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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Dr. Catharine Winstanley – University of British Columbia
Presidential Welcome

After Halifax and Kingston, we are delighted that the 41st CCNP Annual Meeting will be held in beautiful Vancouver. The meetings in the west of the country, usually either in Banff or Vancouver, are always a memorable experience, with a combination of high level scientific content and beautiful location. I hope that the CCNP will always alternate between the east and the west coasts, to be truthful to its values of nationwide representation and catalyst of networking between investigators and students from all Canadian universities.

Organizing a meeting in Vancouver presents many logistic challenges. We are fortunate that Dr. Alasdair Barr, the chair of the Local Organizing Committee, and all the other members took the challenge and made it possible for all of us to meet in downtown Vancouver for three days, which will allow us to be intellectually stimulated and, at the same time, enjoy few escapes here and there to treat our senses with beautiful sceneries, food and drinks. Thank you very much Alasdair and all the members of the LOC for putting the time and energy to keep the tradition going and to make the upcoming Vancouver meeting a success.

In addition to presenting and sharing scientific ideas and progress, the CCNP meeting is a privileged occasion for networking and creating links between investigators and students interested in the neuroscience of behaviour. It is also an opportunity to recognize the great achievements of our community. This year, the awards committee worked very hard to make fair, yet sometimes difficult decisions. The 2018 CCNP award winners are: Dr. Alan Evans (Heinz Lehmann Award), Drs. Isabelle Boileau and Stephanie Borgland (Young Investigator Award), and Dr. Patricia Boksa (CCNP Medal). My warmest 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.

Our field of research has grown tremendously in the last few decades. The explosion of knowledge on the brain and how it relates to behaviours is without precedent. This will of course present new challenges, and also a lot of opportunities. No doubt that “omics”, big data, and artificial intelligence are, and will be very much on the map. We need to embrace this complexity, but also keep refining our clinical intuition and improving our offer of services. Indeed, while these approaches may usher a Copernican revolution in psychiatry, there is a lot that can be achieved by improving and translating some of our well established findings that we have failed to act on. For this, a strong collaboration between clinicians and neuroscientists is needed. I hope the meeting participants will discuss such possibilities. No doubt that the Presidential conference by Dr David Goldbloom, a senior and world renown psychiatrist will help us to glean some insights about the future of our discipline.

Enjoy your meeting and I hope to see you all in June 2019 for the 42nd CCNP Annual Meeting in Montreal!

Ridha Joober
CCNP President
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15:00 – 19:00 CCNP Council Meeting (Telus Boardroom)

THURSDAY JUNE 28, 2018
07:30 – 17:00 Registration (Theatre Foyer)
07:30 – 08:30 Breakfast (Sunroom)
08:30 – 09:00 Welcoming Remarks (Theatre)
09:00 – 10:30 Presidential Symposium (Theatre)
   Dr. David Goldbloom (University of Toronto)
   Thoughts on the future of Psychiatry
      Chair: Dr. Ridha Joober (McGill University)
10:30 – 11:00 Break (Theatre Foyer or Sunroom)
11:00 – 12:30 Symposium 1: The impact of pharmacogenomics on clinical practice
      (Theatre)
         Chair: Dr. Katherine Aitchison (University of Alberta)
            11:00 Dr. Daniel Mueller (University of Toronto)
               Genome-wide association studies suggest an association between DGKB and antipsychotic induced weight gain in Europeans and African Americans
            11:20 Dr. Katherine Aitchison (University of Alberta)
               Drug metabolizing enzyme associations with response to agents used in neuropsychopharmacology
            11:40 Dr. Robert Stowe (University of British Columbia)
               Pharmacogenomics in adult neuropsychiatric practice: real-world examples
            12:00 Dr. Chad Bousman (University of Calgary)
               Selection and dosing of psychiatric medications: do commercial pharmacogenetic-based decision support tools provide equivalent advice?
      12:20 Discussion
12:30 – 13:30 LUNCH/CCNP Business Meeting (All are welcome) (Sunroom)
13:30 – 14:00 CCNP Next Generation Presentation 1 (Theatre)
            13:30 Dr. Julie Blendy (University of Pennsylvania)
               Neurobehavioral effects of early opioid exposure in mice: influence of the OPRM1 A118G single nucleotide polymorphism
13:45 Dr. Francesco Leri (University of Guelph)
*Intersection between nutrition and addiction: sugar and opiates*

