MAO-A and MAO-B catalytic activities were strongly correlated in cortical samples (across all diagnoses), but in hippocampal samples any such correlation was limited to control samples. MAO-A activity and protein were correlated in control cortical samples, but not in cortical AD samples; in contrast, MAO-B activity and protein expression correlated only in hippocampal AD samples. We also observed changes in MAO-A and MAO-B activities that aligned specifically with the donor's biological sex. Levels of acid metabolites, while aligning with diagnoses, did not align well with MAO activity. **Conclusion:** There are very important region- and sex-dependent changes in MAO-A and MAO-B activity in the AD brain. This suggests different disease processes in males and females, which could account for differences in risk as well as inform on specific pharmacological strategies for intervention. It is also important to be aware of the mismatch between MAO activity and MAO protein expression in the human brain, as this suggests different pools of MAO exist (some active; some not). This mismatch needs to be duly considered when using genotyping or neuroimaging to inform on MAO function in the clinical context.

13. Serotonin transporter gene methylation in peripheral tissues in healthy adults: neural correlates and tissue specificity

Ismaylova E. MSc, Di Sante J. BSc, Szyf M. PhD, Nemoda Z. PhD, Yu W-J. MSc, Pomares F.B. PhD, Turecki G. PhD, Gobbi G. PhD, Vitaro F. PhD, Tremblay R.E. PhD, Booij L. PhD Affiliations: Department of Psychiatry, CHU Sainte-Justine Research Centre and University of Montreal, Montreal, Canada; Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada; Department of Psychology, Concordia University, Montreal, Canada; Douglas Mental Health University Institute, Verdun, Canada; Department of Psychiatry, McGill University, Montreal, Canada; School of Psychoeducation, University of Montreal, Montreal, Canada; Department of Psychology and Pediatrics, University of Montreal, Montreal, Canada; School of Public Health, Physiotherapy and Sports Science, University College Dublin, Ireland; Department of Psychology, Queen's University, Kingston, Canada

Introduction: Early adversity may influence gene expression via such epigenetic mechanisms as DNA methylation. Using peripheral tissues is essential in psychiatric epigenetics since methylation generally cannot be assessed in the living human brain. Several studies combining peripheral methylation measures with magnetic resonance imaging (MRI) show associations between peripheral DNA methylation of the serotonin transporter gene (SLC6A4) with frontal-limbic function and/or structure, as well as with the brain's resting-state. Most commonly used samples in these studies are derived from blood, saliva or buccal cells. However, little is known regarding which peripheral tissue is most strongly associated with human brain processes. The aim of the present study was to compare the extent of the association between peripheral SLC6A4 methylation and frontal-limbic function, structure and brain's resting-state in healthy individuals across different peripheral tissues.

Methods: Forty healthy prospectively-followed adults (16 males; mean age of 34 years) underwent an anatomical, resting-state and functional MRI. DNA methylation measurement of blood, saliva and buccal samples was carried out by pyrosequencing.

Results: Saliva-derived SLC6A4 methylation was positively associated with superior frontal gray matter (GM) volume. Blood-derived SLC6A4 methylation was positively associated with superior frontal GM volume as well as with the resting-state functional connectivity between right lateral parietal area (RLP) and frontal pole. Buccal-derived SLC6A4 methylation was positively associated with superior frontal, inferior frontal and anterior cingulate cortical (ACC) GM volumes, as well as with the resting-state functional connectivity between RLP, frontal pole, ACC and medial prefrontal cortex (mPFC).

Conclusions: Current results confirmed the relevance of DNA methylation for frontal-limbic brain processes in humans. Buccal cells may be the most sensitive tissue when studying peripheral SLC6A4 methylation and its associated risk for neural vulnerability and resilience for psychopathologies in which serotonin plays an important role. Further studies are necessary to validate these data in clinical populations.

14. The relationship between inflammatory genes and cognitive flexibility among adolescents with bipolar disorder

Noreen Rahmani, BSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Pharmacology, University of Toronto, Toronto, Canada. Melanie R. Naiberg, HBMSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Pharmacology, University of Toronto, Toronto, Canada. Jessica Hatch, PhD, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Pharmacology, University of Toronto, Toronto, Canada. James L. Kennedy, MD, Psychiatric Neurogenetics, Centre for Addition and Mental Health, Toronto, Canada; Department of Psychiatry, University of Toronto, Toronto, Canada. Benjamin I. Goldstein, MD, PhD, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada.

Introduction: Inflammation is a leading candidate biomarker in bipolar disorder (BD). Findings suggest that inflammatory genes may play a key role underlying neurostructural and neuropathological aberrancies in BD. The question arises as to whether inflammatory genes are pertinent to neurocognitive deficits in BD. We examined the effects of interleukin (IL)-1B genetic variability on cognitive flexibility in BD adolescents. Secondary analyses focused on the effects of a composite variable, comprising IL-1B and three other inflammation-related single nucleotide polymorphisms (SNP), on cognitive flexibility in BD adolescents.

Methods: Participants were 42 BD (17.18 ± 0.27 years) and 54 healthy controls (HC) (16.02 ± 0.24 years). Semi-structured psychiatric interviews determined diagnoses. Genotyping was performed using standard Life Technologies TaqMan® procedures on the Applied Biosystems 7500 Sequence Detection for the following: IL-1B rs16944, IL-6 rs1800795, IL-10 rs1800896, and tumor necrosis factor alpha rs1800629. Saliva was collected using DNA Genotek Oragene-500 kits. Cognitive flexibility was assessed via the intra/extradimensional shift (IED) task (Cambridge Neuropsychological Tests Automated Battery).

Results: Within BD adolescents, IL-1B SNP allele (A) carriers completed more stages of the IED task than non-carriers ($U = 291.50$, $p = 0.004$). Number of risk inflammation-related alleles was significantly positively associated with reduced errors on the extra-dimensional stage of the IED task in BD ($r_s = 0.362$, $p = 0.020$). Inflammatory genotype was not associated with neurocognition among HCs.

Conclusion: Inflammation-related genes are relevant to cognitive flexibility deficits among BD only. Future studies are warranted to examine whether similar findings are observed for other neurocognitive tasks, and whether present findings are mediated by serum levels of inflammatory proteins.

15. Modulation of brain stimulation reward by ionotropic glutamate receptors in the tail of the ventral tegmental area

Marc Fakhoury, M.Eng a, Giovanni Hernandez, PhD a,b, Daniel Lévesque, PhD b, Pierre-Paul Rompré, PhD a, c a Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada. b Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada. c FRQ-S Research Group in Behavioral Neurobiology, Concordia University, Montreal, Quebec, Canada.

Introduction: Previous studies have shown that the ventral tegmental area (VTA) neuronal activity is modulated by afferents originating from the tail of the VTA (tVTA). Since tVTA cells receive a strong glutamatergic input, we assessed the impact of AMPA and NMDA glutamate receptor blockade locally into the tVTA on reward induced by lateral hypothalamus (LH) electrical stimulation.

Methods: Rats were first trained to self-administer electrical pulses in the LH. We then used the curve-shift method to obtain daily measures of reward threshold (M50 index) until stable responding was established ($< 12\%$ variation for three consecutive days). Rats were then injected bilaterally within the tVTA with either saline, the AMPA antagonist, NBQX (0.8 nmol/side), or the NMDA antagonist, PPPA (0.825 nmol/side) in a counterbalanced design. Reward thresholds and maximum response rates were determined before and after each injection. An additional test was performed with endomorphin-1 (EM-1; 1 nmol/side), a highly selective mu receptor agonist. In different rats, we investigated the impact of a decrease in the NMDA receptor subunit GluN1 on reward and operant responding using the small interfering RNA (siRNA) technique.

Results: Blockade of tVTA AMPA and NMDA receptors produced a time-dependent decrease in M50 (reward enhancement) with no change in maximum response rate. When injected into the rostral pole of the tVTA, PPPA, but not NBQX, produced a significant reward enhancement. In both regions, EM-1 produced a transient decrease in M50. Preliminary data also indicate that intra-tVTA infusion of siRNA against GluN1 causes a decrease in operant responding but no change in reward.

Conclusion: Results show that a reduction in glutamatergic excitatory input to the tVTA and a disinhibition by mu receptor activation lead to a selective enhancement of reward; they also suggest a role for tVTA NMDA receptors in operant responding.

16. Synergistic Effect of COMT and KIAA0319 genes in modulating ADHD behaviors

Weam Fageera, MSc^{1,2}, Natalie Grizenko, MD^{1,3}, Sarojini M. Sengupta, PhD^{1,3} and Ridha Joobar, MD, PhD^{1,2,3}. Douglas Mental Health University Institute, Montreal, Quebec, Canada.². Department of Human Genetics, McGill University, Montreal, Quebec, Canada.³. Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Background: ADHD and learning disorder (LD) are complex disorders with genetic and environmental determinants. Twenty to 30% of the children with ADHD have an associated LD. These problems usually persist into adolescence and are associated with chronic academic underachievement and failure to complete school.

Hypothesis: Given the evidence for overlapping heritability between ADHD and LD, we hypothesize KIAA0319, a gene associated with LD, may interact with genes that have shown to be implicated in ADHD. As proof of concept, we have selected the COMT gene because of the well-documented role of its Val/Met polymorphism in modulating dopamine transmission in the frontal cortex. We also anticipated that the interaction between these two genes would be more evident in the school environment.

Methods: 400 children with ADHD (9-12 years old) were included in a double blind placebo controlled study with methylphenidate. Teachers and parents were asked to evaluate the child's behavior at baseline, placebo, and MPH weeks using the appropriate version of Conners' scale. The association between genotypes and ADHD behaviors were tested using repeated measure ANOVA, the two genes were the between-subject factors and the behaviors under the three experimental conditions (EC), were the within-subject factor.

Results: A highly significant 3-way interaction (KIAA0319*COMT*EC) was revealed in two SNPs of the KIAA0319 gene (rs4504469 $p=0.006$ and rs7766230 $p=0.004$) only according to teachers. By stratifying the children according to their COMT genotypes, we found that within the Met/Met genotype group, there were no significant differences in Conner's-T scores at baseline and on Placebo. However, significantly different patterns of response to MPH between KIAA0319 genotype groups were observed.

Conclusions: This is the first study identifying an interaction between a gene involved in LD and a gene implicated in ADHD. This might help to individualize treatments for children with comorbid ADHD and learning disorders.

17. Olfactory functioning in depression and the effects of transcranial magnetic stimulation

Hannah C. Taalman,¹, Roumen V. Milev.² ¹ Centre for Neuroscience Studies, Queen's University, Kingston, ON ² Department of Psychiatry, Queen's University, Kingston, ON

Introduction: Research examining olfactory functioning in depressed individuals has indicated a reciprocal relationship between the two, with depression negatively impacting olfaction. Extensions of this research have demonstrated olfactory function improvement after successful pharmaceutical treatment of depression. It is, however, unknown if transcranial magnetic stimulation (TMS) has a similar effect. Our objective is to determine if individuals receiving TMS for depression exhibit improved olfactory functioning when there is baseline olfactory dysfunction. We hypothesize that depressed individuals will have significantly poorer olfactory functioning compared to controls before treatment, but there will be little to no difference between depressed and controls after successful treatment.

Methods: We recruited twenty depressed individuals receiving TMS at Providence Care Hospital, as well as ten age and gender matched healthy controls from the Kingston community. The

olfaction of depressed patients was tested before and 7-14 days after treatment using Sniffin' Sticks Expanded Test (examining olfactory threshold, discrimination, and identification). Depression severity was also tested using a number of scales, such as the Montgomery-Asberg Depression Rating Scale. Controls were tested in a similar manner with a 5-6 week waiting period in lieu of TMS.

Results: Preliminary results identified a significant difference in olfactory discrimination of depressed before TMS compared to after treatment ($t = -3.537$, $p = 0.003$). However, no other measures of olfaction or depression were significant within-subject. The preliminary analysis demonstrated a significant difference in depression scores between depressed and controls both before and after treatment ($p < 0.001$). No significant difference between the groups on olfactory scores with the exception of discrimination after treatment ($t = 2.180$, $p = 0.44$) where depressed performed significantly better than controls. Final results to follow.

Conclusions: We can conclude that while there is no difference between the olfactory functioning of depressed and controls at baseline, TMS treatment improves the discrimination ability of depressed such that they surpass controls.

18. GPR55 controls metabolic state-dependent bi-directional plasticity of GABA synapses

Emily R Hawken, Catherine P Normandeau, James Gardner Gregory, Bruno Cecyre, Jean-Francois Bouchard, Eric C Dumont

Evidence suggest the lysophospholipid-sensitive cannabinoid receptor GPR55 are integral to metabolism regulation and perhaps energy homeostasis; although, the brain loci and mechanisms remain completely unknown. Here, we investigated GPR55 neurophysiology in the rodent oval subregion of the bed nucleus of the stria terminalis (ovBNST), a collection of nuclei critical for adaptive energy metabolism. We observed metabolic state-dependent bi-directional plasticity of GABA synapses in the ovBNST. In sated rats, low-frequency stimulation (1 Hz/5mins) produces long-term potentiation of GABA_A-inhibitory postsynaptic currents (LTPGABA) that reverses to a CB1-dependent long-term depression (LTDGABA) after acute (24hr) food deprivation. We further discovered that the selective GPR55 antagonist CID16020046 (1 μ M) blocked LTPGABA, uncovering LTDCB1-GABA and that LTPGABA could be mimicked by the GPR55 selective agonist O-1602 (100nM) or the putative endogenous GPR55 ligand LPI (5 μ M). Consequently, our data suggest that GPR55 in a metabolic state-dependent way, determines the direction of bi-directional plasticity of ovBNST GABA synapses. These findings support a potential role of GPR55 in energy homeostasis and identify a potential novel target for eating disorders.

19. Structure and timing of cognitive training in schizophrenia: an EEG analysis

Robyn E. Cardy, BSc Centre for Neuroscience Studies, Queen's University, Kingston, ON Felicia Iftene, M.D., PhD, FRCP(C) Department of Psychiatry, Queen's University, Kingston, ON

Introduction: Recent efforts in the treatment of schizophrenia have focused on enhancing cognitive deficits, as research has demonstrated that cognitive impairments, rather than symptoms, are associated with concurrent and future functional outcome. A key challenge for Cognitive Remediation Therapy research is to determine what techniques and strategies provide the most benefit and how to effectively deliver them. The main purpose of this research is to determine which temporal structure for computerized cognitive training results in greater and more sustained EEG change in patients with schizophrenia: repeated 2-minute bursts of training and rest (for 20-minutes), or sustained 10-minutes of constant training (following 10-minutes of rest).

Methods: One-week after a baseline no-training cognitive assessment visit, participants ($n = 24$) were randomized into one of two training arms (burst or sustained training) and baseline, training, and testing EEG recordings were compared for superiority, with satisfaction questionnaires administered post-testing to determine contentment with training arm. Baseline symptoms of

schizophrenia are assessed before training using a self-report measure (Symptoms of Schizophrenia Inventory) to determine any between-group differences, and a satisfaction questionnaire (Intrinsic Motivation Inventory for Schizophrenia Research) administered post-testing determined contentment with training received.

Results: Recruitment is ongoing; preliminary results will be presented.

Conclusions: This research will inform effective and efficient structuring of cognitive training modules for schizophrenia to optimize delivery of CRT. By identifying the immediate functional brain wave changes of a single “dose” of cognition training in schizophrenia subjects, results will determine the validity of the NeuroNation Cognitive Training Program within this population by comparing the effect of training (Visit 2) to no-training (Visit 1). Lastly, this research will determine the more preferred structure and timing of cognitive training modules, to improve program adherence, increase patient satisfaction of therapy, and ultimately tailor cognitive training to the needs and preferences of patients.

20. The role of inflammatory genes on brain morphology in adolescents with bipolar disorder

Daniel O. Shonibare, BSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Pharmacology, University of Toronto, Toronto, Canada. **Alvi H. Islam**, MSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Pharmacology, University of Toronto, Toronto, Canada. **Ronak Patel**, BSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Institute of Medical Science, University of Toronto, Toronto, Canada. **Arron W.S. Metcalfe**, PhD, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Hurvitz Brain Sciences, Sunnybrook Research Institute, Toronto, Canada. **James L. Kennedy**, MD, Psychiatric Neurogenetics, Centre for Addition and Mental Health, Toronto, Canada; Department of Psychiatry, University of Toronto, Toronto, Canada. **Bradley J. MacIntosh**, PhD, Hurvitz Brain Sciences, Sunnybrook Research Institute, Toronto, Canada; Department of Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, Canada. **Benjamin I. Goldstein**, MD, PhD, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Canada; Department of Psychiatry and Pharmacology, University of Toronto, Toronto, Canada.

Introduction: Bipolar disorder (BD) is among the most heritable psychiatric conditions and is associated with increased pro-inflammatory biomarkers. We therefore examined the effects of three pro-inflammatory single nucleotide polymorphisms (SNPs; IL-1 β rs16944, IL-6 rs1800795, TNF- α rs1800629) and one anti-inflammatory SNP (IL-10 rs1800896) on brain structure in BD vs. healthy control (HC) adolescents.

Methods: Structural magnetic resonance imaging scans (3T) were performed on 41BD and 50HC adolescents (14-20 years). T1-weighted images were processed on FreeSurfer where cortical thickness, surface area, and volume were examined. Regions of interest included hippocampus, amygdala, dorsolateral prefrontal cortex, and caudal anterior cingulate cortex (cACC). General linear models included main effect of each polymorphism and an interaction term; controlling for sex, age, and total intracranial volume. Additionally, effects of cumulative numbers of SNP risk alleles on brain structure were examined.

Results: There was a significant main effect of IL-1 β rs16944 polymorphism, whereby T allele carriers had reduced cACC surface area ($p=0.013$; $?p=0.072$), cACC volume ($p=0.049$; $?p=0.045$), and greater hippocampal volume ($p=0.045$; $?p=0.047$). The effect of number of risk alleles was also significant for cACC surface area ($\beta=-80.5$, $p=0.022$; $?p=0.062$). There were no diagnostic group x SNP interaction effects.

Conclusions: The IL-1 β rs16944 polymorphism is associated with cACC surface area & volume, and hippocampal volume in BD and HC adolescents. Furthermore, cACC surface area is reduced in proportion with increasing number of risk alleles, suggesting a potential “dose” effect. Studies

are warranted to determine whether the observed associations are also related to symptom burden and/or neurocognitive dysfunction.

21. Neurite growth as an endpoint of neuroprogression in bipolar disorder

Bianca Wollenhaupt-Aguiar, PhD; Bianca Pfaffenseller, PhD; Vinicius de Saraiva Chagas, BSc; Mauro A A Castro, MD, PhD; Ives Cavalcante Passos, MD, PhD; Márcia Kauer-Sant'Anna, MD, PhD; Fábio Klamt, PhD, Flavio Kapczinski, MD, PhD Author affiliations: Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada (Drs Wollenhaupt-Aguiar and Kapczinski); Biochemistry Department, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil (Dr Klamt); Post-Graduate Program in Bioinformatics, Federal University of Paraná (UFPR)/Polytechnic Center, Curitiba, PR, Brazil (Drs de Saraiva Chagas and Castro); Department of Psychiatry, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil (Drs Pfaffenseller, Passos, Kauer-Sant'Anna, and Kapczinski)

Introduction: The neuroprogression concept in bipolar disorder (BD) proposes that different stages of illness are associated with distinct neurobiological underpinnings; although much is discussed about the illness progression and the cumulative effects of mood episodes, it is still not known how the biochemical changes lead to brain alteration in BD patients. The aim of this study is to discuss an innovative in vitro approach to evaluate whether biochemical changes in the serum of patients induce neurotoxicity in neuronal cell cultures.

Methods: There is no established methodology for analyzing neurotoxicity in BD patients. Therefore, our group developed a model, challenging the retinoic acid-differentiated human neuroblastoma SH-SY5Y cells with serum of BD patients for 24hs. This in vitro approach was tested in different studies in our lab. Our first attempt was using serum of patients without stratification and the second approach was using serum of twelve euthymic patients stratified at early and late stages of illness, both studies were compared to control group. The outcomes were cell viability and neurite growth as neurotoxic endpoints.

Results: In our first study, we did not find changes in the patients compared to controls. Only in the second approach, when we stratified patients at early and late stages of illness, we were able to identify decreased neurite growth in neurons treated with the serum of patients, mostly patients at late stages of illness ($p = 0.0089$). In addition, neurons challenged with the serum of late-stage patients showed a significant decrease in cell viability ($p = 0.0075$).

Conclusions: The stratification of patients at early and late stages of illness seems to be the better approach to study neurotoxicity in bipolar patients and neurite growth analysis could be a potential tool in the evaluation of neuroprogression in BD patients.

22. Investigating the effects of maternal smoking during pregnancy on brain structure in children with attention deficit-hyperactivity disorder (ADHD)

Nellie Fotopoulos, MSc^{1, 2}, Gabriel A. Devenyi, PhD¹, Mallar M. Chakravarty, PhD^{1, 3, 4}, Sherif Karama, MD, PhD, FRCPC^{3, 5}, Natalie Grizenko, MD, FRCPC^{1, 3} and Ridha Joober, MD, PhD^{1, 2, 3, 1} Douglas Mental Health University Institute, Montreal, Quebec, Canada ² Department Human Genetics, McGill University, Montreal, Quebec, Canada ³ Department of Psychiatry, McGill University, Montreal, Quebec, Canada ⁴ Department of Biological and Biomedical Engineering, McGill University, Montreal, Quebec, Canada ⁵ Montreal Neurological Institute, Montréal, Québec, Canada

Introduction: ADHD is a clinically heterogeneous disorder affecting 5-8 % of children and arises through interplay of genetic and environmental risk factors. Our team previously reported exposure to maternal smoking during pregnancy (MSDP) is highly associated with more severe ADHD. Our current study employs neuroimaging to visualize the effects of MSDP on brain structure in ADHD children. Our objective is to explore the effects of MSDP on brain structure among three groups of children; ADHD exposed to MSDP, ADHD not exposed to MSDP, and

control children. We hypothesize ADHD children exposed to MSDP will have significantly smaller brain structure measurements.

Methods: Participants (6-12 years) are recruited from an ongoing phase-IV clinical trial at the Douglas Institute and scanned using a 3T Siemens MRI for T1 weighted images. Genetic, environmental, cognitive, clinical and structural data are collected. Linear modeling is performed on case/control groups using CIVET and RMINC. Our model uses age, sex, diagnosis, medication and MSDP as predictors, and cortical thickness and surface area measurements as main outcome measures.

Results: In agreement with recent reports that account for motion biases, we found no significant differences in brain measurements between diagnostic groups. Interestingly, we observed increased surface area measurements in ADHD children exposed to MSDP (t-value = 3.61; FDR = 5%) in the left lateral parieto-occipital sulcus in comparison to non-exposed groups.

Conclusion: If reproduced in a larger sample, these findings can provide insight into the etiology of ADHD. In combination with our previous results, these preliminary findings suggest increased surface area measurements in the left parieto-occipital sulcus may be associated with more severe clinical expressions of ADHD in children exposed to MSDP. Our findings can benefit clinical practice by reducing the clinical heterogeneity of ADHD (exposed vs. non-exposed), and promote efforts to diminish preventable and negative outcomes associated with MSDP.

23. Effects of endogenous neuropeptides in the bed nucleus stria terminalis and changes in chronic stress-induced anxiety-like behaviour

Catherine P. Normandeau, Ana Paula Ventura Silva, Emily R. Hawken, Staci Angelis, Calvin Sjaarda, Xudong Liu, José Miguel Pêgo, Éric C. Dumont

Chronic stress is a major cause of anxiety disorders that can be reliably modeled pre-clinically. Stress-mediated deregulation of the bed nucleus of the stria terminalis (BNST) is strongly associated with anxiety-like behaviours. We hypothesized that chronic stress alters neuropeptidergic modulation of BNST synaptic transmission that can precipitate anxiety disorders. Uncovering these changes may provide much needed insight into alternative therapeutic targets for this mental health illness. We use brain slice neurophysiology and behavioural pharmacology to compare the role of locally released neuropeptides on synaptic transmission in the oval (ov) BNST of non-stressed (NS) or chronic unpredictably stressed (CUS) rats. We found that post-synaptic depolarization induced the release of vesicular neurotensin (NT) and corticotrophin releasing factor (CRF) which co-acted to increase ovBNST inhibitory synaptic transmission in 59% of recorded neurons. CUS bolstered this potentiation (100% of recorded neurons) through an enhanced contribution of NT over CRF. In contrast, locally-released opioid neuropeptides decreased ovBNST excitatory synaptic transmission regardless of stress. Consistent with CUS-induced enhanced contribution of the modulatory effects of NT, blockade of ovBNST neurotensin receptor 1 and 2 (NTR1/2) completely abolished stress-induced anxiety-like behaviours in the elevated plus maze paradigm. Our data highlights NT as a key link of chronic stress-induced anxiety behaviours. This is a novel finding as up until now, NT has been largely overlooked.

24. First-episode antipsychotic-naïve patients show high susceptibility for metabolic side effects

Nicole MacKenzie, MEd*¹, Araba Chintoh, MD, PhD*², Mahavir Agarwal MD¹, Chantel Kowalchuk, BSc^{1,3}, Jennifer Wilkin¹, Gary Remington, MD, PhD, FRCPC^{1,2,3}, Margaret Hahn, MD, PhD, FRCPC^{1,2,3}¹ Centre for Addiction and Mental Health, Toronto, Ontario, Canada² Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada³ Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada * =shared primary authorship

Introduction: Second Generation Antipsychotics (SGAs) are known to cause metabolic dysregulation, with youth being particularly vulnerable early on in treatment. Despite this,

antipsychotics (APs) are highly effective in early stages of treatment in first-episode psychosis youth. Moreover, these drugs are being prescribed at alarming rates for off-label uses in youth. The present objective is to measure metabolic side-effects of SGA treatment in AP-naïve youth over the first 3 months of treatment.

Methods: AP-naïve youth (n=12) complete a baseline metabolic assessment including an oral glucose tolerance test, serum lipid measurements, and anthropometric measurements, with measures repeated at 3 months. Pre- and post-abdominal MRI scans are used to quantify adipose tissue (hepatic, visceral). To date, n=6 individuals, prescribed APs considered to have lower metabolic-risk, have completed the study. MR scans are waiting interpretation.

Results: Wilcoxon signed ranks tests reveal significant increases in weight gain, waist circumference, body mass index, and low-density lipoprotein levels at 3 month follow-up compared to treatment initiation. While 2/6 individuals had evidence of impaired glucose tolerance at 3-month follow-up, glucose indices did not demonstrate overall statistically significant change.

Conclusions: These findings demonstrate that SGA prescription in youth (even of lower metabolic risk agents) has pronounced early negative metabolic side-effects. Our preliminary findings have important implications for prescribing practices (i.e. off-label use), risk/benefit assessment, and for prompting early behavioral and pharmacological interventions to mitigate these substantial treatment effects.

25. Structural neuroimaging phenotypes of CACNA1C rs1006737 in adolescents with bipolar disorder and healthy controls

Ronak R. Patel, BSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada **Alvi H. Islam**, MSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada **Daniel O. Shonibare**, BSc, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada **Arron W.S. Metcalfe**, PhD, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Hurvitz Brain Sciences; Sunnybrook Research Institute, Toronto, Ontario, Canada ; **Bradley J. MacIntosh**, PhD, Hurvitz Brain Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada; Department of Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada **James L. Kennedy**, MD, Psychiatric Tanenbaum Centre for Pharmacogenetics, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada **Benjamin I. Goldstein**, MD, PhD, FRCPC, Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Background: The CACNA1C rs1006737 bipolar disorder (BD) risk allele has been implicated in brain structure differences in both BD and healthy control (HC) adults, including the ventro-medial prefrontal cortex (vmPFC), ventro-lateral prefrontal cortex (vlPFC), anterior cingulate cortex (ACC), hippocampus, and amygdala. However, no prior study has examined associations between rs1006737 and brain structure in adolescents.

Methods: Ninety-one adolescents (14-20 years; 41BD, 50HC) underwent 3-Tesla Magnetic Resonance Imaging (MRI). T1-weighted images were processed on FreeSurfer. Regions of interest (ROIs) included vmPFC, vlPFC, ACC, hippocampus, and amygdala. Whole-brain analyses (pcorrected<0.05) examined cortical thickness, volume, and area. General linear models included diagnosis and allele as factors, and controlled for age, sex, and total intracranial volume.

Results: ROI analyses found larger ACC volume (p=0.006, pFDR-corrected=0.054, η^2 p=0.087) and area (p=0.002, pFDR-corrected=0.018, η^2 p=0.111), and smaller vmPFC (p=0.014, pFDR-corrected=0.104, η^2 p=0.069) and vlPFC (p=0.023, pFDR-corrected=0.104, η^2 p=0.059) thickness, in BDs compared to HCs, as well as a diagnosis-allele interaction for vlPFC volume (p=0.040,

pFDR-corrected=0.18, $\eta^2p=0.049$) whereby the risk allele (A) was associated with smaller volume in HCs, but larger volume in BDs. In whole-brain analysis, BDs showed significantly ($p<0.05$) larger area for pars orbitalis, rostral middle frontal and inferior temporal cortex, and smaller area in transverse temporal cortex. The risk allele was significantly ($p<0.05$) associated with larger fusiform volume and lateral orbitofrontal area. No significant interactions were found in whole brain analysis.

Conclusion: The current study provides preliminary evidence for main and interaction effects of rs1006737 on adolescent brain structure. Further investigations of rs1006737 associations with other BD neuroimaging phenotypes are warranted.

26. Convergent epigenetic, transcriptional and morphological evidence associate child abuse with impaired myelination of the anterior cingulate cortex

Arnaud Tanti, PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Pierre-Eric LUTZ**, M.D PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Alicja GASECKA**, PhD. Institut universitaire en santé mentale de Québec, Centre d'optique, photonique et laser, Université Laval, Québec, Canada **Gang G. CHEN**, PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Volodymyr YERKO**, PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Jean-François THEROUX**, M.Sc. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Carl ERNST**, PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Daniel COTE**, PhD. Institut universitaire en santé mentale de Québec, Centre d'optique, photonique et laser, Université Laval, Québec, Canada **Gustavo TURECKI**, M.D PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Canada **Naguib MECHAWAR**, PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University

Introduction: Childhood abuse (CA) has devastating and long-lasting consequences on development, considerably increasing lifetime risk of negative mental health outcomes, including suicide. Yet, the neurobiological processes underlying this increase in vulnerability to psychopathology remain poorly understood. We hypothesized that CA may induce long lasting neuroanatomical changes in the anterior cingulate cortex through epigenetic and transcriptomic reprogramming.

Methods: Well characterized human postmortem ACC samples from control subjects ($n=26$) and depressed suicides with ($n=27$) or without ($n=25$) a history of severe CA, as assessed through psychological autopsies, were used in this study. Genome-wide DNA methylation and gene expression were investigated using Reduced Representation Bisulfite Sequencing and RNA-Sequencing, respectively. Cell-type specific validation of differentially methylated genomic regions was performed using fluorescence assisted cell-sorting and a customized Targeted-Bisulfite sequencing approach. Differential gene expression was validated using Nanostring technology. Finally, the extent to which these molecular adaptations lead to structural changes was assessed using stereology and Coherent anti-Stokes Raman Scattering (CARS) microscopy, representing the first human high-throughput analysis of myelin at the level of individual axonal fibers.

Results: A history of CA was found to be associated with cell-type specific changes in DNA methylation of oligodendrocyte genes, a global impairment of the myelin-related transcriptional program, decreased numbers of oligodendrocyte-lineage cells and a significant reduction in the thickness of myelin sheaths around small-diameter axons in the anterior cingulate cortex.

Conclusion: This study demonstrates that child abuse lastingly disrupts cortical myelination, a fundamental feature of cerebral connectivity, possibly through epigenetic reprogramming. Considering the critical role of myelination in normal brain development, this may represent a key mechanism by which child abuse may have lifelong behavioral consequences.

27. Investigating microglial activation in methamphetamine use disorder: preliminary findings

Gausiha Rathitharan BSc^{1,5}, Junchao Tong PhD¹⁻³, Tina McCluskey MSc¹⁻², Jeffrey Meyer PhD¹⁻⁵, Romina Mizrahi MD PhD¹⁻⁵, Jerry Warsh MD¹⁻⁵, Pablo Rusjan PhD^{1-3,5}, Napapon Sailasuta PhD¹⁻², James L Kennedy MD MSc^{1-3,5}, Shawn Rhind PhD⁵⁻⁶, Sylvain Houle MD PhD¹⁻³, Stephen Kish PhD¹⁻⁵, Isabelle Boileau PhD^{1-3,5}. Research Imaging Centre and ². Campbell Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada ³. Department of Psychiatry, ⁴. Pharmacology and Toxicology and ⁵. Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada 6. Defense Research and Development Canada, Toronto Research Centre, Toronto, Ontario, Canada

Background: Pre-clinical research suggests increased microglial activation upon exposure to methamphetamine (MA). There is a lack of in vivo studies of microgliosis in humans with MA use disorder. Our specific aim was to use positron emission tomography of the translocator protein (TSPO) probe [18F]FEPPA (a reliable biomarker of microglial activation), to test the hypothesis that microglial activation occurs in MA users during early abstinence.

Methods: TSPO binding (VT; [18F]FEPPA with arterial sampling) was measured in 5 MA users (~31.8 years, 2 females) and 11 healthy controls (~29.5 years, 6 females). Saliva samples were collected to genotype a TSPO polymorphism (rs6971) which is linked to high (HAB) and mixed affinity binding (MAB) of [18F]FEPPA. A magnetic resonance image was acquired for delineation of regions of interest on the PET images. RM-ANCOVA (ROI X group with genotype) was conducted to assess statistical significance.

Results: Hair toxicology confirmed use of MA in MA users. Groups were matched with respect to age, sex and genotype. We found no main effect of group on FEPPA VT ($p=0.21$) but a significant interaction ($p = 0.01$) suggesting that the hippocampus and amygdala may be associated with lower FEPPA VT (22% and 17% respectively, NS, Cohen's d : 0.6 and 0.7). **Conclusion:** Our preliminary results suggest no evidence for elevated brain microglial activation in human MA users. Our finding of lower TSPO binding in hippocampus and amygdala might suggest actual loss of microglia in MA users. This is contrary to pre-clinical finding. The possibility that microgliosis occurs at some earlier stages of this condition cannot be ruled out. The sample size of this preliminary study is currently too small to draw conclusions. This study will continue to recruit participants to increase the sample size and consequently improve the statistical power of identifying group differences, if any.

28. Age of onset of obsessive-compulsive disorder predicts behavioural symptom severity in women during the perinatal period

Gabriella F. Mattina^{1,2}, Lauren Mak³, Geoffrey Hall⁴, Meir Steiner^{1,2,4}. ¹McMaster Integrative Neuroscience and Discovery & Study (MiNDS), McMaster University, Hamilton, ²Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, ³Centre for Neuroscience Study, Queen's University, Kingston, ⁴Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada

Introduction: Obsessive-compulsive disorder (OCD) is a debilitating and heterogeneous psychiatric disorder, with sex and age of onset differences. Women are at increased risk for the exacerbation of obsessive-compulsive (OC) symptoms during the perinatal period, where new symptoms focused on the fetus/newborn may emerge. We explored whether age of OC symptom onset was a predictor of OC symptom severity and mood during the perinatal period.

Methods: Eighteen women with OCD, which included comorbid depressive disorders diagnosed by the CIDI-Venus, were seen during 2nd-3rd trimester of pregnancy and 3-6 months postpartum. Behavioural measures collected at each time point included the Perinatal Obsessive-Compulsive Scale (POCS), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Edinburgh Postnatal

Depression Scale (EPDS) and State-Trait Anxiety Inventory (STAI). Age of onset was defined as the age at OC symptom presentation. Linear regression models examined whether age of onset predicted behavioural symptoms during the perinatal period, with age and depression comorbidity as covariates.

Results: Age of onset was a significant predictor of perinatal OC symptom severity (POCS) in postpartum only, $p=0.01$, $R^2=0.44$. During pregnancy, age of onset was found to significantly predict depression scores (EPDS), $p=0.01$, $R^2=0.42$, and state anxiety scores (STAI), $p=0.003$, $R^2=0.53$, but not trait anxiety. It failed to predict non-perinatal OC severity during the perinatal period, as well as anxiety or depressive scores postpartum.

Conclusion: Age of onset was found to predict severity of some symptoms in the perinatal period. Specifically, earlier age of onset was associated with increased state anxiety and depression scores in pregnancy and more severe perinatal OC symptoms in the postpartum period. Women experiencing OC symptoms at an earlier age may be more vulnerable to worsened behavioural symptoms in the perinatal period.

29. Spatiotemporal expression of autism-related and FMRP target genes in the Fmr1 knock out mouse model

Daiana I. Pogacean, Katerina Liaconis, Jonathan K.Y. Lai, and Jane A. Foster

Introduction: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and repetitive behaviours. Fragile X Syndrome (FXS) has become pertinent to elucidating a biological understanding of ASD as FXS is the most common single heritable gene cause of ASD. Significant overlap between Fragile X Mental Retardation Protein (FMRP)-targets and ASD candidate genes have been reported (Cell, 2011:146:247; Am J Hum Genet, 2014: 94:677), thus this study aims to identify the neurobiological underpinnings of FXS by looking into some of these targets. It is hypothesized that fragile X knock out mouse brain tissue will exhibit increased gene expression with respect to the genes at study.

Methods: Using in situ hybridization, spatiotemporal expression in the hippocampus and somatosensory cortex (S1) was measured in brain tissue from wild type and fragile X mice collected during postnatal development. Target genes were selected to meet two criteria: 1) identified gene variants in ASD individuals and 2) known FMRP targets.

Results: Significant differences were observed in PTEN mRNA between wild type (WT) and fragile X mice at postnatal day (P) 21 in the S1, CA1 and dentate gyrus brain ($p<0.05$). No differences were found between WT and fragile X mice for CHD8 and SYNGAP1 mRNAs.

Conclusion: This study examined the differential expression of genes implicated in synaptogenesis in the S1 and hippocampus brain regions of the mouse cortex. This study is part of ongoing work by the Province of Ontario Neurodevelopmental Disorders (POND) network. The aim of POND is to address innovative and better targeted therapeutics to improve the long term outcomes for children with neurodevelopmental disorders. The direct association between phenotype and genotype can lead to the development of biomarkers and prospective studies such as this one will contribute to optimizing therapeutics which are biologically driven, as opposed to behaviourally driven.

30. A cross-sectional neuroimaging mega-analysis identifying sex-dependent atypical cortical thickness in autism spectrum disorder

Saashi Bedford, Min Tae M. Park, Gabriel A. Devenyi, Stephanie Tullo, Evdokia Anagnostou, Simon Baron-Cohen, Michael C. Craig, Christine Ecker, Rhoshel Lenroot, Jason P. Lerch, Michael V. Lombardo, Declan G. M. Murphy, Armin Raznahan, Amber N. V. Ruigrok, Elizabeth Smith, Susan Swedo, Margot J. Taylor, Audrey Thurm, MRC AIMS Consortium, Meng-Chuan Lai, M. Mallar Chakravarty

While sex differences in prevalence and symptomatology in autism spectrum disorder (ASD) have been well-documented, studies of neuroanatomical sex differences in ASD so far have been limited by sample sizes and are often underpowered to detect small-to-medium effect sizes. Using the largest ever-amassed sample, we present a large-scale examination of neuroanatomical sex differences in ASD. Structural MRI scans of 3100 subjects were obtained from the ABIDE (I & II), NIMH, Hospital for Sick Children, and UK MRC AIMS consortium. After stringent quality control and exclusion of sites with fewer than 3 ASD females, 1834 subjects from 18 sites were analyzed (158 Female-ASD, 429 Female-Controls, 561 Male-ASD, 701 Male-Controls, age: 2-65). Cortical thickness (CT) processing, quality control, and analysis was conducted by one author (SB) using CIVET 1.1.12. Statistical analysis was conducted per site in order to account for inter-site differences in imaging acquisitions, using a random-effects vertex-wise meta-analysis technique, and corrected for 5% FDR. Sex-specific brain-wide patterns of increases in CT in ASD males (superior temporal and postcentral gyri, peak Cohen's $d = 0.33$) and females (prefrontal and occipital cortices, peak Cohen's $d = 0.49$) relative to same-sex controls were observed (separate models per sex). Patterning of CT increases are only moderately correlated between sexes (left: $r = 0.25$, right: $r = 0.45$). Sex-by-diagnosis interactions did not survive FDR. When stratified by age, a widespread sex-specific main effect of ASD diagnosis (ASD>Control in both sexes) was observed in subjects <16 years of age (438 ASD/701 Control), with minimal effect of ASD diagnosis in subjects ≥ 17 years (217 ASD/323 Control), suggesting a normalization of CT toward late-adolescence. Our findings suggest that atypical patterning of cortical thickness, substantially modulated by sex, is evident in children and adolescents with autism, but much less so in adults.