14:00 – 15:00 **CCNP Heinz Lehmann Award Lecture** (Theatre)
Dr. Alan Evans (McGill University)
*A brain signature with high positive predictive power of ASD diagnosis*

Chair: Dr. Ridha Joober (McGill University)

15:00 – 15:30 Break (Theatre Foyer or Sunroom)

15:30 – 17:00 **Symposium 2: Novel insights into the neurobiology of major depression** (Theatre)

Chair: Dr. Naguib Mechawar (McGill University)

15:30 Dr. Caroline Menard (Université Laval)
*Social stress induces neurovascular pathology and immune response promoting depression*

15:50 Dr. Etienne Sibille (University of Toronto)
*Targeting gabaergic sst-positive interneurons deficits: implications for cognitive and mood symptoms in depression and other brain disorders*

16:10 Dr. Benoit Labonté (Université Laval)
*Sex-specific transcriptional signatures in human depression*

16:30 Dr. Naguib Mechawar (McGill University)
*The impact of child abuse on oligodendrocytes and myelination in the human brain*

16:50 Discussion

17:00 – 17:30 Free time

17:30 – 19:30 Reception (Sunroom)

**FRIDAY JUNE 29, 2018**

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

07:30 – 08:30 Breakfast (Theatre Foyer)

08:30 – 09:00 Welcoming Remarks (Theatre)
09:00 – 10:30 **Symposium 3: Advancing patient care from bench to bedside – the people and processes driving innovation (and how you can be part of it)** (Theatre)

  Chair: Dr. Thomas Raedler (University of Calgary)

09:00 Dr. Tara Moroz (Pfizer Canada)
* Bench to bedside: the road to a pharmaceutical product *

09:20 Dr. Thomas Raedler (University of Calgary)
* Psychiatry pharmacological pipeline *

09:40 Dr. Pierre Blier (University of Ottawa)
* Pharmacology matters, or does it? An evaluation of generic and innovative medicines *

10:00 Dr. Anthony Phillips (University of British Columbia)
* Canadian research in neuroscience, mental health and addictions – where we are headed? *

10:20 *Discussion*

10:30 – 11:00 Break (Theatre Foyer)

11:00 – 12:30 **Symposium 4: Cannabis and the brain: how Canadian research can lead the world** (Theatre)

  Chair: Dr. Darrell Mousseau (University of Saskatchewan)

11:00 Dr. Richard Huntsman (University of Saskatchewan)
* Cannabidiol enriched cannabis herbal extract in pediatric patients with refractory epileptic encephalopathy – the CARE-E study *

11:20 Dr. Robert Laprairie (University of Saskatchewan)
* Allosteric modulation of type 1 cannabinoid receptor in absence epilepsy *

11:40 Dr. Jane Alcorn (University of Saskatchewan)
* Cannabidiol dosing considerations in paediatric patients *

12:00 Dr. Darrell Mousseau (University of Saskatchewan)
* Changes in CB1 receptor expression in Alzheimer disease, Parkinson’s disease, and depression autopsied samples *

12:20 *Discussion*

12:30 – 14:00 Lunch (HSBC Hall/overflow)

13:00 – 14:00 **CCNP Poster Session 1** (HSBC Hall)

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

  Dr. William Honer (University of British Columbia)
  *Rapid change in fentanyl prevalence in a community-based, high-risk sample*
14:30 – 15:30 **CCNP Young Investigator Award Lecture** (Theatre)

14:30 Dr. Isabelle Boileau (University of Toronto)
*Fatty acid amide hydrolase: investigating potential brain-based biomarkers in post-traumatic stress disorder*

15:00 Dr. Stephanie Borgland (University of Calgary)
*Diet-induced obesity impairs outcome devaluation and alters excitability of the OFC*

Chair: Dr. Ridha Joober (McGill University)

15:30 – 15:45 Break (Theatre Foyer)

15:45 – 17:15 **Symposium 5: Neurostimulation: clinical applications and mechanisms of action** (Theatre)

Chair: Dr. Fidel Vila-Rodriguez (University of British Columbia)

15:45 Dr. Fidel Vila-Rodriguez (University of British Columbia)
*Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D)*

16:05 Dr. Frank MacMaster (University of Calgary)
*Repetitive transcranial magnetic stimulation in adolescents with treatment resistant depression*

16:25 Dr. Faranak Farzan (Simon Fraser University)
*Theta burst stimulation in treatment of youth depression*

16:45 Dr. Zafiris Daskalakis (University of Toronto)
*Neurophysiological mechanisms of rTMS efficacy in treatment resistant depression*

17:05 *Discussion*

18:30 – 19:30 **Gala Dinner** – Cocktails (Vancouver Convention Centre, 1055 Canada Place, Level 2 Ocean Foyer)

19:30 – 20:00 **CCNP Medal Award Presentation to Dr. Patricia Boksa** (Vancouver Convention Centre, 1055 Canada Place, Level 2 Ocean Foyer)
Presenter: Dr. Ridha Joober

**SATURDAY JUNE 30, 2018**

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

07:30 – 08:30 Breakfast (Theatre Foyer)
Symposium 6: New approaches for treatment of mental illness (Theatre)

Chair: Dr. Paul Albert (University of Ottawa)

- Dr. Shimon Amir (Concordia University)
  Regulation and behavioral implications of clock gene expression in the striatum

- Dr. Stephen Ferguson (University of Ottawa)
  CRF receptor1 regulates anxiety behaviour via sensitization of 5-HT2 receptor signaling

- Dr. Paul Albert (University of Ottawa)
  When SSRI’s don’t work: altered 5-HT1A autoreceptor gene repression results resistance to chronic SSRI treatment

- Dr. Pierre Blier (University of Ottawa)
  Novel approaches for early optimized treatment for clinical depression

Discussion

CCNP Next Generation Presentation 3 (Theatre)

- Dr. Jennifer Bossert (National Institute on Drug Abuse)
  Modeling opioid maintenance therapy in rats: effects of chronic buprenorphine and the biased mu-opioid receptor agonist TRV130 on relapse to oxycodone seeking

- Dr. Andrew Townsend (Virginia Commonwealth University)
  Rapid assessment of choice between fentanyl and liquid food in rats: effect of reinforcer magnitude and immunoantagonism

Break (Theatre Foyer)

Symposium 7: Sex, stress and mental health (Theatre)

Chair: Dr. Eric Dumont (Queen’s University)

- Dr. Eric Dumont (Queen’s University)
  Sex-specific estrogenic neurophysiology in homeostasis brain circuits

- Dr. Victor Viau (University of British Columbia)
  Sex differences in the hypothalamic-pituitary adrenal (HPA) axis and stress habituation

- Dr. Nafissa Ismail (University of Ottawa)
  Pubertal probiotic treatment promotes resilience to stress-induced mood disorders
12:00 Dr. Seema Bhatnagar (University of Pennsylvania)
*Sex differences in the role of orexins in mediating habituation to repeated stress and stress-induced changes in sleep and cognitive function*

12:20 Discussion

12:30 – 14:00 Lunch (HSBC Hall/overflow)

13:00 - 15:00 **CCNP Poster Session 2** (HSBC Hall)

15:00 – 16:30 **Symposium 8: Antidepressant effects of ketamine: synaptic mechanisms and network dynamics** (Theater)

Chair: Dr. Tak Pan Wong (McGill University)

15:00 Dr. Tak Pan Wong (McGill University)
*Roles of the location of NMDA receptors in the antidepressant effects of ketamine*

15:20 Dr. Yu Tian Wang (University of British Columbia)
*Critical roles of glutamatergic receptors and synaptic plasticity in ketamine antidepressant actions*

15:40 Dr. Conor Liston (Cornell University)
*Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced synaptogenesis*

16:00 Dr. Alexander McGirr (University of Calgary)
*Cortical glutamatergic functional hyperconnectivity after chronic stress and selective network effects of subanesthetic ketamine*

16:20 Discussion

16:30 **Poster Awards Presentation & Closing Remarks** (Theatre)

Dr. Ridha Joober (McGill University)
Thursday, June 28, 2018
Abstracts for Oral Presentations

Presidential Symposium

Thoughts on the future of Psychiatry
Dr. David Goldbloom, OC, MD, FRCPC, Senior Medical Advisor, Centre for Addiction and Mental, Professor of Psychiatry, University of Toronto, 250 College Street, Toronto, ON, Canada M5T 1R8

April 11, 2018 marked the 80th anniversary of the world’s first electroconvulsive treatment for severe mental illness and the dawn of modern era of current biological treatments in psychiatry. Eighty years later, where are we and what lies ahead? This lecture provides a personal, speculative and idiosyncratic view of some of the current challenges and areas for growth as psychiatry evolves in the 21st century. Because it is about the future, there will be no data – and no slides.