31. mGluR5 availability in emerging adults at risk for addictions: a high-resolution PET [11C]ABP688 study

Sylvia M.L. Cox, Ph.D. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 Natalia Jaworska, Ph.D. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 Maria Tippler, B.A. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 France Durand, M.Sc.N. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 Dominique Allard, B.Sc.N. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 Canada Chawki Benkelfat, M.D., DERBH. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 Alain Dagher, M.D. Department of Neurology and Neurosurgery, Montreal, Quebec, Canada
 Frank Vitaro, Ph.D. School of Psychoeducation, Université de Montréal, Quebec, Canada
 Mara Brendgen, Ph.D. Université de Québec à Montréal, Quebec, Canada
 Michel Boivin, Ph.D. Department of Psychology, Université Laval, Laval, Quebec, Canada
 Robert O. Pihl, Ph.D. Department of Psychology, McGill University, Montreal, Quebec, Canada
 Richard E. Tremblay, Ph.D. Departments of Psychology and Pediatrics, Université de Montréal, Quebec, Canada
 Jean R. Séguin, Ph.D. Department of Psychiatry, Université de Montréal, Quebec, Canada
 Marco Leyton, Ph.D. Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: The excitatory neurotransmitter glutamate has been implicated in experience-dependent neuroplasticity and drug-seeking behaviours. Type 5 metabotropic glutamate receptors (mGluR5) might play a particularly important role in these processes. In laboratory animals, mGluR5 ligands affect reward-related learning, the acquisition of drug self-administration, and the rate at which drug conditioned place preferences extinguish. In those with substance use disorders, reductions in mGluR5 availability have been observed. Since these reductions could reflect either pre-existing vulnerability traits or effects of drug use, we used positron emission tomography (PET) with the tracer [11C]ABP688 to measure mGluR5 receptor availability in emerging adults at elevated risk for addictions.

Methods: Fifty-nine participants (18-20 y.o.) were recruited from a longitudinal cohort that has been followed since birth ($n=2692$). Based on diverse externalizing traits and behaviours (e.g., impulsivity, risk-taking and aggression) during early- to mid-adolescence (11-16 y.o.) that predict

future substance use problems, half of the participants were at low risk (n=31, 20 females) while half were at high risk (n=28, 16 females). Participants were scanned on a high-resolution research tomography (HRRT) PET scanner with [^{11}C]ABP688, and had 3T magnetic resonance imaging for anatomical co-registration.

Results: Compared to low risk volunteers, those at elevated risk for substance use disorders had lower [^{11}C]ABP688 binding values in the ventral striatum, medial orbitofrontal cortex, insula, amygdala and parahippocampus (gender-controlled, cluster-level $p < 0.05$ FWE corrected). Correcting for individual differences in alcohol use strengthened the statistical significance of the group differences.

Conclusion: Emerging adults at elevated risk for addictions have altered mGluR5 availability in cortico-limbic regions. These features might affect learning processes and increase susceptibility to acquiring drug-related behaviors.

32. T cells influence brain and immune development before adolescence in mice

Shawna L. Thompson⁽¹⁾, Kelly C. Rilett⁽²⁾, Jonathan Y.K. Lai⁽²⁾, Dawn M. Bowdish⁽³⁾, Jane A. Foster⁽²⁾. ¹ MiNDS Neuroscience Graduate Program, ² Department of Psychiatry and Behavioural Neurosciences, ³ Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON

Introduction: As immune dysfunction is increasingly implicated in psychiatric disorders, immune-brain communication has become a critical focus for today's researchers and clinicians. Research from our laboratory and others demonstrates that deficiencies in adaptive immune cells cause changes in brain structure and behaviour that can be detected in adulthood. Specifically, T cells are essential for the normal development of anxiety-like, exploratory behaviour, learning and memory, and brain structure. Here we investigate roles for T cells in postnatal and adolescent development using mice lacking the β and δ chains of the T cell receptor (TCR β -/- δ -/-).

Methods: Righting reflex was measured during the first postnatal week in TCR β -/- δ -/- and wild type (WT, C57Bl/6) mice of both sexes. This was followed by ultrasonic vocalizations (USV) in response to maternal separation at postnatal day 7 (P7), activity in the open field at P17, and sociability at P24 and self-grooming at P25. In a separate cohort of mice, peripheral immune cells were quantified by FACS at 4, 8, and 14 w of age that correspond to pre-puberty, early adulthood, and adulthood.

Results: TCR β -/- δ -/- mice of both sexes showed delay in righting reflex development. Increased number of USVs and increased activity in the open field test were also shown in both sexes. Female TCR β -/- δ -/- mice showed increased duration of self-grooming. No genotype or sex difference was detected in sociability. In addition, T cell deficient mice showed an altered trajectory of peripheral monocyte profiles through adolescence, and neutrophil numbers were decreased compared to controls.

Conclusions: T cells influence both behaviour and peripheral immune cell populations during development.

33. Low FAAH as a potential predictor of relapse in treatment-seeking alcohol users: preliminary observations

Laura M. Best, B.Sc.^{1,4,9}, Belinda Williams, B.Sc.¹, Richard Bazinet Ph.D.¹¹, Esmaeil Mansouri, B.Sc.¹, Bernard Le Foll, M.D., Ph.D.³⁻¹⁰, Vincenzo De Luca M.D., Ph.D.^{5,7,9}, Dina Lagzdins, M.D.⁵, Pablo Rusjan, Ph.D.^{3,4,7,9}, Rachel F. Tyndale, Ph.D.^{3,7,8}, Alan A. Wilson, Ph.D.^{3,4}, Markus Heilig, M.D. Ph.D.¹², Sylvain Houle M.D., Ph.D.^{3,4,7}, Stephen J. Kish, Ph.D.^{2-4,7-9}, Junchao Tong, Ph.D.^{1-4,7} and Isabelle Boileau, Ph.D.^{1-4,7,9} ¹Addiction Imaging Research Group, ²Human Brain Lab, ³Campbell Family Mental Health Research Institute, ⁴Research Imaging Centre, ⁵Translational Addiction Research Laboratory, ⁶Alcohol Research and Treatment Clinic, Centre for Addiction and Mental Health, Toronto, ON, Canada ⁷Department of Psychiatry, ⁸Department of Pharmacology & Toxicology, ⁹Institute of Medical Sciences, ¹⁰Department of

Family and Community Medicine, ¹¹Department of Nutritional Sciences, University of Toronto, Toronto, ON, Canada ¹²Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

Introduction: Fatty acid amide hydrolase (FAAH) is a key determinant of endogenous cannabinoid (endocannabinoid) activity in the brain through the degradation of anandamide, one of the main endocannabinoid neurotransmitters. Preclinical data suggests that elevated endocannabinoid tone, due to low FAAH, increases alcohol self-administration. Recently, we provided the first in vivo evidence that FAAH levels are decreased in the brains of alcohol users during early abstinence using positron emission tomography (PET) measurement of the FAAH probe [¹¹C]CURB. Here, we investigated whether impaired degradation of endocannabinoids might be involved in relapse in treatment-seeking alcohol users.

Methods: FAAH levels were measured with PET using the FAAH radioligand [¹¹C]CURB (with arterial blood sampling) in 11 (12M/1F) alcohol users during early abstinence (5.3 +/- 4.0 days). Peripheral endocannabinoids were also measured in blood samples taken at scan time. Following the scan, continued abstinence was monitored for a month (mean: 20.1 +/- 3.7 days) using urine levels of ethyl glucuronide.

Results: 5/11 alcohol users provided urine samples positive for ethyl glucuronide (relapsers) during monitored abstinence vs 6 (non-relapsers) who did not. Groups were matched for days of abstinence at scan, alcohol use, age, and FAAH C385A (rs324420) genotype. A RM-ANOVA revealed that FAAH levels were reduced by 10-24% across brain regions in relapsers vs non-relapsers ($p = 0.117$, Cohen's $d = 1.16$). Conversely, peripheral levels of anandamide were increased by 29% in relapsers compared to non-relapsers ($p = 0.158$, Cohen's $d = 1.03$). Across both groups, FAAH brain levels were correlated with recent alcohol use ($r = -0.59$, $p = 0.026$).

Conclusion: This preliminary finding suggests that low FAAH might predict relapse in treatment-seeking alcohol users. Although this needs to be confirmed in a larger sample, this finding suggests that decreasing endocannabinoid signaling may improve clinical outcome in treatment-seeking patients with alcohol use disorder.

34. Are smoker characteristics related to the probability of study completion in human nicotine and tobacco research

Sean P Barrett, PhD; Department of Psychology & Neuroscience, Dalhousie University, Halifax Nova Scotia

Introduction: In order to control for the potential confounding effects of research tobacco use, many experimental models use to examine nicotine related effects require that participants abstain from smoking for a set period prior to the completion of their experimental sessions (typically 12 hours). However little attention has been given to the extent to which this practice impacts study completion.

Methods: To begin test the hypothesis that abstinence requirements may lead to sample biases a secondary analyses of participant screening data was completed to compare the cigarette smoking characteristics of study completers versus those who enrolled in a study but failed to show up for their experimental session using data from three studies that were designed to assess acute nicotine effects following 12 hour abstinence (Schlagintweit et al. 2014; 2015; Schlagintweit & Barrett in press).

Results: Across all three studies study 'completers' were less tobacco dependent and smoked significantly fewer cigarettes per day relative to those who enrolled in the study but failed to show up for their session (p values <0.05).

Conclusion: Findings suggest that study abstinent requirements may lead to samples comprised of less dependent, lighter smokers relative to the entire pool of interested participants. This could potentially limit the generalizability of experimental findings.

35. DNA methylation and brain morphometry in depressed individuals

Julian Chiarella, M.Sc.^{1,2}, Florence Pomares, Ph.D.^{1,2}, Leonardo Tozzi M.D.³, Thomas Frodl, Ph.D.³, Lyndall Schumann, Ph.D.⁴, Moshe Szyf, Ph.D.⁵, Zsafia Nemoda, M.D., Ph.D.⁵, & Linda Booij, Ph.D.^{1,2}. ¹ Department of Psychology, Concordia University, Montreal ² CHU Sainte-Justine, University of Montreal, Montreal ³ Department of Psychiatry, Trinity College, Dublin ⁴ Department of Psychology, Queen's University, Kingston ⁵ Department of Pharmacology, McGill University, Montreal

Introduction: Individuals with depression display differences in brain structure in areas relevant to reward and emotion processing when compared to healthy controls (Palazidou, 2012). DNA methylation is an epigenetic process by which environmental factors may regulate the expression of key genes involved in depression. Because HPA axis functioning has been found to be altered in depression, one gene which has received particular interest is the FKBP5 binding protein (FKBP5) gene, which codes for FKBP5, a protein involved in regulating the sensitivity of glucocorticoid receptors (Klengel et al., 2013). The objective of this study was to examine the association between methylation of the FKBP5 gene and brain structure in individuals with depression.

Methods: Eighty depressed individuals ranging in age from thirteen to sixty years old participated in the study. Peripheral level of DNA methylation was assessed using pyrosequencing. Grey matter volume was assessed using Voxel Based Morphometry on T1-weighted MRI scans. A whole brain multiple regression analysis was conducted to determine the relationship between FKBP5 methylation and grey matter volume.

Results: Greater FKBP5 methylation was associated with greater grey matter volume of the right superior and middle frontal gyrus, left inferior frontal gyrus, left putamen, left parietal operculum, left middle temporal gyrus, right pallidum, left lateral orbital gyrus and middle cingulate ($p < .001$ uncorrected, $k > 10$).

Conclusions: It is known that glucocorticoids have an influence on brain structure. These results suggest that the impact of glucocorticoids on brain structure may be partly regulated by FKBP5 methylation in depressed individuals. Further, they highlight the potential involvement of epigenetic mechanisms in the development of depression. Future analyses will attempt to determine whether FKBP5 methylation mediates the effects of environmental stress on the brain.

36. Unravelling genomic contributions to duloxetine and placebo response in major depressive disorder using a genome-wide approach

Victoria S. Marshe, HBSoc.^(1,2); Malgorzata Maciukiewicz, PhD.⁽¹⁾; Arun K. Tiwari, PhD.^(1,3); Trehani M. Fonseka, MSc.^(1,4,5); Natalie Freeman, MSc.⁽¹⁾; Susan Rotzinger, PhD.^(3,4); Jane A. Foster, PhD.^(4,6); James L. Kennedy, MD MSc.^(1,2,3); Sidney H. Kennedy, MD.^(3,4,5); Daniel J. Mueller, MD PhD.^(1,2,3) ⁽¹⁾ Pharmacogenetic Research Clinic, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada ⁽²⁾ Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada ⁽³⁾ Department of Psychiatry, University of Toronto, Toronto, ON, Canada ⁽⁴⁾ University Health Network, Toronto, ON, Canada ⁽⁵⁾ Department of Psychiatry, St. Michael's Hospital, Toronto, ON, Canada ⁽⁶⁾ Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, ON, Canada

Background: Genomic analyses may identify markers associated with antidepressant response and unravel novel pathways for drug discovery. We utilized a hypothesis-free, genome-wide approach to investigate genetic contribution to antidepressant (i.e., duloxetine) and placebo response for patients with major depressive disorder (MDD), followed by construction of preliminary, predictive machine learning (ML) models.

Methods: We performed a GWAS in MDD patients treated with duloxetine (N=186) or placebo (N=205) for up to 8 weeks. Individuals were genotyped using the Illumina PsychChip, followed by

imputation, resulting >2 million variants per individual under standard quality control. We investigated percentage change of MADRS score corrected for baseline depression severity, length of treatment and cohort. We also constructed preliminary ML models using the best genetic and clinical predictors using LASSO regression for response (>50% of MADRS decrease). Subsequently, we utilized classification-regression trees (CRT) and support vector machines (SVM) to construct models, using ten-fold, repeated cross-validation.

Results: For duloxetine response, we observed top hits ($p < 10^{-6}$) on chromosomes 1, 7 and 19 implicating previously under-investigated intergenic variants. For placebo response, there was a significant hit on chromosome 3 ($p = 1.87 \times 10^{-9}$) located 150kb from STAC1, implicated in neuron-specific signal transduction expressed in nociceptive neurons. Carriers of the C/C genotype improved on average by 49.6% of MADRS score while non-carriers improved clinically significantly worse by 23.9%. Furthermore, there was a suggestive association ($p < 10^{-6}$) within a marker located in the TPO gene involved in thyroid functioning. None of the top variants replicated between duloxetine and placebo samples. Preliminary ML models achieved an accuracy of 63.43% for CRT and 78.93% for SVM when predicting response to duloxetine.

Conclusions: Our data provide new insights into genetic pathways implicated in response to antidepressants and placebo, rejecting the notion that similar pathways are involved. Replication studies in comparable samples including IRLGRey, CAN-BIND-I and STAR*D are pending.

37. Decreased serum L-arginine and L-citrulline levels in major depression

Hess S, Baker G, Newman S, Gyenes G, Tsuyuki R, Le Melleo J-M

Introduction: It has been suggested that decreased production by the endothelium of the gas nitric oxide (NO) may contribute to the consistently observed increased risk of developing cardiovascular disease (CVD) in physically healthy patients suffering from major depression (MD). NO is a gas synthesized from L-arginine (a conditionally essential amino acid) and oxygen by endothelial nitric oxide synthase (e NOS). The end products of NO production include both NO and L-citrulline. NO is rapidly reduced to nitrite and nitrate, classically referred to as NO metabolites. We and others have replicated findings of decreased serum NO metabolites (a surrogate measurement for endothelial NO production) in the serum of MD patients. The mechanism of this decreased production of NO by the endothelium has not yet been elucidated.

Methods: Serum levels of L-arginine and L-citrulline were measured using a Biochrom 30 amino acid analyzer in 35 unmedicated physically healthy MD patients and 36 health controls (HCs).

Results: L-arginine and L-citrulline concentrations were significantly lower in MD patients than in healthy controls (73.54 ± 21.53 $\mu\text{mol/L}$ and 84.89 ± 26.16 , $p = 0.04$ and 31.58 ± 6.05 $\mu\text{mol/L}$ and 35.19 ± 6.85 $\mu\text{mol/L}$, $p = 0.03$ respectively).

Conclusions: The decrease in L-arginine levels in MD patients is a possible explanation for the observed decrease in NO metabolites observed in MD patients. The decrease in L-citrulline levels is also consistent with the suggested decreased endothelial NO production. It remains to be determined whether therapeutic normalization of the L-arginine levels in MD patients would normalize NO endothelial production and ultimately help improve the increased CV risk observed in MD patients.

Friday, June 09, 2017

07:30 – 12:30 Registration (Limestone Foyer)

07:30 – 08:30 Breakfast (Old Stone Room)

08:30 – 10:00 [Symposium 4](#) (Limestone Ballroom)

What brain imaging can tell us about diagnosis, treatment and mechanisms

Co-Chairs: Dr. Verner Knott (University of Ottawa) and Dr. Natalia Jaworska (McGill University)

08:30 – 08:50 **Dr. Alexander Neumeister** (University of Ottawa)

Molecular imaging provides an opportunity for evidence-based treatment developments in posttraumatic stress disorder

08:50 – 09:10 **Dr. Natalia Jaworska** (McGill University)

Neural profiles in depression – utility in response prediction

09:10 – 09:30 **Sara de la Salle** (University of Ottawa)

Electrophysiological effects of ketamine and implications of antidepressant response

09:30 – 09:50 **Dr. Rébecca Robillard** (Netherlands Institute for Neuroscience, The Netherlands)

Considering chronobiology and sleep profiles to tailor treatment strategies for mood disorders

09:50 – 10:00 **Discussion**

[CCNP Next Generation Presentation 3](#)

10:00 – 10:15 **Chantel Kowalchuk** (Centre for Addiction and Mental Health)

Antipsychotic-induced hypothalamic inflammation as a potential mediator of metabolic side effects

10:15 – 10:30 **Shamik Sen** (Queen's University)

Evaluation of a stigma management psychoeducational and behavioural modification course for people with mood and anxiety disorders

11:00 – 12:30 [Symposium 5](#) (Limestone Ballroom)

Neurocircuitry of binge eating: alterations in reward processing

Chair: Dr. Mary Olmstead (Queen's University)

- 11:00 – 11:20 **Amanda Maracle** (Queen's University)
Dopaminergic contributions in the BNST to compulsive responding for sucrose
- 11:20 – 11:40 **Dr. Alfonso Abizaid** (Carleton University)
A role for ghrelin receptors in the ventral tegmental area (VTA) in caloric intake in a mouse model of binge eating disorder
- 11:40 – 12:00 **Dr. Iris Balodis** (McMaster University)
Neuroimaging studies in binge eating disorder: linking findings with treatment outcome
- 12:00 – 12:20 **Dr. Caroline Davis** (York University)
The etiology of binge eating disorder from a psychobiological perspective
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12:30 – 14:00 Lunch (Old Stone Room)

13:00 – 14:00 [CCNP Poster Session 2](#) (Gibraltar Room)

14:00 – 15:00 [CCNP Innovations in Neuropsychopharmacology Award Lecture](#)
(Limestone Ballroom)
Dr. Yu Tian Wang (University of British Columbia)
AMPA endocytosis in synaptic plasticity – is it a therapeutic target for improving memory?