Symposium 1: The impact of pharmacogenomics on clinical practice

Genome-wide association studies suggest an association between DGKB and antipsychotic induced weight gain in Europeans and African Americans
Dr. Daniel Mueller, University of Toronto, Toronto, ON

Malgorzata Maciukiewicz, PhD¹, Arun K. Tiwari, PhD¹,², Clement C. Zai, PhD¹,², Eva J. Brandl, MD³, Natalie Freeman, MSc¹, Jeffrey A Liebermann MD⁴, Herbert Y Meltzer MD⁵, James L. Kennedy, MD¹,²,⁶, Daniel J. Mueller MD PhD¹,²,⁶ ¹. Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. ². Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. ³.Degree of Psychiatry, Charité Campus Mitte, Charité Universitätsmedizin Berlin, Germany. ⁴. Department of Psychiatry, College of Physicians and Surgeons, Columbia University and the New York State Psychiatric Institute, New York City, NY, USA.⁵. Department of Psychiatry and Behavioral Sciences, Northwestern University, Chicago, IL, USA. ⁶. Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Schizophrenia (SCZ) is a severe, debilitating disorder with a lifetime prevalence of 1%. The first line of treatment for schizophrenia is antipsychotic (AP) medications, which despite their clinical efficacy have been repeatedly found to be associated with severe side effects, such as antipsychotic-induced weight gain (AIWG). The objective of this investigation was to conduct a genome-wide association study (GWAS) of A1WG, followed by comprehensive, post-GWAS approaches.

Methods: We investigated n=201 schizophrenia or schizoaffective disorder patients of European and African American ancestry who were treated mostly with clozapine or olanzapine. We conducted genome-wide association analysis for AIWG defined primarily as a percentage of weight change from baseline.

Results: In the entire sample, we observed genome-wide significant association between a gene variant of the DGKB gene and AIWG (β=0.411; p=3.15×10⁻⁹). The association was nominally significant in both Europeans (β=0.271; p=0.002) and African Americans (β=0.579; p=5.73×10⁻⁵) with the same risk allele. In Europeans, the top variant (β=0.406; p=1.26×10⁻⁶) was located upstream of the STC2 gene. We noticed no significant enrichment in metabolic pathways for SNPs, but our top genes (p<5×10⁻⁵) were enriched in GWAS catalog for the risk of obesity and
schizophrenia. Top genes also interacted with the known risk factors for obesity (G6PD) and schizophrenia (NDEL1) and are targeted by miRNAs related to schizophrenia (mir-34a) and obesity (mir-19b). Polygenic risk score analyses did not provide support for major genetic overlap between obesity and the risk of AIWG.

Conclusions: Our findings suggested that a gene variant in the DGKB gene is associated with AIWG in both African American and European ancestry patients.

Drug metabolizing enzyme associations with response to agents used in neuropsychopharmacology

Dr. Katherine Aitchison, University of Alberta, Edmonton, AB

Diego L. Lapetina, PhD;¹ Yabing Wang, PhD;¹ Xiuying Hu, MD;¹ Beatriz Carvalho Henriques, BSc;¹ Matthew Maju Koola, MD;² Kopal Tandon, MD;³ Mark Kinirons, MD;⁴ Evangelia M. Tsapakis, MD;⁵ Dawon Lee, BSc;¹ Robin M. Murray;⁶ Katherine J. Aitchison, PhD;¹ Departments of Psychiatry and Medical Genetics, University of Alberta, Edmonton, Canada. ¹ Department of Psychiatry and Behavioural Sciences, George Washington University, DC, USA ³ The Mind Brain Behaviour Group, the University of Nottingham, Nottingham, UK ⁴ Department of Ageing and Health, Guy’s and St Thomas’ Hospitals, London, UK ⁵ Agios Charalambos Clinic, Crete ⁶ Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK

Introduction: Drug metabolizing enzymes are relatively understudied in pharmacogenomics as applied to neuropsychopharmacological agents. The objective of this presentation is to review associations between drug metabolizing enzymes and response to neuropsychopharmacological agents, and to outline some recent advances in technologies for identifying drug metabolizing enzyme variants.