15:00 – 16:30 [Symposium 6](#) (Limestone Ballroom)

Novel signaling mechanisms for treatment of anxiety and depression

Chair: Dr. Paul Albert (University of Ottawa)

- 15:00 – 15:20 **Dr. Hsiao-Huei Chen** (University of Ottawa)
Cannabinoid signaling in anxiety: anxious moments for the protein tyrosine phosphatase PTP1B
- 15:20 – 15:40 **Dr. Sheena Josselyn** (Hospital for Sick Kids)
Probing fear and anxiety circuits in mice
- 15:40 – 16:00 **Dr. Cecilia Flores** (McGill University)
MicroRNA regulation of DCC and susceptibility to depression-like behaviors in humans and mice
- 16:00 – 16:20 **Dr. Paul Albert** (University of Ottawa)
Novel transcriptional pathways regulating 5-HT and anxiety-depression phenotypes
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16:30 **Closing Remarks** (Limestone Ballroom)
Dr. Ridha Joober (McGill University)

Friday, June 09, 2017
Abstracts for Oral Presentations

Symposium 4 – What brain imaging can tell us about diagnosis, treatment and mechanisms

Molecular imaging provides an opportunity for evidence-based treatment developments in posttraumatic stress disorder

Dr. Alexander Neumeister, University of Ottawa

Development of novel interventions for posttraumatic stress disorder (PTSD) is clearly of high priority as available treatments provide often only minimal benefit. An understanding of the processes underpinning the symptoms has been important in the advancement in treatment interventions. In a series of molecular imaging studies using [11C]OMAR and [11C]LY2795050 and PET, we determined volumes of distribution (V_T) and linked them to endophenotypes and individual symptoms of PTSD. These studies suggest that an impaired endocannabinoid system mediates increased severity of hyperarousal symptoms, whereas an impaired kappa opioid system mediates increased severity of dysphoria symptoms in trauma survivors with PTSD. Such data not only implicate these systems in the etiology of PTSD, but also guide the development of targeted treatments and provide an opportunity for evidence-based developments of the next generation of PTSD treatments.

Neural profiles in depression – utility in response prediction

Dr. Natalia Jaworska, Department of Psychiatry, McGill University, Montreal, QC, Canada

Assessments of electrocortical activity in major depressive disorder (MDD) revealed that prior to antidepressant treatment, MDD individuals exhibited distinct electrocortical profiles from controls (e.g. greater alpha power/cortical hyperactivity in MDD). Eventual antidepressant treatment responders vs. non-responders also exhibited distinct pre-treatment profiles (e.g. greater alpha power/cortical hyperactivity in responders). Our work found that several electrocortical features proved useful in differentiating adults with and without MDD, and in indexing response. Brain structural assessments in depressed youth are sparse. Using structural neuroimaging (MRI), our work found that depressed youth exhibited smaller hippocampi than controls, and that those with comorbid anxiety have smaller subgenual anterior cingulate cortex volumes; both structures are highly implicated in MDD. This furthers our understanding of brain alterations in the early stages of MDD.

Electrophysiological effects of ketamine and implications of antidepressant response

Sara de la Salle, School of Psychology, University of Ottawa, Ottawa, ON, Canada

Resting state electroencephalographic (EEG) activity and event-related potentials (ERP) are examined in response to subanesthetic infusions of ketamine in healthy volunteers and in patients with major depressive disorder (MDD). In controls, acute ketamine modelled EEG features and sensory/cognitive processes commonly associated with schizophrenia, both of which correlated with psychotomimetic symptoms. Preliminary analysis and results of pre-treatment EEG/ERP in MDD will be explored in relation to short- and long-term treatment response to ketamine.

Considering chronobiology and sleep profiles to tailor treatment strategies for mood disorders

Dr. Rébecca Robillard, Sleep and Cognition Group, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Disturbances in biological rhythms and sleep can play an important role in the pathophysiology of mood disorders. Our recent results in people with depression suggest the presence of distinct profiles in the 24-hour cycle of melatonin and core body temperature, as well as abnormal heart rate changes across the sleep period. Later circadian preference, poorer circadian rhythmicity and lower sleep quality are associated with more severe depressive and manic symptoms. In addition, over one third of young patients referred to a specialised psychiatric sleep clinic who did not respond to standard antidepressant treatment have severe breathing disturbances during sleep which correlate with persistent depressive symptoms. Building evidence indicates that chronobiological and sleep interventions such as phototherapy, melatonin supplementation and continuous positive airway pressure significantly improve both sleep and mood in some individuals. Early chronobiological and sleep assessment can thus inform treatment strategies for identifiable subgroups of patients with mood disorders.

CCNP Next Generation Presentation 3

Antipsychotic-induced hypothalamic inflammation as a potential mediator of metabolic side effects

Chantel Kowalchuk, BSc a, b, Denise Belsham, PhD c, d, Gary J. Remington MD, PhD, FRCPC a, b, e, Margaret K. Hahn, MD, PhD, FRCPC a, b, e a Centre for Addiction and Mental Health, Toronto, Ontario, Canada b Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada c Department of Physiology, University of Toronto, Toronto, Ontario, Canada. d Departments of Medicine and Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada. e Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Introduction: Antipsychotics (AP)s are the cornerstone treatment for schizophrenia but cause serious metabolic dysregulation. The hypothalamus is the primary brain region responsible for energy regulation, and inflammation in this region has been implicated in impaired energy homeostasis resulting in insulin resistance and weight gain. Thus, hypothalamic inflammation could be involved in the metabolic disturbances seen with AP use.

Methods: The rat hypothalamic cell line, rHypoE-19, was treated with 100uM of olanzapine. Quantitative real-time PCR was performed to determine changes in the mRNA expression of tumor necrosis factor (TNF- α), interleukin (IL)-6, and brain derived neurotrophic factor (BDNF), and western blot was used to detect changes in the activation of the insulin signaling pathway (IRS-AKT-GS3K), and components of the MAPK pathway (ERK1/2 and JNK), the latter which are linked to inflammation.

Results: There was a significant increase in BDNF and TNF- α expression with olanzapine treatment versus the control. There was a trend toward an increase in IL-6 expression with olanzapine treatment, but it was not significant. Olanzapine also significantly increased activation of ERK1/2, with a trend towards an increase in JNK.

Conclusions: Olanzapine increased the expression of TNF- α , and activated the MAPK pathway, suggesting that olanzapine can induce hypothalamic inflammation. Olanzapine also increased BDNF; this may potentially be therapeutic as decreases in BDNF have been linked to the underlying etiology of schizophrenia. Our findings suggestive of olanzapine-induced hypothalamic neuroinflammation may link to AP-induced metabolic dysfunction, while also suggesting a potential therapeutic mechanism through upregulation of BDNF.

Evaluation of a stigma management psychoeducational and behavioural modification course for people with mood and anxiety disorders

Shamik Sen, Author, B.Sc., Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada
Roumen Milev, Author, PhD., Department of Psychiatry, Providence Care, Kingston, ON, Canada

Introduction: Prejudice and discrimination that manifests itself as self-stigmatizing thoughts in people with mental illness can often be a challenge for personal recovery. To address this, The Overcoming Stigma in Mood and Anxiety Disorders (OSMAD) course has been designed to help people with mood and anxiety disorders better manage self-stigma, improve feelings of self-efficacy, and promote recovery. The current study aims to evaluate the efficacy of this group-based, psychoeducational and behavioural modification intervention in reducing the impact of mental-illness-related stigma.

Methods: The evaluation of this course is critical in order to determine its efficacy in reducing the impact of mental-illness-related stigma. Primary outcomes are measured through qualitative analysis of focus group discussion regarding experiences with the course and the perception and experience of stigma. An additional pre-test-post-test design measures changes to various psychosocial impacts of stigma for participants with mood and/or anxiety disorders using a modified 12-item Stigma Impact Scale from the Inventory of Stigma Experiences.

Results: Quantitative data from the pilot OSMAD intervention reported a significant decrease to five of the twelve stigma impact items, including: self-esteem, social contacts, personal goals, family relationships and physical health. Qualitative analysis is currently underway to generate a greater depth of understanding regarding themes revolving around the course's contribution to recovery. Final results to follow.

Conclusion: Quantitative results from the pilot showed promising reductions in stigma experiences in areas of life that are under personal control. Further qualitative data will be pivotal in understanding how to reduce structural stigma regarding areas of life outside of personal control. This study will be an important step towards developing evidence-based interventions to overcome self-stigma and manage social stigma to have a full and meaningful life.

Symposium 5 – Neurocircuitry of binge eating: alterations in reward processing

Dopaminergic contributions in the BNST to compulsive responding for sucrose

Amanda Maracle, Dept. Psychology, Queen's University, Kingston, ON

Binge eating in humans is defined as consumption of an objectively large amount of food within a discrete period of time (e.g., 2 hrs). The behaviour can be modeled in rodents by exposing animals to a combination of stress and food restriction or by providing them with intermittent access to a highly palatable food, such as sucrose. Ms. Maracle will present work using this paradigm showing that sucrose bingeing leads to compulsive responding, an effect that is moderated by infusions of dopaminergic antagonists into the bed nucleus of the stria terminalis.

A role for ghrelin receptors in the ventral tegmental area (VTA) in caloric intake in a mouse model of binge eating disorder

Dr. Alfonso Abizaid, Dept. Neuroscience, Carleton University, Ottawa, ON

Dr. Abizaid will also discuss work with animal models, examining the relationship between stress and fat bingeing in mice. This effect appears closely linked to the function of VTA ghrelin receptors in that VTA administration of ghrelin triggers feeding, whereas intra-VTA infusions of an antagonist blocks the orexigenic effect of circulating ghrelin and blunts rebound feeding following

fasting. Taken together, these data suggest that the mesolimbic reward circuitry is targeted by peripheral ghrelin to influence physiological mechanisms related to feeding.

Neuroimaging studies in binge eating disorder: linking findings with treatment outcome

Dr. Iris Balodis, Dept. Psychiatry & Behavioural Neuroscience, McMaster University, Hamilton, ON

Dr. Balodis will discuss human neuroimaging studies showing that BED individuals exhibit diminished reward processing in fronto-striatal areas relative to a non-BED obese and a lean control group. Additionally, reward neurocircuitry recruitment in the BED group is linked to treatment outcome: those individuals demonstrating persistent binge eating at the end of treatment had reduced anticipatory striatal recruitment at treatment onset. These findings provide insight into potential biomarkers of specific obese subtypes, and distinguish neural correlates related to eating-behaviour patterns from those associated with obesity.

The etiology of binge eating disorder from a psychobiological perspective

Dr. Caroline Davis, School of Kinesiology and Health Sciences, York University, Toronto, ON

Dr. Davis will present the hypothesis that BED reflects a high sensitivity to rewarding stimuli, especially related to hyper-palatable food. This predisposition distinguishes the condition as a unique sub-type of obesity. Both psycho-behavioural and genetic evidence will be used to support the view that BED may be seen as a 'Reward Surfeit' syndrome, with origins in a once-adaptive genotype, now 'mismatched' with our current superfluous food environment.

CCNP Innovations in Neuropsychopharmacology Award Lecture

AMPA endocytosis in synaptic plasticity – is it a therapeutic target for improving memory?

Dr. Yu Tian Wang, Division of Neurology, Department of Medicine and Brain Research Centre, University of British Columbia, Vancouver, BC V6T 2B5, Canada

Recent studies have provided strong evidence that various forms of synaptic plasticity, particularly the long-term potentiation (LTP) and depression (LTD), are critical components of neurobiological processes underpinning the memory persistence and forgetting. One of the most well characterized form of synaptic plasticity is the hippocampal LTP. Hippocampal LTP can be temporally and mechanistically classified into early phase LTP (E-LTP) and late phase LTP (L-LTP). While the non-decaying nature of L-LTP is thought to be dependent on protein synthesis and contributes to memory maintenance, little is known about the mechanisms and roles of the decaying E-LTP. Here, we demonstrate that inhibiting endocytosis of postsynaptic α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptors (AMPA) prevents the decay of E-LTP, thereby converting it into L-LTP. Conversely, releasing AMPAR endocytosis by inhibiting PKM ζ causes L-LTP to decay, thereby converting it into E-LTP. Similarly, inhibition of AMPAR endocytosis is able to prolong memory retention in normal animals, and reduce memory loss in Alzheimer's transgenic mice. These results strongly suggest that the decay of E-LTP is mediated by an active process involving AMPAR endocytosis, and inhibiting this process can prolong the longevity of LTP as well as memory under both physiological and pathological conditions.

Symposium 6 – Novel signaling mechanisms for treatment of anxiety and depression

Cannabinoid signaling in anxiety: anxious moments for the protein tyrosine phosphatase PTP1B

Dr. Hsiao-Huei Chen, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON

Dr. Chen will discuss how a serendipitous observation of anxiety behaviors in transgenic mice with brain insulin and leptin resistance led to the discovery of a novel amygdalar intracellular cascade that impairs endocannabinoid signaling and underlies stress-induced anxiety disorders. In particular, how activation of the protein tyrosine phosphatase PTP1B disrupts 2-AG production and the therapeutic potential of PTP1B inhibition to treat stress-induced anxiety disorders.

Probing fear and anxiety circuits in mice

Dr. Sheena Josselyn, Hospital for Sick Kids, University of Toronto, Toronto, ON

Anxiety Disorders are the most common mental disorders with a total lifetime prevalence of 15% - 20%. The core symptom of most anxiety disorders is excessive or inappropriate fear/worry. Therefore understanding how “healthy” fear may transition to an anxiety disorder will likely be the key to developing new and better treatment strategies for what may be a chronic life-long disorder. Dr. Josselyn uses rodent models to understand how fearful stimuli are encoded in the brain and how they may transition to anxiety. She uses a range of techniques (optogenetics, chemogenetics, molecular intervention, imaging and detailed behavioural analysis) to examine this important question.

MicroRNA regulation of DCC and susceptibility to depression-like behaviors in humans and mice

Dr. Cecilia Flores, Douglas Mental Health University Institute, McGill University, Montreal, QC

Variations in expression of the guidance cue receptor *DCC* appear to confer resilience or susceptibility to psychopathologies involving prefrontal cortex dysfunction. Using a translational approach, Dr. Flores recently identified miR-218 as a posttranscriptional repressor of *DCC* and find opposite *DCC* and miR-218 expression in the prefrontal cortex as a consistent trait of susceptible mice to stress and of major depressive disorder in humans. Upregulation of *Dcc* in the mouse prefrontal cortex causes vulnerability to stress-induced social avoidance and anhedonia. Conversely, upregulation of miR-218 in this region protects against these traits. Finally, miR-218 expression in blood reflects levels of miR-218 in the prefrontal cortex and predicts vulnerability to stress-induced depression-like behaviors. Dr. Flores will propose that (a) by regulating *DCC*, miR-218 may be a switch of susceptibility versus resilience to stress-related disorders; (b) circulating miR-218 could serve a novel marker of vulnerability to stress and a promising target for early interventions.

Novel transcriptional pathways regulating 5-HT and anxiety-depression phenotypes

Dr. Paul Albert, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON

Altered activity of the serotonin system has been implicated in both anxiety and depression disorders, but the mechanisms by which this occurs remain unclear. The 5-HT_{1A} receptor plays a crucial role in regulation of 5-HT activity, both as an autoreceptor that negatively regulates 5-HT neurons, and as a post-synaptic heteroreceptor implicated in anxiety and depression. Dr. Albert will present evidence from cell and animal models and human association studies that dysregulation of the 5-HT_{1A} receptor gene, by promoter polymorphisms or specific transcription factors leads to anxiety and depression, and can affect response to antidepressant treatment.

These studies suggest that by resetting the transcription of the 5-HT_{1A} receptor gene, sustained improvement in anxiety and depression can be achieved.

*Poster Session 2 – Friday, June 09, 2017
13:00 – 14:00 – Gibraltar Room*

1. Atorvastatin in the treatment of lithium-induced nephrogenic diabetes insipidus: protocol for a pilot randomized controlled trial

Jocelyn Fotso Soh, MSc¹, Gabriela Torres-Platas, PhD¹, Serge Beaulieu, MD, PhD², Outi Mantere, MD, PhD², Sybille Saury, MSc², Robert Platt, PhD³, Istvan Mucsi, MD, PhD⁴, Andrea Levinson, MD, MSc⁵, Ana C. Andreazza, Pharm, PhD⁵, Benoit H. Mulsant, MD, MS⁵, Daniel Müller, MD, PhD⁵, Ayal Schaffer, MD⁶, Annemiek Dols, MD, PhD⁷, Anthi Stefatos, MD⁸, Nancy Low, MD, MSc⁹, Pablo Cervantes, MD⁹, Nathan Herrmann, MD⁶, Birgitte M. Christensen, PhD¹⁰, Francesco Trepiccione, MD, PhD¹¹, Tarek Rajji, MD⁵, Soham Rej MD, MSc^{1,2}. ¹Geri-PARTy Research Group, Jewish General Hospital, Montreal, Canada; ²Douglas Mental Health University Institute, Montreal, Canada; ³Department of Epidemiology, Biostatistics and Occupational Health, McGill University Health Centre, Montreal, Canada; ⁴Division of Nephrology, University Health Network, University of Toronto (UofT); ⁵Department of Psychiatry, Centre for Addiction and Mental Health & Department of Psychiatry, University of Toronto; ⁶Department of Psychiatry, Sunnybrook Research Institute, University of Toronto; ⁷Department of Psychiatry, GGZ, Geest, Amsterdam; ⁸Department of Psychiatry, Queen's University, Kingston, Canada; ⁹Department of Psychiatry, McGill University Health Centre, Montreal, Canada; ¹⁰Department of Biomedicine, University of Aarhus; Denmark; ¹¹Division of Nephrology, University of Naples, Naples, Italy.

Background: Lithium is the gold-standard treatment for bipolar disorder, is highly effective in major depressive disorder. Approximately 350,000 Canadians use lithium and more could benefit. However, clinicians are avoiding lithium, largely due to fears of renal toxicity, including chronic kidney disease (CKD). Nephrogenic Diabetes Insipidus (NDI) occurs in 20% of lithium users and predicts a 2-3 times increased risk of CKD. We recently found that statins are associated with lower NDI risk in a cross-sectional study (n=71 lithium users): 0% (0/17) of statin users compared to 20.4% (11/54) of non-users had NDI (p=0.055). We present the protocol for a pilot RCT of statins in NDI to guide the implementation of a larger confirmatory RCT.

Methods: We will conduct a 12-week, double-blind placebo-controlled RCT of atorvastatin in patients with lithium-induced NDI at McGill University, Montreal, Canada. We will recruit 60 patients, age 18-85, who have been on a stable lithium dose for ≥ 2 months and who have NDI, defined as a 10-hour fluid restriction urine osmolality (UOsm) < 300 mOsm/kg. We will randomize patients to atorvastatin (20 mg/day) or placebo for 12 weeks and examine whether this improves measures of NDI: 10-hour water-restriction urine osmolality. Groups will be compared using repeated measures methods. The main objectives will be to generate effect size estimates for a larger trial, as well as assess feasibility (e.g. ability to recruit). Whether atorvastatin treatment affects aquaporin (AQP2) excretion will also be assessed.

Results: The protocol of this study will be presented. Results will be ready in late 2019.

Conclusion: If atorvastatin is useful in treating NDI, lithium could be used more safely in patients with a reduced subsequent risk of CKD, hyponatremia, and acute kidney injury (AKI). This could also allow with bipolar disorder, depression, or other psychiatric/neurological conditions to benefit from lithium.