Methods: 196 individuals treated with escitalopram in the GENDEP (Genome-based therapeutic drugs for depression) study were examined for an association between steady-state escitalopram concentration and CYP2C19 and CYP2D6 genotypes. 41 patients with treatment-refractory depression treated with tricyclic antidepressants were analysed for association between concentrations, response and CYP2D6 and CYP2C19. Individuals with a history of multiple intolerances to different antipsychotic medications were investigated for combined drug metabolizing enzyme deficiencies.

Results: In the GENDEP patients, there was an association between CYP2C19 genotypic category and escitalopram concentration, adjusting for age and CYP2D6 genotype (Bonferroni corrected p=0.0012; Huezo-Diaz et al., 2012). In the patients treated with tricyclic antidepressants, response to the tricyclics was associated with CYP2C19 genotype (p=0.013). Various technologies have been used to identify multiple different drug metabolizing enzyme deficiencies in those with multiple intolerances to antipsychotics.

Conclusion: Drug metabolizing enzyme genotype is associated with response to antidepressants and with adverse drug reactions to antipsychotics, and recent technological advances permit more accurate genotypic identification.

Pharmacogenomics in adult neuropsychiatric practice: real-world examples

Dr. Robert Stowe, University of British Columbia, Vancouver, BC

Robert M. Stowe, MD, Departments of Psychiatry and Neurology (Medicine), University of British Columbia, Vancouver, BC, Canada Monica Hrynchak, MD, Cytogenetic Laboratory, Royal Columbian Hospital, Vancouver, BC, Canada Agata Minor, PhD, Cytogenetic Laboratory, Royal Columbian Hospital, Vancouver, BC, Canada Christine Tyson, PhD, Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
**Introduction:** This presentation will illustrate the utility and challenges of using genetic information to inform pharmacotherapy in neuropsychiatry at the individual case level.  

**Methods:** Case examples will be presented, incorporating data from research and commercial pharmacogenomic panels in patients and chromosomal microarrays to demonstrate therapeutic relevance in patients with complex, treatment-resistant bipolar and psychotic spectrum presentations.  

**Results:** In the cases presented, pharmacogenomic data was generally helpful in guiding therapy and interpreting previous treatment failures and side effects, although they also illustrate the limitations of applying current knowledge and technology at the bedside.  

**Conclusion:** Pharmacogenomic panels that focus on pharmacokinetic and limited pharmacodynamic variants can be useful, but more comprehensive genotyping will likely be essential in developing precision medicine strategies in individual patients.

**Selection and dosing of psychiatric medications: do commercial pharmacogenetic-based decision support tools provide equivalent advice?**  
Dr. Chad Bousman, University of Calgary, Calgary, AB

Chad Bousman, MPH, PhD Departments of Medical Genetics, Psychiatry, and Physiology and Pharmacology, Cumming School of Medicine, University of Calgary; Calgary, AB, Canada Boadie Dunlop, MD Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

**Introduction:** Several companies have developed pharmacogenetic-based decision support tools (DSTs), marketed to prescribers to inform the process of medication selection and dosing for individual patients. However, the degree to which these DSTs agree on their genotypes, predicted phenotypes and medication recommendations is not known. As such, we evaluated the degree of agreement between commercial DSTs in the context of major depressive disorder (MDD) treatment.  

**Methods:** Four DSTs were selected for examination based on peer-reviewed evidence suggesting their potential clinical utility. Five outpatients with a primary diagnosis of MDD and a minimum of two previous antidepressant failures were tested using each of the four DSTs. Genotypes and predicted phenotypes associated with 14 genes as well as medication recommendations for 24 antidepressants, 18 antipsychotics, 12 anxiolytics/hypnotics, and seven mood stabilizers provided by each DST for each participant were assessed for agreement.  

**Results:** None of the DSTs evaluated the same combination of genes or variants on their testing panels. However, seven pharmacokinetic (CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, UGT2B15) and seven pharmacodynamic (BDNF, COMT, HLA-A, HTR2A, HTR2C, OPRM1, SLC6A4) genes were included on two or more of the four DST testing panels. Among these overlapping genes, genotype (33% - 100%) and predicted phenotype (20% -100%) agreement varied substantially. Medication recommendation agreement was greatest for mood stabilizers (84%), followed by antidepressants (56%), anxiolytics/hypnotics (56%) and antipsychotics (55%). Approximately one-quarter (2%) of all medication recommendations were jointly flagged by two or more DSTs as ‘actionable’ but 19% of these recommendations provided conflicting advice (e.g. dosing) for the same medication.  