2. Comparison of 3-monthly versus 1-monthly paliperidone palmitate for time to onset and time to resolution of extrapyramidal symptoms in patients with exacerbated schizophrenia

Maju Mathews, M.D.⁽¹⁾, Isaac Nuamah, Ph.D.⁽¹⁾, Adam Savitz, M.D., Ph.D.⁽¹⁾, David Hough, M.D.⁽¹⁾, Dean Najarian, Pharm.D., BCPP.⁽²⁾, Edward Kim, M.D.⁽²⁾, Srihari Gopal, M.D.,

M.H.S.⁽¹⁾⁽¹⁾Janssen Research & Development, LLC, New Jersey, USA⁽²⁾Janssen Scientific Affairs, LLC, New Jersey, USA

On behalf of the authors: Mira Francis, BPharm, PhD, MBA, Janssen Medical Affairs, Toronto (ON), Canada

Introduction: This phase 3 study was planned to demonstrate noninferiority of the long-acting injectable (LAI) paliperidone palmitate (PP) 3-monthly (PP3M) to 1-monthly (PP1M) in patients with schizophrenia previously stabilized on PP1M. The purpose was to compare overall incidence, time-to-onset (TTO) and time-to resolution (TTR) of extrapyramidal symptoms (EPS)-related treatment-emergent adverse events (TEAEs) in PP3M vs. PP1M. **METHODS:** Following a 17-week, flexible-dose, open-label (OL) phase with PP1M treatment (N=1429 patients), patients were randomized (1:1) to receive either PP1M (50, 75, 100, or 150 mg eq., n=512) or PP3M (175, 263, 350, or 525 mg eq. [3.5 multiple of PP1M], n=504) in a 48-week double-blind (DB), fixed-dose phase. EPS-related TEAEs were summarized by grouped terms (overall, and further classified into dystonia, dyskinesia, hyperkinesia, Parkinsonism and tremor), study phases (OL: PP1M, DB: PP1M or PP3M), TTO and TTR. Further, TTO and TTR were analyzed by final OL dose (50/75, 100 and 150 mg eq.) and age (18-25, 26-50 and >50 years) subgroups.

Results: Overall incidence of EPS-related TEAEs was 12.6% (180/1429) during OL phase (PP1M), reducing to 8.3% (42/504, PP3M) and 7.4% (38/512, PP1M) during DB phase. Median TTO for all EPS-related TEAEs was 17 days (range: 1-120) after PP1M OL treatment; 115 days (range: 1-323) with PP3M, and 98.5 days (range: 1-322) with PP1M (DB phase). Median TTR was 36.5 days (range: 1-127) in PP1M group (OL) and was generally similar for PP3M (91 days [range: 1-336]) vs. PP1M (85.5 days [range: 1-337]) during DB phase. Overall median TTO and TTR values were comparable between PP3M and PP1M formulations. Subgroup analysis revealed no clear dose-response or age-related differences in TTO and TTR of EPS-events for the two formulations.

Conclusions: The overall incidence of EPS-related TEAEs, TTO and TTR of EPS-related TEAEs were comparable in patients with schizophrenia receiving LAI PP3M or PP1M.

3. Does the timing of maternal immune activation affect neuroanatomical and behavioural outcomes in the offspring?

Elisa Guma, Jurgén Germann, Daniel R Gallino, M Mallar Chakravarty

Maternal immune activation (MIA) during gestation, a known risk factor for mental illness in humans, has been shown to induce schizophrenia- and autism-related deficits in rodent offspring. We examine how timing of MIA alters neuroanatomical and behavioural development. Offspring of dams (C57bl/6) with MIA by Poly I:C (5mg/kg, intraperitoneally) in early (day 9; n=8) or late (day 17; n=5) gestation were examined. Structural MRIs (100um isotropic) were collected in vivo at postnatal day 21, 38-39, and 89-95. Deformation based morphometry was performed to investigate voxel-level volume differences in the developmental trajectories of the maturing brain. MIA timing by age interactions were examined using a linear mixed effects model (corrected using False Discovery Rate [FDR]). Assessment of locomotion, social preference, marble burying, and prepulse inhibition (PPI) were performed at second (adolescent) and third (adult) timepoints. MIA timing by age effects were tested using linear models. Trajectories in the hippocampus (CA3), thalamus, amygdala, anterior cingulate cortex, and medial septum differed significantly. Local volumes in early MIA start lower than those of late MIA at but show accelerated growth. Late MIA exhibit stunted growth in these regions (<1% FDR). Early MIA offspring exhibit greater PPI deficits at adolescence (p=0.006), bury more marbles (p=0.08), show decreased locomotor activity (p=0.02), and have impaired social behaviour (p=0.06) at adolescence and adulthood. Mice exposed to early MIA show greater deviations in their neurodevelopmental trajectories and more behavioural deficits compared to late MIA. A better understanding of the timing of MIA could help elucidate mechanisms underlying neurodevelopmental disorders.

4. DRD4 exon 3 genotype as predictor of symptom severity and treatment outcomes in children with ADHD: gene-treatment and gene-environment interaction study

Darya Naumova (^{1,2}), BSc; Sarojini M. Sengupta (^{2,3}), PhD; Natalie Grizenko (^{2,3}), MD; and Ridha Joobar (^{1,2,3}), MD PhD. (¹) Department of Human Genetics, McGill University, Montreal, Quebec, Canada (²) Douglas Mental Health University Institute, Montreal, Quebec, Canada (³) Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Both genetic and environmental factors have been implicated in the etiology of ADHD, but there is a need for further characterisation of the risk factors. This study presents a comprehensive analysis of the role of dopamine receptor 4 (DRD4) gene polymorphism in childhood ADHD. First, we examine the effect of DRD4 exon 3 genotype on response to methylphenidate (MPH). Second, we explore an interaction between the genotype and exposure to maternal stress during pregnancy and their effect on symptom severity in children with ADHD. Methods: Children (ages 6-13) were recruited from an ongoing 2-week, placebo-controlled, double blind, crossover trial at the Douglas Institute (Montreal, QC). Response to MPH was evaluated by parents and teachers using Conner's Global Index; information on symptom severity was extracted from Child Behavioral Checklist (CBCL) questionnaire completed by the parents; stress during pregnancy was classified into low (no and mild) and high (moderate, severe and extreme). DNA samples were collected and extracted from 404 subjects. Subject were divided into three genotype groups: homozygotes for short alleles, homozygotes for long alleles, and heterozygotes for both.

Result: There was a significant interaction between DRD4 genotype and treatment course ($p=.037$, effect size of 0.013). Homozygotes for long allele had a better response to placebo, and lower symptomatology at both placebo and active medication weeks, as evaluated by parents. There was a significant effect of gene-by-environment interaction ($p=.003$, effect size of 0.030) on overall CBCL score.

Conclusion: According to the parents, children homozygous for long DRD4 exon 3 allele should better response to MPH. In addition, an interaction between genotype and high stress during pregnancy resulted in significantly higher CBCL scores, reflecting more behavioral problems in these children. The results suggest DRD4 genotype could be used to predict the strength of treatment and clinical outcomes in children with ADHD.

5. Prenatal fluoxetine exposure selectively reduces communication and increases anxiety in male mice, while increasing repetitive behaviors in both sexes

Melanie P. Leussis, PhD, Emalee Peterson, Alex Powers, Tasneem Mitchell. Department of Psychology, Emmanuel College, Boston, MA 0²¹¹⁵, USA.

Introduction: Genetic and environmental factors contribute to autism spectrum disorder (ASD), yet little is known about which environmental factors increase the risk for ASD. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy has increased. Epidemiological studies have linked SSRI use during pregnancy to an increased risk of ASD. The specific long-term neurobiological consequences of prenatal SSRI exposure require further evaluation. This study examined the effects of prenatal exposure to fluoxetine in mice on behaviors relevant to ASD from neonatal development through adulthood.

Methods: C57BL/6J dams were administered fluoxetine at 0.6 (low) or 6.0 (high) mg/kg/day or saline from embryonic days 8 to 18. Juvenile mice were tested in a developmental test battery that measured ultrasonic vocalizations and neuromotor reflex development. Adult offspring were tested in a battery designed to examine changes in ASD-related social/communicative behaviors, repetitive behaviors, and anxiety behaviors.

Results: In juvenile mice, prenatal exposure to fluoxetine sex-dependently reduced the frequency of ultrasonic vocalizations in male mice. Fluoxetine did not detrimentally affect neuromotor

development. Both adult males and females prenatally exposed to high, but not low, doses of fluoxetine exhibited an increase in repetitive behaviors in the marble burying task. However, males exposed to fluoxetine exhibited an increase in anxiety in the elevated plus maze, whereas females did not show any change in anxiety. Fluoxetine exposure did not affect behavior in the social preference test, self-grooming or passive avoidance.

Conclusion: Results suggest that males are more sensitive than females to disruptions in serotonin balance during prenatal development, producing long-term changes in behaviors including communication deficits, increased repetitive behaviors, and heightened anxiety. These findings highlight the need for more systematic studies to evaluate the impact of fluoxetine exposure during other periods of prenatal or early neonatal development.

6. Impact of biological rhythms on perinatal anxiety: a prospective investigation in pregnant women with mood disorders

Anastasiya Slyepchenko^{1,2}; Benicio N. Frey^{1,2,3,1}) McMaster Integrated Neuroscience Discovery and Study (MiNDS), McMaster University, Hamilton, ON;²) Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, ON; ³) Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

Background: Disruptions in sleep and biological rhythms are linked to mood and anxiety disorders. Here we prospectively investigated the influence of biological rhythms on anxiety in women with mood disorders during the perinatal period.

Methods: Fifty-six euthymic women (N=29 with bipolar or major depressive disorder, N=27 controls) completed 15-day actigraphy and the self-reported Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) at three time points: 3rd trimester of pregnancy, 1-3 weeks and 6-12 weeks postpartum. Anxiety symptoms were assessed using the Generalized Anxiety Disorder-7 (GAD7) and the Edinburgh Postnatal Depression Scale anxiety subscale (EPDS3A).

Results: Anxiety scores (GAD7) were higher in the mood group during pregnancy ($p=0.005$) and at 6-12 weeks postpartum ($p=0.049$) compared to controls. During pregnancy, the mood group had poorer sleep efficiency, longer wake after sleep onset (WASO), higher intradaily variability and more awakenings. At 1-3 weeks postpartum, the mood group had lower interdaily stability compared to the control group, while at 6-12 weeks postpartum the mood group only differed by a shorter mesor compared to controls (all $p<0.05$). Pregnancy: Linear regression model combining sleep efficiency, intradaily variability, WASO, awakenings and BRIAN scores, revealed that awakenings ($p=0.004$) and BRIAN scores ($p=0.009$) were independent predictors of GAD7 ($F_{5,38}=4.16$, $p=0.004$, $r^2=0.27$), but not EPDS3A scores. 1-3 Weeks Postpartum: In a linear regression model of BRIAN scores, acrophase and interdaily stability revealed that BRIAN scores ($p=0.006$) were predictive of EPDS3A ($F_{3,23}=5.13$, $p=0.007$, $r^2=0.34$), but not GAD7 scores. 6-12 Weeks Postpartum: In a linear regression model using BRIAN scores and mesor, BRIAN scores ($p=0.005$) predicted GAD7 ($F_{2,21}=7.47$, $p<0.004$, $r^2=0.36$), but not EPDS3A scores.

Conclusion: Both subjective and objective measures of sleep and biological rhythms predicted perinatal anxiety symptoms.

7. Effect of stress and polygenic risk scores on suicidal ideation in schizophrenia patients

Samia Tasmim, BSc.; Ali Bani-Fatemi, MSc.; Vincenzo De Luca, MD, PhD Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

Introduction: Around 5% of schizophrenia patients commit suicide, and suicide attempt is often preceded by suicidal ideation, which can be worsened by stress. Recently, 108 risk loci were validated by the Schizophrenia Working Group of the Psychiatric Genomics Consortium, which together confer a polygenic risk score for schizophrenia. This score is likely to influence how

stress affects suicidal ideation. This study aims to determine if higher polygenic risk scores confer a higher risk for suicide in individuals exposed to high stress conditions. The hypothesis being tested is that stress predisposes schizophrenia patients with a high polygenic risk score to increased suicidal ideation.

Methods: We assessed prospectively a sample of 90 subjects with schizophrenia. Stress was measured using the Perceived Stress Scale (PSS), and suicidal ideation was measured using the Beck Scale for Suicide Ideation (BSS) and the Columbia-Suicide Severity Rating Scale (C-SSRS). The measurements were done at baseline, 3 months, and 12-months. Genomic DNA was extracted from venous blood and genotyped, and the polygenic risk scores were calculated. We used a logistic regression model to predict subjects with emergent suicidal ideation using short term stress and polygenic risk scores as predictors.

Results: In our preliminary logistic regression analysis, the presence of short term stress measured by the PSS had 62.5% ability ($p < 0.05$) to predict worsening in suicidal ideation measured by the C-SSRS for the 3-month follow up.

Conclusion: Stress can worsen suicidal ideation, and in people with high polygenic risk scores for schizophrenia, the effect could be amplified. This study thus proposes a novel stress-gene interaction model to predict suicide. This study can increase our understanding of the risk genes that predispose stress-exposed people to suicide and help us understand which pathways we can target for future drug interventions.

8. Amphetamine disrupts prefrontal cortex development only during a defined critical period in adolescence

Lauren M. Reynolds, B.Sc.^{1, 2}; Leora Yetnikoff, Ph.D.³; Michael Wodzinski, B.Sc.²; Julia G. Epelbaum²; Laura C. Lambert, B.Sc.²; Mu Yun He²; Matthew Pokinko, M.Sc.^{1, 2}; Marie-Pierre Cossette, M.Sc.⁴; Andreas Arvanitogiannis, Ph.D.⁴; Cecilia Flores, Ph.D.^{2, 1} - Integrated Program in Neuroscience, McGill University, Montréal, QC, Canada² - Department of Psychiatry and Department of Neurology and Neurosurgery, McGill University, Douglas Mental Health University Institute, Montréal, QC, Canada³ - Department of Psychology, College of Staten Island, CUNY, New York, New York, USA⁴ - Center for Studies in Behavioural Neurobiology, Department of Psychology, Concordia University, Montréal, QC, Canada

Introduction: Onset of drug use during adolescence increases the risk of addiction across the lifetime, with greater vulnerability conferred to younger initiates. Here we report that drugs of abuse interfere with prefrontal cortex development and cause distinct deficits in cognitive control that persist throughout adulthood only when drug exposure occurs during the earliest stage of adolescence.

Methods: We treated mice with a regimen of an abused dose of amphetamine (4 mg/kg) or saline during three developmental periods: early adolescence (PND 22±1 - 31±1), mid-adolescence (PND 35±1 - 44±1), or adulthood (PND 75±15 - 84±15). Six weeks later, when all mice were adults, we measured behavioral inhibition with a Go/No-Go task as well as risk-taking behavior and locomotor activity in the open field. We then assessed the organization of dopaminergic synapses and the baseline dopamine content in the medial prefrontal cortex (mPFC).

Results: Amphetamine exposure specifically during early adolescence impaired behavioral inhibition and increased risk taking in adulthood. These impairments were not observed when amphetamine treatment occurred during mid-adolescence or adulthood. Concomitantly, only amphetamine exposure during early adolescence reduced the synapse density of mPFC dopamine axons while decreasing the levels of the extracellular dopamine metabolite HVA (homovanillic acid), indicating a decrease in mPFC dopamine turnover.

Conclusions: Our findings establish early adolescence as a critical period of vulnerability to the enduring effects of amphetamine, and demonstrate that such vulnerability is due to the unique action of the drug on early adolescent mPFC development. This conclusion is further bolstered

by evidence from our previous studies showing that only early adolescent exposure to amphetamine downregulates the expression of the Netrin-1 receptor DCC in dopamine neurons, which determines the extent of their innervation to the mPFC. Alterations to adult prefrontal cortex dopamine function and cognitive behaviors may contribute to addiction vulnerability in early user populations.

9. Injectable vs. oral antipsychotic: a 1-year longitudinal neuroimaging study in first-episode of psychosis

Michael Bodnar, PhD, Department of Psychiatry, McGill University, Montreal, Canada
Carolina Makowski, BSc, Integrated Program in Neuroscience, McGill University, Montreal, Canada
M. Mallar Chakravarty, PhD, Department of Psychiatry, McGill University, Montreal, Canada
Ridha Joober, MD, PhD, Department of Psychiatry, McGill University, Montreal, Canada
Ashok K. Malla, MBBS, Department of Psychiatry, McGill University, Montreal, Canada
Martin Lepage, PhD, Department of Psychiatry, McGill University, Montreal, Canada

Introduction: There is evidence of an antipsychotic type on the basal ganglia, with typical antipsychotics shown to positively affect the volume. However, no study has explored for effects related to injectable versus oral antipsychotics.

Methods: Explore grey matter changes in the basal ganglia [striatum, globus pallidus (GP), thalamus] over a 1 year period in first-episode of psychosis (FEP) patients taking injectable or oral form of risperidone or paliperidone. Final sample: 45 controls and 28 patients separated into 'Injectable' (n=16) and 'Oral' (n=12) subgroups. Scans (1.5T MRI) were acquired within three months of entry into an early intervention service and again one year later. Volume estimations were acquired using a multiatlas label-fusion based methodology (MAGeT-Brain). Surface-area metrics were estimated using nonlinear deformations fields. Treatment response was defined as change in total of the Scale for the Assessment of Positive Symptoms (SAPS) over the interscan interval.

Results: For volume, analyses revealed a significant "Time×Structure×Group" interaction; limited to the GP ($P<0.001$). The 'Injectable' subgroup displayed an increase of 99.2 mm³, that significantly differed from the 'Oral' subgroup (mean=32.1mm³; $P<0.05$) and controls (mean=-3.8mm³; $P<0.001$). For surface area (SA), the 'Injectable' subgroup displayed a significant increase in left ventral GP compared to both the 'Oral' subgroup and controls (FDR-corrected, $P_s<0.05$). Treatment response correlated with Full-IQ ($r=-0.48$, $P=0.01$), SAPS Total at Scan1 ($r=0.47$, $P=0.01$), and Ventral-GP SA change ($r=0.43$, $P=0.02$). Multiple-level regression revealed that increase in Ventral-GP SA equated to a 24.1% and 5.1% increase in accounted variance for the 'Injectable' ($P=0.03$) and 'Oral' ($P=0.44$) subgroups, respectively.

Conclusions: A specific change in SA in the GP on the ventral side appears associated with taking an injectable antipsychotic but not an oral antipsychotic. Further exploration of this specific region is warranted to verify if targeting this area is indeed related to an improvement in positive symptoms.

10. Association between P300 and neuroticism

Vincenzo De Luca, Bowen Xiu, Renee Marie Ragguet, Z Jeff Daskalakis

The P300 (P3) wave is an event related potential (ERP) component thought to reflect decision making process. The P300 wave can be found in EEG recordings involving decision-making tasks, appearing as a positive-going potential which peaks approximately 250 to 500ms after the stimulus, due to a delay in response to the stimulus. In this study we investigated the relationship between P300 amplitude measured during the 2-back task and neuroticism scores measured using the NEO-FFT questionnaire in 61 healthy individuals. The median for the neuroticism score in our sample was 30, therefore subjects with a score higher than 30 were included in the high neuroticism group and those with a score below 30 were included in the low neuroticism group. The

P300 amplitude and latency did not show difference in the two groups, furthermore the performance at the 2-back task was similar in the two groups. Overall, our investigation shows that the late components of the ERPs do not differ in subjects with high neuroticism and low neuroticism, implying that other biomarkers are differentiating the cognitive profiles of subjects with different personality profile.

11. The development of the dopamine input to the orbital prefrontal cortex is protracted and sensitive to amphetamine in adolescence

Daniel Hoops^{1,2}, PhD, Jose-Maria Restrepo-Lozano¹, BSc & Cecilia Flores^{1,2}, PhD ¹ Douglas Hospital Research Centre, Douglas Mental Health University Institute, Montreal, Quebec, Canada ² Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Exposure to drugs of abuse in adolescence alters prefrontal cortex development and adult function. We now know that exposure to abused doses of amphetamine in adolescence alters the development of the dopamine input to the medial prefrontal cortex (mPFC) and that this is dependent on the guidance cue receptor DCC. In contrast, the impact of drug exposure on orbital prefrontal cortex (oPFC) dopamine development is unknown. We do know that the maturation of oPFC-dependent behaviours depends on DCC signalling in dopamine neurons and is altered by amphetamine in adolescence. To examine the potential impact of drugs of abuse in the oPFC, we first determined whether dopamine development in the oPFC is protracted across adolescence. Then, we examined whether exposure to abused doses of amphetamine during adolescence disrupts oPFC dopamine development, and if DCC is implicated in this disruption.