**Conclusions:** The level of disagreement in medication recommendations across the pharmacogenetic DSTs indicates that these tests cannot be assumed to be equivalent or interchangeable. Additional efforts to standardize genetic-based phenotyping and to develop medication guidelines are warranted.
Neurobehavioral effects of early opioid exposure in mice: influence of the OPRM1 A118G single nucleotide polymorphism

Dr. Julie Blendy, University of Pennsylvania, Philadelphia, PA, USA

Shivon A. Robinson, PhD Center for Neurobiology and Behavior, Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, Philadelphia, PA, USA Michelle E. Ehrlich, MD Department of Neurology and Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA Julie A. Blendy, PhD Center for Neurobiology and Behavior, Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, Philadelphia, PA, USA

Background: Opioid use among pregnant women is a significant public health concern. Infants exposed to opioids in utero are at high risk of exhibiting Neonatal Opioid Withdrawal Syndrome (NOWS), a combination of somatic withdrawal symptoms including high pitched crying, sleeplessness, irritability, gastrointestinal distress, and in the worst cases, seizures. We developed a mouse model of opioid exposure to cover either the equivalent length of human pregnancy or the third trimester only. Clinical findings suggest that genomic variation in the OPRM1 gene (A118G SNP) may influence NOWS severity with the G-allele specifically associated with shorter length of stay in the hospital and less likelihood of receiving any treatment compared to infants without the SNP.

Methods: We implanted C57Bl6/J dams with osmotic minipumps containing morphine 10 mg/kg/day or saline. Postnatal day (PND) 1-14 in rodents is considered equivalent to the third trimester in humans, therefore we continued morphine exposure by injecting pups with morphine 10 mg/kg. To determine if early morphine exposure produces long-lasting effects we measured affective behavior in adolescents (marble burying, elevated zero maze and the light-dark box). In addition, we assessed drug sensitivity to either morphine or cocaine in adulthood following spontaneous withdrawal using a locomotor sensitization paradigm.

Results: Mice with the G-allele do not show morphine-induced delays in reaching developmental milestones. Morphine reduced ultrasonic vocalizations but withdrawal precipitated an increase in USVs which may reflect the increased crying present in NOWS babies. Morphine exposure significantly reduced the anxiety in the marble burying task in A-but not G-allele mice. In adult mice morphine exposure blunted locomotor sensitization to repeated morphine and cocaine.

Conclusions: Our model of NOWS recapitulates robust withdrawal symptoms that reflect clinically relevant behaviors and enables the study of genetic contributions and suggests a protective effect of the Oprm1 G-allele.

Intersection between nutrition and addiction: sugar and opiates

Dr. Francesco Leri, University of Guelph, Guelph, ON

Meenu Minhas, MSc & Francesco Leri, PhD Department of Psychology, University of Guelph, Guelph, Ontario, Canada.

Could a diet high in refined sugars enhance vulnerability to opiate addiction? There is substantial experimental evidence that refined sugar can promote addictive behaviors by activating brain’s rewards centers in much the same way as addictive drugs. Opiate addiction is also associated with poor dietary habits, including preferences for sugar-rich foods, as well as malnutrition. These connections have led to questions of whether excessive consumption of refined sugar can affect vulnerability to opiate addiction, and whether exposure to opioid drugs can lead to excessive sugar consumption. At this symposium, we will present data obtained in rats exposed to methadone or naltrexone and tested on operant intraoral self-administration of high fructose corn
syrup (HFCS); a refined sugar produced by chemically processing of corn commonly used as sweetener in North America. We will also describe the effects of HFCS pre-exposure on intravenous self-administration of oxycodone, oxycodone place preference, and oxycodone-induced dopamine concentration in the nucleus accumbens, a biomarker of drug reward. Our findings, and those of other laboratories, strongly suggest that prevention of unhealthy diets may not only help reduce the obesity epidemic, but also reduce environmental factors that may predispose to opiate addiction.

**CCNP Heinz Lehmann Award Lecture**

**A brain signature with high positive predictive power of ASD diagnosis**

Dr. Alan Evans, Professor of Neurology/Neurosurgery, Biodmed. Eng., Med. Physics, McGill University, Montréal, QC

Characterizing brain organizational abnormalities in ASD have been hindered by considerable subject heterogeneity. We therefore sub-categorized a ASD cohort based on connectivity information. Data from the ABIDE-1 database (182 ASD, 188 TDC, mean age 16.9) yielded cortical thickness (CT, using CIVET) measures and individualized seed-based functional connectivity (FC, using NIAK) measures for 20 networks. We extracted 5 features, each being the average value (CT or FC) in a homogeneous subgroup of the data. Individual similarity with the extracted sub-features is the subtype weight. The normalized subtype weights of 5 CT subtypes, 5 * 20 FC subtypes, and individual Age, Brain volume, and mean FC scores were used as features (108 features in total) to train our Highly Predictive Signature (HPS) model. We first identified subjects that were consistently correctly classified by a support vector machine on 1000 random subsamples of the data. Then we trained a regularized logistic regression to predict only these easy cases. Model performance on new data was estimated through 10-fold cross-validation. Lastly, we trained the model on the full dataset to investigate features with non-zero weight. 40% of ASD patients were either mostly (>90%) or rarely (<10%) correctly classified. The cross-validated specificity (SPC) and sensitivity (SEN) of the model was 96.8% and 18.7%. This translated to a precision (PPV) of 85.4%. The precision of our prediction (SPC 96.8, SEN 18.7, PPV 85.4) is higher than the average of three published models (SPC 80.2, SEN 79.3, PPV 79.9), opening up new avenues for targeted intervention.

**Symposium 2: Novel insights into the neurobiology of major depression**

**Social stress induces neurovascular pathology and immune response promoting depression**

Dr. Caroline Menard, Université Laval, Montréal, QC

Caroline Menard, Department of Psychiatry and Neurosciences, Faculty of Medicine, Université Laval & CERVO Brain Research Center, Quebec City (QC), Canada

Studies suggest that heightened peripheral inflammation contributes to the pathogenesis of major depressive disorder. We investigated the effect of chronic social defeat stress, a mouse model of depression, on blood-brain barrier (BBB) permeability and infiltration of peripheral immune signals.
We found reduced expression of endothelial cell tight junction protein claudin-5 (cldn5) and abnormal blood vessel morphology in nucleus accumbens (NAc) of stress-susceptible but not resilient mice. CLDN5 expression was also decreased in NAc of depressed patients. Cldn5 down-regulation was sufficient to induce depression-like behaviors following subthreshold social stress while chronic antidepressant treatment rescued cldn5 loss and promoted resilience. Reduced BBB integrity in NAc of stress-susceptible or AAV-shRNA-cldn5-injected mice caused infiltration of peripheral cytokine interleukin-6 (IL-6) into brain parenchyma and subsequent expression of depression-like behaviors. These findings suggest that chronic social stress alters BBB integrity through loss of tight junction protein cldn5, promoting peripheral IL-6 passage across the BBB and depression.

**Targeting gabaergic sst-positive interneurons deficits: implications for cognitive and mood symptoms in depression and other brain disorders**

**Dr. Etienne Sibille, University of Toronto, Toronto, ON.**

**Background:** The brain excitation inhibition balance (EIB) is characteristically disrupted in neuropsychiatric disorders, including major depressive disorder (MDD), bipolar disorder (BPD), anxiety disorders, and schizophrenia (SCZ). Nearly three decades of research demonstrate a role for reduced GABA level and function in altered EIB. In MDD, recent evidence from human postmortem and animal studies suggests a selective vulnerability of GABAergic interneurons that co-express the neuropeptide somatostatin (SST).

**Methods:** To investigate the EIB in MDD, we used human post-mortem samples and genetic rodent models, combined with genomic and bioinformatics approaches. To target deficient GABAergic function, we used medicinal chemistry, pharmacological approaches and rodent behavioral models.