Methods: We counted dopamine varicosities in the oPFCs of adolescent and adult mice using neuroanatomical methods established in our laboratory. We then treated adolescent mice with saline or amphetamine using a treatment regimen known to disrupt mPFC dopamine development via DCC. Once the mice reached adulthood, we counted dopamine varicosities and dopamine/DCC varicosities.

Results: Dopamine varicosity density doubles between early adolescence and adulthood in the lateral and ventroinsular oPFC, indicating protracted dopamine development across adolescence. Remarkably, chronic administration of amphetamine during adolescence dramatically reduces (by ~30%) adult dopamine varicosity density in these regions. This drug effect results in more DCC-expressing axons in the oPFC.

Discussion: We show that protracted adolescent dopamine development is not limited to the mPFC, but also encompasses the oPFC. Exposure to abused doses of amphetamine during adolescence negatively impacts oPFC dopamine development, resulting in few dopamine varicosities across the oPFC. These findings provide a potential mechanism underlying the changes in oPFC-mediated behaviours linked to adolescent drug abuse.

12. Symptom and functional recovery over two years of treatment for first episode psychosis: predictive value of early sub-threshold psychotic symptoms

Rachel Rosengard, BA.: Department of Psychiatry, McGill University, Montreal, Quebec, Canada
Jai Shah, MD: Department of Psychiatry, McGill University, Montreal, Quebec, Canada;
Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada
Ashok K. Malla, MD.: Department of Psychiatry, McGill University, Montreal, Quebec, Canada; Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada
Ridha Joobar, MD, PhD.: Department of Psychiatry, McGill University, Montreal, Quebec, Canada; Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada
Michael Bodnar, PhD: Department of Psychiatry, McGill University, Montreal, Quebec, Canada; Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada
Martin Lepage, PhD.: Department of Psychiatry, McGill University,

Montreal, Quebec, Canada; Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Montreal, Quebec, Canada

Introduction: Individuals with attenuated positive and sub-threshold psychotic symptoms (APSPS) are considered at-risk for psychosis. However, few studies involving first episode psychosis (FEP) differentiate between FEP patients with and without a reported history of APSPS (APSPS+ and APSPS-, respectively). Our study is the first longitudinal investigation comparing outcome between APSPS+ and APSPS- FEP patients.

Methods: The 263-patient sample was recruited from PEPP-Montreal, a FEP clinic at the Douglas Mental Health University Hospital, and followed for two years of treatment. The Circumstances of Onset and Relapse Schedule was administered to probe for APSPS leading up to illness onset. Patients were categorized as APSPS+ if they reported at least one of nine consensus-selected APSPS. Symptom severity was measured using the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS). Level of functioning was measured using the Global Assessment of Functioning (GAF) and the Social and Occupational Functioning Assessment Scale (SOFAS). Scores were analyzed at three time-points: Entry into PEPP (T1), after 1 year (T2), and after 2 years of treatment (T3). Exploratory analyses were performed between groups (APSPS+/-) with no a priori hypotheses.

Results: Mixed ANOVAs revealed a significant and trending group by time interaction for GAF and SAPS scores respectively, and a significant main effect of group for SOFAS scores ($p < 0.05$). Analyses revealed no between-group differences at T1, but APSPS+ patients exhibited significantly more severe positive symptoms and lower functioning at T2. Lower SOFAS scores persisted among APSPS+ patients in T3 while other group differences resolved.

Conclusion: These results suggest that: (1) APSPS+ patients exhibit worse outcome across domains in the first year of treatment and, (2) after two years of treatment, group differences persist only in functioning. Our findings provide domain-specificity for the application of retrospective APSPS assessment to predict FEP outcome.

13. Intracortical myelin signal intensity predicts cognitive performance in young adults with bipolar I disorder

Manpreet Sehmbi¹, Christopher D. Rowley¹, Luciano Minuzzi MD, PhD^{2,3}, Piumi Rajasekera², Flavio Kapczinski MD, PhD, FRCPC², Nicholas A. Bock PhD⁴, Benicio N. Frey MD, MSc, PhD^{2,3}, ¹Graduate Student, MiNDS Neuroscience Graduate Program, McMaster University, Canada; ²Mood Disorders Program, Department of Psychiatry & Behavioural Neurosciences, McMaster University, Canada; ³Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Canada; ⁴Department of Psychology, Neuroscience, and Behaviour, McMaster University, Canada

Introduction: Although poor cognitive function persists through euthymic states in bipolar disorder (BD), its neurobiological correlates remain undetermined. We studied whole-brain intracortical myelin (ICM) content and cognition in individuals with BD-I and controls (HC). We predict that greater abnormalities in ICM signal will be associated with poorer cognitive performance.

Methods: Participants completed the SCID-I (DSM-IV-TR) to determine current and lifetime psychiatric diagnoses. T1-weighted images (3T MRI) from 35 BD-I and 60 HC (ages 16-45) were analyzed using a surface-based approach to sample ICM content at the mid-depth of the cerebral cortex. Cognitive performance was measured using the CNS-VS computerized testing battery. Linear regression was calculated to predict cognitive performance based on ICM signal.

Results: ICM predicted changes in verbal memory throughout the cortex in BD-I ($R^2 = 0.12-0.29$). Processing speed was predicted by ICM in the bilateral rostral superior temporal, posterior cingulate, midcingulate and anterior cingulate cortices, the left caudal and lateral medial visual cortices, and the right medial parietal cortex in BD-I ($R^2 = 0.09-0.23$). Reaction time was predicted by ICM in the bilateral dorsomedial motor cortex, and the left ventral inferior parietal, dorsal

inferior parietal, superior parietal, ventral motor, and midcingulate cortices in BD-I ($R^2=0.09-0.14$). None of the above models were significant in HC (all $p>0.05$).

Conclusion: This is the first evidence of an association between regional ICM and verbal memory in BD. Both processing speed and reaction time performance are partially predicted by ICM in association cortices. Verbal memory dysfunction is a trait characteristic of BD, persisting through asymptomatic states, and is one of the most replicated cognitive findings in BD. ICM has previously been associated with neural synchrony and integrity of local neural connections. Therefore, our results have potentially significant implications for persistent cognitive dysfunction in BD.

14. miR-218: a key target for the alterations in dopamine development induced by abused doses of amphetamine in adolescence

Santiago Cuesta^{1, 2}, José Maria Restrepo-Lozano¹, Steven Silvestrin¹ and Cecilia Flores^{1, 2} (¹) Douglas Mental Health University Institute, Montréal, Québec, Canada. (²) Department of Psychiatry, McGill University, Montréal, Québec, Canada

Introduction: Initiation of drug use in adolescence is a strong predictor of lifetime abuse. How drugs of abuse interact with ongoing adolescent developmental processes is unknown. We showed that abused doses of amphetamine in adolescence disrupt prefrontal cortex dopamine development, altering cognitive functions in adulthood. These effects are mediated by drug-induced alterations in the expression of the guidance cue receptor gene, *Dcc*, in ventral tegmental area (VTA) dopamine neurons. We showed that while amphetamine in adolescence downregulates *Dcc* expression in dopamine neurons, it upregulates the microRNA repressor of *Dcc*, miR-218. Here we used specific in vivo antagomiR technology to examine whether miR-218 in dopamine neurons mediates adolescent amphetamine-induced effects on *Dcc* expression, mesocortical development, and behavior in adulthood. We also examined possible cellular mechanisms mediating drug-induced changes in miR-218.

Methods: To inhibit miR-218 in vivo, we infused a miR-218 antagomiR in the VTA of early adolescent mice, 1 day before repeated amphetamine exposure. Then, we determined drug effects on *Dcc* expression, dopamine innervation, and behavior. To begin examining the mechanisms mediating amphetamine-induced increases in miR-218, we administered the dopamine D2-like receptor antagonist Raclopride, 30min prior to drug or saline injections. One week after treatment termination, we quantified miR-218, *Dcc* and another miR-218-validated target, *Robo1*, to verify specificity.

Results: Increased miR-218 levels in dopamine neurons are required for abused doses of amphetamine in adolescence to downregulate *Dcc* and to induce lasting developmental effects. Furthermore, the effects of amphetamine on miR-218 and, consequently, on *Dcc*, are mediated by dopamine D2 receptor activation. *Robo1* mRNA was unchanged in all the experiments conducted.

Conclusions: MiR-218 regulation of *Dcc* expression in dopamine neurons is a mechanism by which environmental events, like exposure to abused drugs, produce enduring molecular, developmental, and behavioral effects. Our results suggest strongly that miR-218-mediated repression of *DCC* by amphetamine is target-specific.

15. The impact of antibiotics on the gut-brain axis

Rachael Horne, BSc, James St. Pierre, Sufian Odeh, MSc, and Jane A. Foster, PhD Department of Psychiatry & Behavioural Neurosciences McMaster University, Hamilton, ON, Canada

Background: Scientists have established a link between microbiota and anxiety-like behaviours in animal models and with emotional brain regions in healthy people. This emerging area of research has scientists and the public starting to take notice of microbes and the mind. We and others have demonstrated that host genetics influence both brain structure and behaviour, but the

mechanisms involved are not known. Lui et al, 2016 demonstrated direct alteration of bacterial gene expression and gut microbiota composition by the production of host-derived microRNA in mice (Cell Host & Microbe; 19:32). Here, strain-related differences in microbiota composition and how manipulations of microbiota composition influence intestinal permeability in 2 inbred strains of mice are investigated. Also, we examined if strain-specific differences in microbial populations and permeability are influenced by host genetics via microRNA production.

Methods: Mice were administered broad-spectrum antibiotics for 2 weeks. Profiling of 16SrRNA gene was carried out using a modified bar coded Illumina sequencing method in the McMaster Genome Center. Intestinal permeability was assessed by gavaging a fluorescent probe (FITC) and measuring recovery in the serum. Ongoing miRNA analysis of gut epithelial cells and fecal samples uses nanostring technology and RT-qPCR.

Results: Strain differences in microbiota diversity were observed with reduced alpha diversity in Balb/C compared to C57Bl/6 mice. Beta diversity analysis revealed differences in microbiota composition; principal coordinates analysis (PCoA) showed 2 distinct clusters separated by strain. The taxonomic profile showed significant differences in relative abundance of clinically relevant commensals such as Bifidobacterium, Lactobacillus, Alistipes, and Prevotella. Strain-related differences in permeability were observed in response to antibiotics. Ongoing analysis will determine if specific microbiota are associated with barrier function. miRNA analysis is ongoing.

Conclusion: This approach will help us gain an understanding of the mechanism of how host genetics influence differences in the microbiome.

16. Probiotics and depression: preliminary findings and future directions

Caroline Wallace, PhD Candidate, Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada, Jane Foster, PhD, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada, Sidney H. Kennedy, MD, FRCPC, University Health Network, Toronto, Ontario, Canada, Roumen Milev, MD, PhD, FRCPC, FRCPsych, Department of Psychiatry, Queen's University, Kingston, Ontario, Canada

Introduction: Preclinical and clinical studies have shown that consuming probiotics can improve mood, anxiety, and cognition, as well as alter brain activity in both rodents and healthy humans. Data from our recent open-label, 8-week pilot study provided the first evidence of these effects in depressed patients, with significant improvements observed in overall mood, anhedonia, and sleep quality. To further support this evidence and expand upon the search for biomarkers in depression, data from this pilot study is being used to plan a 16-week, double-blind randomized placebo-controlled trial to assess the effects of probiotics on depression.

Methods: Participants diagnosed with depression recruited from the greater Kingston area will orally consume a probiotic supplement containing *Lactobacillus helveticus* and *Bifidobacterium longum* (Probio'Stick®, Lallemand Health Solutions) or placebo once daily. Participants will undergo clinical assessments measuring mood, anxiety, cognition, and sleep using a battery of validated clinical scales to assess efficacy of the probiotic alleviating depressive symptoms; sleep will also be assessed objectively with an ambulatory polysomnogram. Neuroimaging data will be collected using magnetic resonance imaging and electroencephalography to look at functional, structural, and electrical changes in the brain associated with consumption of the probiotic. Molecular data will be collected from blood, stool, and urine samples to look at levels of cytokines and serotonin, and explore potential genes and proteins that may predict outcomes in depression. An informatics-based approach will be used to integrate clinical, neuroimaging, and molecular data to look for biomarkers that indicate disease state and predict antidepressant-like response to the probiotic.

Results: We expect results to replicate and expand on our pilot data, demonstrating that probiotics are effective in alleviating symptoms of depression, and to find biomarkers that will predict these outcomes.

Conclusions: The findings from this study will contribute robust scientific data that is currently lacking in this emerging field.

17. MiR-218 is a molecular switch for resilience to chronic stress

Angélica Torres-Berrio, PhD (C), Integrated Program in Neuroscience, McGill University, Montréal, Québec, Canada. Dominique Nouel, PhD, Douglas Mental Health University Institute, Montréal, Québec, Canada. Santiago Cuesta, PhD, Department of Psychiatry, McGill University, Montréal, Québec, Canada. Gustavo Turecki, MD, PhD, Department of Psychiatry, McGill University, Montréal, Québec, Canada. Eric J. Nestler, MD, PhD, Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY USA. Cecilia Flores, PhD, Department of Psychiatry, McGill University, Montréal, Québec, Canada.

Introduction: We recently identified miR-218 as repressor of the guidance cue receptor gene DCC (Deleted in colorectal cancer). Indeed, low miR-218, but exaggerated DCC, expression in the prefrontal cortex (PFC) are consistent traits of human depression, and stress-induced depression-like behaviors in mice. Remarkably, miR-218 can be measured in blood, suggesting its potential role as novel biomarker of vulnerability to depression.

Methods: Here we used C57BL/6 mice, viral-mediated gene transfer, and quantitative-PCR to assess whether (1) direct manipulation of miR-218 in the PFC determines resilience or susceptibility to chronic social defeat stress (CSDS), (2) miR-218 expression in blood correlates with depression-like behaviors, and (3) variations in blood expression of miR-218 depends on changes in levels of miR-218 in PFC.

Results: We report that miR-218 is expressed by pyramidal neurons in the mouse PFC. We then find that overexpression of miR-218 selectively in PFC pyramidal neurons prior to CSDS promotes resilience to stress by reducing social avoidance. Conversely, blocking the function of miR-218 in the PFC before a single social defeat exposure induces susceptibility to stress. We also find that expression of miR-218 in blood correlates with depression-like behaviors and that susceptible, but not control or resilient, mice exhibit low levels of miR-218 in blood. Most importantly, we demonstrate that changes in blood expression of miR-218 resemble the ones observed in the PFC.

Conclusion: Our results reveal that miR-218 in the PFC functions as a molecular switch that determines resilience or susceptibility to chronic stress. Remarkably, stress-induced variations in PFC levels of miR-218 can be readily detected in blood. We are currently assessing whether miR-218 levels in both PFC and blood change in response to antidepressant treatment. We propose that blood expression of miR-218 might function as potential biomarker of vulnerability to stress and predict the outcome of therapeutic or pharmacological interventions.

18. A genetic risk score approach for cognitive functioning in late life depression

Malgorzata Maciukiewicz, PhD¹; Victoria S. Marshe, HBS^{1,2}; Arun K. Tiwari, PhD^{1,3}; Etienne Sibille, PhD^{1,4}; Daniel Blumberger, MD PhD^{2,3}; Jordan Karp, MD PhD⁵; Eric J. Lenze, MD⁶; Charles F. Reynolds III, MD⁵; James L. Kennedy, MD MSc^{1,2,3}; Benoit H. Mulsant, MD^{1,2,3}; Daniel J. Müller, MD PhD^{1,2,31}; Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada ²Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada ³Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada ⁴Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada ⁵Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA ⁶Healthy Mind Lab, Department of Psychiatry, Washington University, St. Louis, MO, USA

Introduction: Difficulties in processing speed, memory, and executive functioning are common neuropsychologic deficits in late life depression (LLD). The current study aimed to explore associations between BDNF, CAC1C, COMT, DRD2, GRM3, NCAN and MTFR variants and

cognitive performance in a diverse sample of LLD patients, as these genes have previously been implicated in cognitive performance.

Methods: We included 444 LLD patients (N=394 European-ancestry, N=43 African-ancestry and N=7 Asian-Pacific-ancestry) in our exploratory study of cognitive performance using baseline scores for Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Delis–Kaplan Executive Function System (DKEFS). To reduce the number of phenotypes, we ran factor analysis to get a weighted sum of correlated phenotypes. We combined 14 gene variants reported to be associated with cognitive performance in psychiatric patients into an unweighted genetic risk score (GRS or sum of risk alleles) and applied linear regression to investigate its associations with cognition. Our secondary analyses included single-variant ANCOVAs, corrected for age at onset, sex and education.

Results: We extracted two factors from our data with high fit indices (TLI =0.81, RMSEA=0.02). In individuals of African-ancestry, GRS was significantly associated with the first factor derived from RBANS and DKEFS scores ($\beta = 0.341$; $p=0.025$; adjusted $R^2 = 0.49$). A trend and a weak correlation between the Attention Index and GRS was observed among patients of European-ancestry ($p=0.076$, $\beta = -0.09$; $\rho = -0.14$, $p=0.005$, respectively). Our secondary analyses suggested that marker rs1006737 of the CAC1C gene was nominally associated with the Attention Index Score in individuals of European ancestry ($p = 0.016$, $F(2,382) = 4.12$).

Conclusions: Our results suggest preliminary role of GRS in predicting cognitive performance in LLD patients. However, associations between GRS and factor need to be interpreted carefully, as factor represents indirect assessment of cognitive performance. Replication in independent, comparable depression samples is required.

19. Loss of resting-state functional complexity in schizophrenia and bipolar disorder with psychosis

Tushar Das¹²³ PhD, Mingli Li⁴⁵⁶ MD, Lena Palaniyappan¹²³ MD&PhD ¹Robarts Research Institute & The Brain and Mind Institute, University of Western Ontario, London, Ontario, Canada ²Department of Psychiatry, University of Western Ontario, London, Ontario, Canada ³Lawson Health Research Institute, London, Ontario, Canada. ⁴Mental Health Center, West China Hospital of Sichuan University, Chengdu, P R China ⁵State Key Laboratory of Biotherapy, Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, P R China ⁶West China Brain Research Center, West China Hospital of Sichuan University, Chengdu, P R China

Introduction: Regional inhomogeneity in the brain possesses generative functional mechanisms in diversified spatiotemporal scales, which were shown to exhibit the scale-free brain activity in previous studies. Any alternation of this scale-free activity could reduce nonlinear complexity in functional magnetic resonance imaging (fMRI) signals and could promote pathological conditions. Earlier fMRI studies in functional connectivity and Hurst-exponents (HE) were used to reveal dysfunctional brain activity in autism. Our objectives are to investigate (i) Hurst-exponents and (ii) structure-function correspondence in resting state fMRI data for understanding the altered scale-free mechanisms in schizophrenia (SCZ) and bipolar patients, compared to controls.

Method: We included 32 controls, 16 bipolar and 34 SCZ patients to study HE in AAL atlas based 90 ROIs. Two types of activities were investigated: (i) persistent (HE > 0.5) and (ii) anti-persistent (HE < 0.5). The 'cosine similarity' calculation was carried out between FA-based degree (using the diffusion tensor imaging (DTI) data) and each of these functional categories.

Results: Degree of FA in different brain lobes was presented by using ANOVA with FDR corrections. Increased degree connectivity in parietal and parietal-subcortical regions were noted for bipolar and SCZ groups, compared to the control. Results of HE indicated significantly different regional compensation mechanisms in disease states, compared to healthy controls. Increased similarity of structure-function correspondence was noted in the bipolar group, compared to control and SCZ groups.

Discussion: Some brain regions are in the persistence mode while others are anti-persistent within the brain during rest. Schizophrenia patients show increased persistence in some areas, while reduced in others. Patients with bipolar disorder differ from SCZ in key brain regions. High similarity of structure-function relations indicates the reduced complexity in bipolar patients, but not globally reduced in schizophrenia. This may be due to neurochemical disturbances e.g., persistence due to loss of E/I imbalance.

20. Effects of stress in adolescence on socioemotional function dissipate, whereas those of CB1 receptor antagonism emerge in adulthood, in male rats

Jonathan J. Simone, Gillian E. Cattle, Jennet L. Baumbach, & Cheryl M. McCormick

Introduction: The endocannabinoid system continues to mature in adolescence, however, little is known about the consequences of altered endocannabinoid signalling during this period. We hypothesized that repeated CB1 receptor antagonism during adolescence would increase neuroendocrine stress responses and anxiety, and that these effects would be potentiated when paired with repeated isolation stress in male rats.

Methods: Male rats received either no injection, vehicle injection, or AM251 (1 mg / kg) injection and either returned to the homecage (NoStress) or underwent 1h isolation (Stress) daily on postnatal days (P)30-44. On P45, measures were obtained in subgroups on anxiety in the elevated plus maze (EPM), plasma corticosterone release to isolation stress, and baseline expression of cannabinoid-associated proteins in the hippocampus and prefrontal cortex. Another subgroup was tested on P46 for responses to a novel environment, a novel object, and a novel conspecific, then tested as adults on anxiety behaviours in the EPM, and plasma corticosterone release to restraint stress.

Results: Adolescent stress increased the number of entries onto a closed arm of the EPM ($p = 0.002$). Corticosterone concentrations immediately after 1 hour isolation were lower in Stress animals compared to NoStress animals ($p = 0.039$). Adolescent stress increased the expression of the GABAergic marker GAD67 in the ventral hippocampus ($p < 0.001$). Adolescent stress (injection stress) increased the amount of time spent in a social interaction ($p = 0.037$). Adolescent AM251 exposure decreased anxiety in the EPM in adulthood compared with non-injected rats ($p = 0.008$).

Conclusions: Whereas adolescent stress produced more immediate effects on stress-induced corticosterone concentrations, social interactions, and hippocampal GABAergic expression, AM251 effects on anxiety were delayed and did not emerge until adulthood, suggesting a role for adolescent endocannabinoid signalling in the development of emotional behaviours in male rats.

21. Emotional conflict task performance in individuals with major depressive disorder and healthy controls

Gésine L. Alders, MSc, McMaster Integrative Neuroscience Discovery & Study Program (MiNDS), McMaster University, Hamilton, Ontario, Canada; Andrew Davis, Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, Canada; Benicio N. Frey, MD, PhD, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada; Jonathan Downar, MD, PhD, Department of Psychiatry, University Health Network, University of Toronto, Jacqueline Harris, MSc, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada; Mojdeh Zamyadi, MSc, Rotman Research Institute, Baycrest, Toronto, Ontario, Canada; Gulshan B. Sharma, PhD, Department of Mechanical and Manufacturing Engineering, University of Calgary, Calgary, Alberta, Canada; Stephen R. Arnott, PhD, Rotman Research Institute, Baycrest, Toronto, Ontario, Canada; Stephen C. Strother, PhD, Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; Stefanie Hassel, PhD, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada; Glenda M. MacQueen, MD, PhD, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada; Luciano Minuzzi, MD, PhD, Department of Psychiatry and

Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada; Geoffrey B. Hall, Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, Ontario, Canada.

Introduction: Etkin and colleagues (2006) introduced an Emotional Conflict Task, demonstrating slower reaction time (RT) and reduced accuracy in healthy control participants processing stimuli on trials with incongruence between task-relevant and task-irrelevant stimulus attributes (Conflict Generation, or the Stroop effect – cl trial), compared to trials with congruent stimulus attributes. This RT slowing was partially resolved when incongruent trials were preceded by an incongruent trial (Conflict Resolution – il trial). Patients with major depressive disorder (MDD) are biased in processing emotional information. We hypothesized that this Conflict Generation/Resolution of emotionally-valenced stimuli may be greater in persons with MDD, and would improve with favourable medication response.

Methods: Data from 60 unmedicated MDD participants and 41 control participants who performed an Emotional Conflict Task in an MRI was examined. MDD subjects were tested at baseline, and 8 weeks after starting antidepressant pharmacotherapy. Control participants were tested along similar intervals.

Results: A Group (MDD, Control) x Time (Baseline, Week 8) x Task (RT: congruent, incongruent) analysis of variance (ANOVA) indicated a significant within-subjects Stroop effect of reaction time (incongruent vs congruent), $F(1,99) = 133.065$, $p < .0001$. Similarly, a Group x Time x Task ANOVA indicated a significant within-subjects Stroop effect of accuracy (incongruent vs congruent), $F(1,99) = 153.548$, $p < .0001$. Changes in accuracy scores between cl ($M = .081$, $SD = .013$) and il trials ($M = .90$, $SD = .011$), or “emotional conflict resolution”, was observed in the control group at Week 8, $t(40) = -4.460$, $p < .0001$, but not in MDD subjects in any time points.

Conclusion: MDD and control groups demonstrated a robust Stroop effect across time. The Emotional Conflict Resolution Task was not helpful in differentiating between healthy control participants, and participants with MDD.

22. Individual differences in the circadian rhythms are associated with anxiety- and depression-like behavior

Anyan, J., Ph.D. Candidate, Amir, S., Ph.D. Center for Studies in Behavioral Neurobiology, Concordia University, Montreal, QC, Canada

Various psychiatric conditions are associated with disrupted circadian rhythms. For example, individuals with mood and anxiety disorders often experience aberrant sleep/wake cycles, body temperature rhythms, activity patterns, and hormone and endocrine release. Remarkably, circadian disruptions do not appear to be caused by these disorders, but rather, may be implicated in their pathogenesis. Circadian rhythms in mammals are coordinated by an endogenous circadian clock in the suprachiasmatic nucleus (SCN). It was recently shown that individual differences in SCN neuron coupling correlate with individual differences in circadian locomotor rhythms. The purpose of this project is to investigate whether individual differences in circadian locomotor parameters correlate with anxiety- and depression-like behaviors. The circadian phenotype of Lewis rats was characterized by analyzing wheel running behavior under standard 12h:12h LD cycle, constant dark, constant light, and rate of re-entrainment to a phase advance. Rats were then tested on a battery of behavioral tests: activity box, restricted feeding, elevated plus maze (EPM), and forced swim test (FST). Circadian locomotor parameters were correlated with the behavioral measures to determine which circadian variables are associated with mood-related behaviors. Under 12h:12h LD conditions, activity in the light phase and variability in onset correlates positively with latency to immobility in the FST. Variability in onset also correlates positively with anxiety-like behavior in the EPM. Rate of re-entrainment correlates positively with anxiety-like behaviors in the activity box and EPM. Lastly, we found that free running period under constant dark correlates with anxiety-like behaviors in the activity box and

EPM. Our results demonstrate that individual differences in circadian locomotor parameters correlate with anxiety- and depression-like behaviors. A greater understanding of the relationship between individual differences in circadian rhythms and mood could aid in the identification individuals at risk for developing certain disorders.

23. Effects of THC and CBD on reconsolidation of conditioned fear

Murkar A., BSc. Psychology, University of Ottawa, Ottawa, Ontario, Canada. Kent P., PhD. The Royal's Institute of Mental Health Research associated with the University of Ottawa, Ottawa, Ontario, Canada. Cayer C., MSc. The Royal's Institute of Mental Health Research associated with the University of Ottawa, Ottawa, Ontario, Canada. James J. The Royal's Institute of Mental Health Research associated with the University of Ottawa, uOttawa, Ottawa, Ontario, Canada. Durst, T., PhD. Department of Chemistry and Biomolecular Sciences, uOttawa, Ottawa, Ontario, Canada. Merali Z., PhD. The Royal's Institute of Mental Health Research associated with the University of Ottawa, Ottawa, Ontario, Canada,

Introduction: The objective was to explore the effects of Δ^9 -Tetrahydrocannabinol (THC) and Cannabidiol (CBD) on fear-memory reconsolidation, with emphasis on relevance for future treatment of fear-based disorders. We hypothesized CBD would significantly attenuate reconsolidation of learned-fear, while THC would have no such effect.

Method: Male Sprague-Dawley rats received six 1.0 mA continuous footshocks. 24h later, rats were re-exposed to the context. Immediately following memory retrieval (reactivation) rats received oral administration of one of five treatments: 1) THC (5mg/kg dose), 2) CBD alone (50mg/kg dose), 3) CBD + THC (50mg/kg THC + 50mg/kg CBD), 4) 30% background alone (all remaining plant components following extraction), or 5) Vehicle. 24h later rats were assessed for fear expression upon re-exposure to the fearful stimulus.

Results: Results revealed a significant main effect of group, $F(6,53) = 5.509$ ($p < 0.001$). Subsequent bonferroni corrected pairwise comparisons revealed 50mg/kg CBD significantly attenuated reconsolidation of learned fear ($p < 0.05$). In contrast, 5mg/kg THC had no effect ($p > 0.05$). CBD+THC (50mg/kg each) also significantly attenuated fear-memory reconsolidation ($p < 0.05$). In addition, background material alone significantly attenuated reconsolidation of fear memory ($p < 0.05$). A control condition confirmed that in the absence of fearful memory-trace reactivation there was no significant effect of drugs on freezing behavior, $F(4,40) = 0.919$ ($p > 0.05$).

Conclusions: Our findings suggest that oral CBD may significantly attenuate reconsolidation of conditioned fear-memory. In addition, THC seemed to produce no amnesia for the learned fear responses. This is consistent with prior findings suggesting that CBD and THC have opposite effects in many regards. Interestingly, background material alone also significantly attenuated fear-memory reconsolidation. Further research is warranted into both the potential of CBD as a modulator of fear-memory reconsolidation for potential clinical application, as well as to explore other active components of plant background material.

24. The effects of intermittent theta-burst stimulation on working memory in depressed patients

Yu Qing L. MSc. Department of Health Sciences, Queen's University, Kingston, ON, Canada Hannah T. MSc. Department of Health Sciences, Queen's University, Kingston, ON, Canada Roumen M. MD PhD FRCPsych FRCPsych. Department of Psychiatry, Queen's University, Kingston, ON, Canada

Introduction: People with depression often struggle with debilitating cognitive impairments such as decreased working memory, executive functioning, attention, concentration, and processing speed. The brain areas associated with cognition, such as the prefrontal cortex and hippocampus are negatively affected by depression; studies have shown decreased volume, activity, and

disturbed brain connectivity in those two areas. The objective of the present study was to determine whether Intermittent Theta-Burst Stimulation (iTBS) treatment is associated with improvement in working memory, and activity changes during resting state and in the prefrontal cortex and hippocampus during a working memory task.

Methods: We recruited 10 patients with major depressive disorder (MDD). Patients received the standard 25 days of iTBS treatment, once per day. We decided to use the n-back task to test working memory during a functional magnetic resonance imaging scan (fMRI). Participants received the fMRI scan before (Time 1) and after the final iTBS treatment (Time 2). Participants also completed depression related clinical measures before and after their iTBS treatments.

Results: We predict that the MDD group will perform significantly better on the n-back task after 25 days of iTBS treatments compared to baseline. The MDD group will also show significant changes in the functional activity during resting-state and in the prefrontal cortex and the hippocampus during the n-back task before and after the iTBS treatment. Results are currently being analyzed.

Conclusion: Our pilot study aims to provide evidence for iTBS as a valuable treatment tool for cognitive impairments associated with depression. We also hope to provide some new insights and understandings into some of the mechanisms behind the therapeutic effects of iTBS.

25. Reduced mesocorticolimbic connectivity in humans with DCC haplotype

Daniel Vosberg, BSc, Integrated Program in Neuroscience (IPN), McGill University, Montreal, Quebec, Canada Yu Zhang, PhD, Montreal Neurological Institute (MNI), McGill University, Montreal, Quebec, Canada Amanda Chalupa, MSc, Psychiatry, McGill University, Montreal, Quebec, Canada Dominique Allard, BScN., Psychiatry, McGill University, Montreal, Quebec, Canada France Durand, MSc, Psychiatry, McGill University, Montreal, Quebec, Canada Alain Dagher, MD, Montreal Neurological Institute (MNI), McGill University, Montreal, Quebec, Canada Chawki Benkelfat, MD, CSPQ, DERBH, Psychiatry, McGill University, Montreal, Quebec, Canada Myriam Srouf, MDCM/PhD, Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada Ridha Joober, MD/PhD, Psychiatry, Douglas Institute, Montreal, Quebec, Canada Franco Lepore, PhD, Psychology, Université de Montréal, Montreal, Quebec, Canada Guy Rouleau, MD/PhD, Montreal Neurological Institute (MNI), McGill University, Montreal, Quebec, Canada Hugo Theoret, PhD, Psychology, Université de Montréal, Montreal, Quebec, Canada Cecilia Flores, PhD, Psychiatry, Douglas Institute, Montreal, Quebec, Canada Marco Leyton, PhD, Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: The axon guidance molecule receptor DCC (deleted in colorectal cancer) plays a critical role in directing the development of mesocorticolimbic dopamine pathways. In laboratory rodents, DCC haploinsufficiency leads to increased dopamine projections to the medial prefrontal cortex (mPFC), and, in turn, blunted mesolimbic dopamine transmission. In the present study, we had the opportunity to map mesocorticolimbic connectivity in members of a Quebec family who are haploinsufficient for DCC. It was predicted that anatomical connectivity in the DCC mutation carriers would be (i) increased between the substantia nigra/ventral tegmental area (SN/VTA) and mPFC, and (ii) unchanged between the SN/VTA and ventral striatum.

Methods: Diffusion tensor imaging (DTI) data were acquired for 18 DCC mutation carriers, 12 relatives without the DCC mutation, and 19 unrelated healthy controls. Probabilistic tractography was performed using the SN/VTA as a seed region, and targets were the ventral medial prefrontal cortex (vmPFC) and ventral striatum.

Results: Statistically significant main effects of group were found between the SN/VTA seed and both the ventral striatum ($F(2,46)=4.36$, $p<0.05$) and vmPFC ($F(2,46)=3.27$, $p<0.05$). These effects reflected reduced anatomical connectivity in DCC mutation carriers in both the ventral striatum (related controls $p<0.01$; unrelated controls $p<0.05$) and vmPFC (related controls $p<0.05$; unrelated controls $p<0.01$).

Conclusion: DCC haploinsufficiency is associated with disrupted mesocorticolimbic connectivity. Since DTI alone cannot discern the neurochemical properties of neurons, further study is required to determine if the affected pathways are dopaminergic.

26. Abrogated Freud-1/CC2D1A repression of 5-HT1A autoreceptors induces a treatment-resistant anxiety-depression phenotype

Faranak Vahid-Ansari, MSc, OHRI (Neuroscience), UOttawa Brain and Mind Research Institute, Ottawa, ON, CA Mireille Daigle, BSc, OHRI (Neuroscience), UOttawa Brain and Mind Research Institute, Ottawa, ON, CA M. Chiara Manzini, PhD, Department of Pharmacology and Physiology, The George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA Jonathan James, The Royal's Institute of Mental Health, affiliated with the University of Ottawa, Ottawa, ON, CA Zul Merali, PhD, The Royal's Institute of Mental Health, affiliated with the University of Ottawa, Ottawa, ON, CA Paul R. Albert, PhD, OHRI (Neuroscience), UOttawa Brain and Mind Research Institute, Ottawa, ON, CA

Introduction: Up-regulation of serotonin-1A (5-HT1A) autoreceptors reduces 5-HT tone and has been associated with major depression, suicide, and resistance to antidepressant treatment. Freud-1/CC2D1A represses the 5-HT1A receptor gene in vitro is strongly expressed in 5-HT neurons. We hypothesized that Freud-1 regulation of 5-HT1A autoreceptors occurs in vivo and plays a role in anxiety/depressive phenotype and response to antidepressants.

Methods: We generated cF1KO mice with a 5-HT neuron-specific conditional knockout of Freud-1 by crossing TPH2-CreERT2 and Flx-Freud-1 mice. To address whether the behavioral phenotype induced by loss of Freud-1 is dependent on 5-HT1A/autoreceptor overexpression, we also generated conditional Freud-1/5-HT1A double knockout (cF1/1A dko) in serotonin neurons by crossing F1-cKO mice with flx-5-HT1A mice.

Results: In cF1ko compared to wild-type mice, we observed increased 5-HT1A autoreceptor protein and binding levels, and augmented DPAT-induced hypothermia response indicating increased 5-HT1A autoreceptor levels and function. In the dorsal raphe, 5-HT content and neuronal activity were reduced. The cF1ko mice displayed increased depression- and anxiety-like behavior that was resistant to chronic antidepressant (fluoxetine) treatment, while wild-type mice responded. The cF1/1A dko mice lacked both Freud-1 and 5-HT1A expression only in 5-HT neurons, and showed no increase in anxiety- or depression-like behaviour compared to 1Ako background; instead a reduction in depression-like behaviour emerged.

Conclusion: These findings establish the importance of presynaptic Freud-1 in 5-HT1A autoreceptor regulation in vivo, and in anxiety and depression. These actions are complementary its role in the forebrain in anxiety and cognitive function, suggesting that enhancing Freud-1 expression or function may provide a useful target for treatment-resistant forms of these diseases. Supported by HSF-CPSR (FVH) and CIHR (PRA).

27. Clinical correlates of single versus repeated suicide attempts in individuals with mood disorders

Amanda Ceniti, HBSc [^{1,2,3}] Sakina Rizvi, PhD [^{1,2,3,4}] David Muzina, MD [⁵] Roman Dale, MD [⁵] Roger S. McIntyre, MD [^{3,4}] Sidney H. Kennedy, MD [^{1,2,3,4}] [¹] Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada [²] ASR Suicide & Depression Studies Program, St. Michael's Hospital, Toronto, Ontario, Canada [³] Dept. of Psychiatry, University Health Network, Toronto, Ontario, Canada [⁴] Dept. of Psychiatry, University of Toronto, Toronto, Ontario, Canada [⁵] Cleveland Clinic, Cleveland, Ohio, USA

Introduction: There is growing evidence to suggest that individuals with history of a single suicide attempt and those with repeated suicide attempts represent two distinct subgroups of individuals. Past research has shown that about 23% of individuals who have attempted suicide will go on to make another attempt, but there is limited data on how these repeat attempters differ from those

who make only a single attempt. The current project aims to compare the demographic and clinical characteristics of these two groups in a sample of individuals with mood disorders.

Methods: This naturalistic cross-sectional study utilized data from the International Mood Disorders Collaborative Project (IMDCP). Patients who met criteria for Major Depressive Disorder or Bipolar Disorder were stratified into three groups: (1) no past suicide attempts, (2) one past suicide attempt, (3) two or more past suicide attempts. Chi-square analyses and independent sample t-tests were performed to evaluate differences between individuals with one past attempt or multiple past attempts.

Results: Among those who had attempted suicide (n=304), 48% had made multiple attempts. Individuals with repeated suicide attempts were younger at onset of first mood symptoms ($p=0.016$, 95% CI [0.90, 6.58]), had a higher rate of attention deficit hyperactivity disorder ($p=0.008$), and were more likely to have attempted suicide within the past month ($p=0.026$). Depression severity was not significantly different between groups, but repeat suicide attempters were found to have higher levels of anhedonia ($p=0.023$, 95% CI [-0.11, 0.61]), as measured by the interest/pleasure item of the Montgomery-Åsberg Depression Rating Scale.

Conclusions: These findings demonstrate clinical differences between individuals with single and repeated suicide attempts. Notably, higher levels of anhedonia in the repeat suicide attempt group may reflect individuals' perceptions of the value of living. Implications of these findings on identification of potential risk factors for future suicide attempt are discussed.

28. Clinical predictors of suicide attempt risk in major depressive disorder: results from the international mood disorders collaborative project

Nicole Edgar, Sakina Rizvi, Roger McIntyre, Sidney H. Kennedy

Introduction: In individuals with major depressive disorder (MDD), approximately two-thirds report suicidal ideation, while only 15-20% go on to make an attempt. However in clinical settings, no factor is able to reliably predict suicide attempt. The purpose of this study was to identify clinical variables to predict MDD patients who are at high risk of suicide attempt.

Methods: Participants were enrolled in the International Mood Disorders Collaborative Project between 2008-2013. Inclusion criteria were: DSM-IV diagnosis of MDD, ages 18-65, outpatient status, and current suicide risk of low, moderate or high, based on the MINI International Interview-Suicide Module. Demographic information was collected along with the Hamilton Rating Scale for Depression (HAM-D-17), Sheehan Disability Scale (SDS), Trimodal Anxiety Questionnaire, personality inventories, history of child abuse, current medications, as well as medical and psychiatric comorbidities.

Results: A total of 162 individuals were included in the analysis. The primary difference among low and high risk suicide individuals was a greater level of anhedonia, as measured by question 7 of the HAM-D-17, in the high suicide risk group ($p>0.001$). There was also a significant decrease in function, based on the SDS in the high risk group ($p=0.028$). No significant difference was observed for depression severity, measured by the HAM-D-17 total score ($p=0.31$). Additional variable including the effects of comorbidities, and life events will also be discussed.

Conclusion: These results provide preliminary information on identifying potential clinical variables that could be used to better identify those who are at highest risk for making a suicide attempt and develop directed treatment interventions.

29. Social instability stress in adolescence increases the intake of ethanol, but not sucrose in rats

Marcolin ML, MSc a; Hodges TE, MSc b; McCormick CM, PhD ab a. Department of Biological Sciences, Brock University, ON, Canada b. Department of Psychology, Brock University, ON, Canada

Introduction: Social instability stress in adolescent rats (SS; postnatal day 30-45, daily 1 hour isolation + new cage partner) alters behavioural responses to psychostimulants, but differences in voluntary consumption of natural and drug rewards is unknown. SS also increases anxiety and reduces aspects of social behaviour, although not the reward value of social interactions. Lastly, the social context may modify the intake of rewards. Here, we investigated whether SS rats would show increased consumption of rewards relative to CTL, particularly in the presence of an unfamiliar peer.

Methods: Male no-stress (CTL) and SS rats were placed in an apparatus divided in half by a mesh, either alone or with an unfamiliar partner (social) on the other side of the mesh, and were randomly assigned to have access to 10% ethanol (EtOH) or 1% sucrose.

Results: For EtOH groups, CTL rats had a longer latency to drink than SS rats ($p=0.015$) and alone rats had a longer latency than social rats ($p=0.023$). SS rats spent more time drinking EtOH than did CTL rats ($p=0.012$). Alone rats spent more time drinking ($p=0.040$) than social rats. For Sucrose groups, there were no effects on latency to drink. Alone rats spent more time drinking ($p=0.004$) than social rats.

Conclusions: The increased EtOH consumption of SS rats compared with CTL may be associated with evidence of increased anxiety in SS rats and the anxiolytic properties of EtOH. SS and CTL rats do not differ in sucrose intake, which suggests no differences in sensitivity to the “hedonic” properties of sucrose. The effect of peer presence on intake in both conditions is in the opposite direction to previous reports with sweetened EtOH, which suggests that the effect of peers may depend on the degree of reward value of the substance.

30. Baseline predictors of nutritional status in moderate to severe AD

Chelsea Sherman, BSc, Department of Pharmacology and Toxicology, University of Toronto, Sunnybrook Health Sciences Centre, Canada; Myuri Ruthirakuhan, MSc, Department of Pharmacology and Toxicology, University of Toronto, Sunnybrook Health Sciences Centre, Canada; Eileen Abraham, BA, Neuropsychopharmacology research group, Sunnybrook Health Sciences Centre, Canada; Nathan Herrmann, M.D., Department of Psychiatry, University of Toronto, Sunnybrook Health Sciences Centre, Canada; Krista Lanctôt, PhD., Department of Psychiatry, University of Toronto, Sunnybrook Health Sciences Centre, Canada

Introduction: Nutritional status (NS) is important in those with Alzheimer's disease (AD), as risk of malnutrition has been found in up to 80% of individuals. Poor NS has been associated with increased cognitive, behavioural and functional impairments, as well as with increased frailty and morbidity. AD patients at risk of malnutrition have demonstrated greater agitation levels compared to those who were well nourished but the association between NS and agitation remains unclear. The goal is to investigate the association between agitation and NS in AD patients.

Methods: All patients were recruited from a clinical trial in AD patients with clinically significant agitation. Patients were dichotomized based on nutritional status into 1) normal/at risk, or 2) malnourished as defined by the Mini Nutritional Assessment Short-Form. Baseline medication history, cognitive and behavioural measures (neuropsychiatric inventory (NPI) and Cohen Mansfield Agitation Inventory (CMAI)) were compared between groups.

Results: To date, 26 patients ($n=16$ normal/at risk, $n=9$ malnourished) have been recruited (69.6% male, mean (SD) age=86.6 (11.10), NPI=32.4 (14.32), CMAI=67.6 (18.59). Malnourished patients had significantly greater scores on the CMAI/physical aggressive subscore ($t(23)=1.36$, $p=0.05$) and NPI irritability subscore ($t(23)=0.52$, $p=0.02$) and significantly lower scores on the NPI anxiety

subscore ($t(23)=5.13$, $p=0.01$) compared to patients who had normal nutritional status/risk of malnutrition.

Conclusion: Compared to normal/at risk patients, malnourished individuals had greater physical/aggressive symptoms, irritability, but lower anxiety. By identifying the link between NS and neuropsychiatric symptoms, such as agitation, efficacious interventions may be established to manage these symptoms such that an improvement in one may benefit the other.

31. Examining parent-of-origin effects in attention-deficit/hyperactivity disorder

Shaza Mokhtar^{1,2}, Sarojini M. Sengupta^{1,3}, Aurelie Labbe^{3,4}, Ridha Joobar^{1,2,3,1}. Douglas Mental Health University Institute, Montreal, Quebec, Canada.². Department of Human Genetics, McGill University, Montreal, Quebec, Canada.³. Department of Psychiatry, McGill University, Montreal, Quebec, Canada.⁴. Department of Epidemiology, Biostatistics & Occupational Health, McGill University

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common behavioral disorders in school-aged children. It is characterized by developmentally inappropriate levels of attention and/or motor hyperactivity/impulsivity. ADHD is a multifactorial highly heritable disorder, and there is considerable evidence suggests the role of parent-of-origin in the disorder; i.e. differential effects of alleles depending on whether they have been transmitted from mothers or fathers. Aim: To examine parent-of-origin effect in selected candidate genes in children with ADHD.

Methods: 600 children diagnosed with ADHD aged between 6-12 years and their parents have been genotyped for selected polymorphisms in candidate genes selected based on their potential implications in the neurophysiological processes relevant for ADHD. Parent-of-origin effects will be explored with both affection status as well as the quantitative traits that are relevant for ADHD, including response to MPH.

Conclusions: Parents-of-origin are genetic mechanisms rarely explored in complex disorders. Our study may shed some light on their involvement in ADHD.

32. Susceptibility to chronic social defeat stress is related to increased hippocampal engram cells in the hippocampal CA1 region

Zhang, T.R., BSc, Douglas Mental Health University Institute, Montreal, QC, Canada. Wong, A.S., Douglas Mental Health University Institute, Montreal, QC, Canada Wong, V., Douglas Mental Health University Institute, Montreal, QC, Canada Wong, T.P., PhD, Douglas Mental Health University Institute, Montreal, QC, Canada

Introduction: Apart from mood changes, depression has been associated with cognitive biases such as a biased memory for negative stimuli. Imaging studies suggest the processing of negative information is related to the functioning of the hippocampus. We hypothesize that the facilitated formation of hippocampal engram cells, cellular substrates for memory, is related to the memory bias for negative stimuli in depression.

Methods: We employed a chronic social defeat model to examine the relationship between hippocampal engram cells and depression-related behaviours. We used transgenic TetTag mice that allows the tagging of activated neurons by reporter gene LacZ at an earlier time point to compare with activated neurons later. TetTag mice were stressed by chronic social defeat, consisting of daily attacks by and co-housing with aggressive mice. After 8 days of defeat, mice were separated into susceptible (exhibiting social avoidance) and resilient groups according to social behaviour. Engram cells were reactivated by another social defeat to induce cFos expression. Neurons with both LacZ and cFos labeling represent engram cells.

Results: We found more LacZ labeled hippocampal CA1 neurons in susceptible mice compared with resilient and nonstressed mice, suggesting a more sensitive hippocampus. Such group difference was gone when comparing the dorsal and ventral hippocampus separately. Intriguingly,

we found significantly more engram cells in the dorsal and ventral CA1 of susceptible mice compared to other groups. No difference in labeling was found in the dentate gyrus.

Conclusion: Our findings suggest animals exhibiting depression-related behaviour may have an enhanced hippocampal memory for social stress.

33. The endocannabinoid system and risk for alcohol use disorder: the first measurement of fatty acid amide hydrolase in youth using pet radiotracer [11c]curb

Laura M Best^{1,5}, Christian Hendershot^{2-4,6,7}, Samantha Jagasar¹, Junchao Tong^{1,3,6}, Bernard Le Foll^{1-3,5-7,9,10}, Sylvain Houle^{1,3,7}, Rachel F Tyndale^{3,7,9}, Stephen J Kish^{1,3,6,7,9} and Isabelle Boileau^{1,3,6,7}¹Research Imaging Centre, Centre for Addiction & Mental Health, Toronto, ON ²Addiction Medicine Division, Centre for Addiction & Mental Health, Toronto, ON ³Campbell Family Mental Health Research Institute, Centre for Addiction & Mental Health, Toronto, ON ⁴Institute for Mental Health Policy Research, Centre for Addiction & Mental Health, Toronto, ON ⁵Alcohol Research and Treatment Clinic, Centre for Addiction and Mental Health, Toronto, ON ⁶Institute of Medical Sciences, University of Toronto ⁷Department of Psychiatry, University of Toronto ⁸Graduate Department of Psychological Clinical Science, University of Toronto ⁹Department of Pharmacology & Toxicology, University of Toronto ¹⁰Department of Family and Community Medicine, University of Toronto

Introduction: Fatty acid amide hydrolase (FAAH) determines endogenous cannabinoid (endocannabinoid) tone through hydrolysis of anandamide, a main endocannabinoid neurotransmitter. It has been suggested that altered FAAH levels might be associated with risk for alcohol use disorder (AUD). Preclinical studies found reduced FAAH levels in rats bred to prefer alcohol prior to alcohol exposure, and we recently confirmed that humans with AUD have reduced FAAH brain levels using positron emission tomography (PET). The goal of this study was to determine whether FAAH brain levels are reduced in youth with a family history of alcohol use disorder, and associated with behavioural phenotypes of risk for alcohol use disorder.

Methods: FAAH levels were measured with PET imaging using the FAAH radioligand [11C]CURB in 25 healthy subjects aged 19 to 25, with either direct family history of AUD (n = 12) or no family history of AUD (n = 13). Subjects also completed an intravenous alcohol infusion to assess alcohol sensitivity. Blood samples were taken to determine FAAH C385A genotype (rs324420) and peripherally-circulating endocannabinoid levels.

Results: There was no significant difference in FAAH brain levels between family history positive and family history negative subjects. Lower FAAH brain levels was associated with higher scores on the Alcohol Use Disorders Identification Test ($r=-0.480$; $p=0.013$). Lower FAAH was also associated with decreased experience of the sedative effects of alcohol in family history negative subjects ($r=0.697$; $p=0.008$).

Conclusion: Preliminary observations in this small sample show no association between family history of AUD and reduced FAAH levels in brain. Family history of AUD as a risk factor for alcohol addiction may not be sensitive to changes in the endocannabinoid system. Recruitment of a larger sample and further analyses might reveal a relationship between the endocannabinoid system and behavioural phenotypes of risk for AUD.

34. Evaluation of a stigma management psychoeducational and behavioural modification course for people with mood and anxiety disorders

Shamik Sen, Author, B.Sc., Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada Roumen Milev, Author, PhD., Department of Psychiatry, Providence Care, Kingston, ON, Canada

Introduction: Prejudice and discrimination that manifests itself as self-stigmatizing thoughts in people with mental illness can often be a challenge for personal recovery. To address this, The Overcoming Stigma in Mood and Anxiety Disorders (OSMAD) course has been designed to help

people with mood and anxiety disorders better manage self-stigma, improve feelings of self-efficacy, and promote recovery. The current study aims to evaluate the efficacy of this group-based, psychoeducational and behavioural modification intervention in reducing the impact of mental-illness-related stigma.

Methods: The evaluation of this course is critical in order to determine its efficacy in reducing the impact of mental-illness-related stigma. Primary outcomes are measured through qualitative analysis of focus group discussion regarding experiences with the course and the perception and experience of stigma. An additional pre-test-post-test design measures changes to various psychosocial impacts of stigma for participants with mood and/or anxiety disorders using a modified 12-item Stigma Impact Scale from the Inventory of Stigma Experiences.

Results: Quantitative data from the pilot OSMAD intervention reported a significant decrease to five of the twelve stigma impact items, including: self-esteem, social contacts, personal goals, family relationships and physical health. Qualitative analysis is currently underway to generate a greater depth of understanding regarding themes revolving around the course's contribution to recovery. Final results to follow.

Conclusion: Quantitative results from the pilot showed promising reductions in stigma experiences in areas of life that are under personal control. Further qualitative data will be pivotal in understanding how to reduce structural stigma regarding areas of life outside of personal control. This study will be an important step towards developing evidence-based interventions to overcome self-stigma and manage social stigma to have a full and meaningful life.

35. Genome-wide association study of anhedonia in GENDEP using a linear mixed model identifies candidates with relevant biological function

Hongyan Ren¹, Chiara Fabbri², Rudolf Uher⁸, Marcella Rietschel³, Ole Mors⁴, Neven Henigsberg⁵, Joanna Hauser⁶, Wolfgang Maier⁷, Anne Farmer², Peter McGuffin², Cathryn M. Lewis², Katherine J. Aitchison¹ ¹Departments of Psychiatry and Medical Genetics, University of Alberta, Edmonton, AB, Canada, ²MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, United Kingdom, ³Division of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany, ⁴Clinical Medicine, Aarhus University, Aarhus, Denmark, ⁵Croatian Institute for Brain Research, University of Zagreb, Zagreb, Croatia, ⁶Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland, ⁷Clinic for Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany, ⁸Department of Psychiatry, Dalhousie University, Halifax, NS, Canada

Introduction: A key feature of major depressive disorder (MDD) is anhedonia, which is a predictor of response to antidepressant treatment.

Methods: In order to shed light on its genetic underpinnings, we conducted a genome-wide association study (GWAS) followed by investigation of biological pathway enrichment using the anhedonia dimension for 796 patients with MDD in the GENDEP.

Results: The GWAS identified 19 SNPs associated at genome-wide significance with the top one being an intronic SNP (rs9392549) in PRPF4B (pre-mRNA processing factor 4B) located on chromosome 6 ($P = 2.07 \times 10^{-9}$) while gene set enrichment analysis returned one gene ontology term, axon cargo transport (GO: 0008088) with a nominal P value (1.15×10^{-5}). Furthermore, on exploratory analysis, the genetic association was positively correlated with that of Parkinson's disease ($rg = 0.803$) and negatively correlated with that of nucleus accumbens gray matter volume ($rg = -0.649$).

Conclusions: We found some markers significantly associated with anhedonia, and some suggestive findings of related pathways and biological functions, which could be further investigated in other studies. Keywords: Anhedonia, MDD, GWAS, linear mixed model, genetic correlation.

36. Stress susceptibility is regulated by hippocampal extrasynaptic NMDA receptor function in the CA1 region

Yiu Chung Tse, PhD, Douglas Mental Health University Institute, Montreal, Quebec, Canada
Joëlle Lopez, PhD, Douglas Mental Health University Institute, Montreal, Quebec, Canada
Alice Shui Ming Wong, Douglas Mental Health University Institute, Montreal, Quebec, Canada
Tak Pan Wong, PhD, Douglas Mental Health University Institute, Montreal, Quebec, Canada

Introduction: N-methyl-D-aspartate receptors (NMDARs) have been implicated in the pathogenesis of depression. Indeed, NMDAR antagonists such as ketamine exhibit fast-acting antidepressant effects. NMDARs can be found inside and outside glutamate synapses. Although extrasynaptic NMDARs (exNMDAR) have been implicated in the computation of synaptic currents and in neuronal death, their contribution to depression-related behavior remains unknown.

Methods: We used a chronic social defeat model to separate stressed mice into 2 groups: susceptible (expressing social avoidance) or resilient animals (normal social behavior). Non stressed mice were used as controls. NMDAR function in the hippocampal CA1 region was examined by electrophysiological techniques.

Results: We found that mice that were susceptible to chronic social defeat had lower hippocampal CA1 exNMDAR function than non-stressed control and stressed mice that were resilient to this stressor. However, no differences in synaptic NMDAR (sNMDAR) function was observed between these animal groups. In addition, we found that sNMDAR is more sensitive to ketamine-induced blockade than exNMDAR, suggesting this fast-acting antidepressant may enhance the ratio of exNMDAR/sNMDAR function. However, memantine, which preferentially inhibited exNMDAR currents, rendered mice more susceptible to chronic social defeat. Finally, N-acetylcysteine, a drug that facilitates extrasynaptic glutamate release from cystine-glutamate antiporters on astrocytes, not only selectively facilitated exNMDAR function, but also reduced mice susceptibility to chronic social defeat.

Conclusion: Our findings strongly suggest that mice susceptibility to chronic social defeat is related to low hippocampal exNMDAR function.

37. Gene-gene interaction between COMT and NET in modulating ADHD behaviors

Weam Fageera, MSc^{1, 2}, Natalie Grizenko, MD^{1, 3}, Sarojini M. Sengupta, PhD^{1, 3} and Ridha Joobar, MD, PhD^{1, 2, 3}. Douglas Mental Health University Institute, Montreal, Quebec, Canada.². Department of Human Genetics, McGill University, Montreal, Quebec, Canada.³. Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Background: Cortico-subcortical circuit dysfunction plays an important role in the manifestation of ADHD symptoms. Dopamine (DA) and norepinephrine (NE) are major players in the fine regulation of these circuits. Both of these neurotransmitters are major players in maintaining alertness, increasing focus, sustaining thoughts, and facilitating many cognitive functions. Thus, perturbation of either NE, DA (or both) signaling could be implicated in the pathogenesis of ADHD.

Hypothesis: Given the dynamic nature of the brain neuromodulation, where any action on one system may reverberate in the other systems, we hypothesize that NE transporter gene could interact with a gene that is essential for the metabolism of DA (COMT Val108/158Met) on modulating ADHD behaviors. METHODS: 481 children with ADHD (9-12 years old) were included in a 2 week double blind placebo controlled study with methylphenidate. Teachers and parents were asked to evaluate the child's behavior at baseline, placebo, and MPH weeks. Repeated measure ANOVA with between-subject factor of both genes and within-subject factor of experimental conditions (EC) was used.

Results: A highly significant 3-way interaction (NET*COMT*EC) was revealed in three SNPs of the NET gene (rs41154 p= 0.002, rs187714 p= 0.001, and rs2242447 p= 0.006) according to the parents' evaluation. By stratifying the children according to their COMT genotypes, we observe that all children behave in a similar fashion at baseline but respond differently to placebo and

MPH. In the Met/Met and Val/Val genotype groups, children who are carrying the AG genotype of rs41154, CT genotype of rs41154, and CT genotype of rs41154 tend to respond poorly compared to patients with the GG, CC, and CT genotypes respectively on placebo and MPH.

Conclusions: Taken together, the current results suggest the epistatic interaction between COMT and NET genetic polymorphisms on response to pharmacological probes. Suggesting that complex gene-by-gene interactions may be important to personalize pharmacological treatment.

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