**Results:** We reported consistent reductions of SST and other markers of GABAergic neurons targeting pyramidal cell dendrites in post-mortem samples of MDD patients. We and others have extended these findings to BPD, SCZ and Alzheimer’s disease (AD). Our rodent studies demonstrate that reduced SST+ cell induces changes in behavioural emotionality. Novel small molecule compounds with positive allosteric modulation at the alpha5-containing GABA-A receptor, which partly mediate the function of SST+ neurons, now show dose-dependent robust precognitive and antidepressant effects. Results have been confirmed using series of related compounds (adult C57B6 mice; n=8-10/group/dose, 50% female; alpha=0.05).

**Conclusions:** Reduced SST expression and SST-positive cell function is frequently observed in MDD and other brain disorders, suggesting a selective vulnerability of these cells and a deficit in regulating excitatory input onto pyramidal neurons. Targeting these deficits through augmenting GABA function at receptors mediating SST cell function has procognitive and antidepressant potential.

**Sex-specific transcriptional signatures in human depression**

**Dr. Benoit Labonté, Université Laval, Montréal, QC**

Benoit Labonté Assistant Professor CERVO Brain Research Centre Department of Psychiatry and Neurosciences Faculty of Medicine, Laval University 60, Chemin de la Canardière Québec

While the incidence, symptoms and treatment of MDD all point toward major sex differences, the molecular mechanisms underlying this sexual dimorphism remain largely unknown. Recently, we provided a comprehensive characterization of male and female transcriptional profiles associated with MDD across 6 brain regions. Our results show limited overlap between males and females. Performing interspecies analyses, we showed that different models of stress reproduce various transcriptional alterations relevant to MDD in a sex-specific fashion. Capitalizing on converging
pathways, we defined the molecular and physiological mechanisms underlying the expression of stress susceptibility in males and females. We identified key regulators of sex-specific gene networks and confirmed their sex-specific impact as mediators of stress susceptibility. For instance, downregulation of the female-specific hub gene DUSP6 in prefrontal cortex mimics stress susceptibility in females only by increasing ERK signaling and pyramidal neuron excitability. Together, our findings reveal dramatic sexual dimorphism at the transcriptional level in MDD.

The impact of child abuse on oligodendrocytes and myelination in the human brain
Dr. Naguib Mechawar, McGill University, Montréal, QC

Naguib Mechawar, PhD; Department of Psychiatry, McGill University & Douglas Hospital Research Centre, Montreal (QC), Canada.

Introduction: Child abuse has devastating and long-lasting consequences on individuals, considerably increasing the lifetime risk of negative mental health outcomes such as depression and suicide. Yet, the neurobiological processes underlying this increase in vulnerability remain poorly understood. Here, we investigated the hypothesis that epigenetic, transcriptomic and cellular adaptations may associate in the anterior cingulate cortex with a history of child abuse.

Methods: Postmortem brain samples from a total of N=78 human subjects and from a rodent model of the impact of early-life environment (N=24) were analysed. Groups were constituted of depressed individuals who died by suicide, with (N=27) or without (N=25) a history of severe child abuse, as well as of psychiatrically healthy controls (N=26). 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 loci was performed following fluorescence activated cell sorting of oligodendrocyte and neuronal nuclei. Differential gene expression was validated using Nanostring technology. Finally, oligodendrocytes and myelinated axons were analysed using stereology and Coherent Anti-stokes Raman Scattering microscopy.

Results: A history of child abuse associated with cell-type specific changes in DNA methylation of oligodendrocyte genes and a global impairment of the myelin-related transcriptional program. These effects specifically occurred as a function of child abuse, as they were absent in depressed suicides with no history of early life adversity, and strongly correlated with myelin gene expression changes observed in the animal model. Furthermore, a selective and significant reduction in the thickness of myelin sheaths around small-diameter axons was observed in individuals with history of child abuse.

Conclusion: This study indicates that child abuse, in part through epigenetic reprogramming of oligodendrocytes, may lastingly disrupt cortical myelination, a fundamental feature of cerebral connectivity.
Symposium 3: Advancing patient care from bench to bedside – the people and processes driving innovation (and how you can be part of it)

Bench to bedside: the road to a pharmaceutical product
Dr. Tara Moroz, PhD, Medical Affairs, Pfizer Canada

Over the past century, many new medicines have advanced patient care by substantially improving overall health and quality of life, supporting disease prevention, management, and outcomes, and contributing to medical and scientific knowledge. Drug development is a multi-step process of diverse activities, spanning many years. It includes drug discovery, non-clinical testing, clinical development (phase I, II, and III clinical trials), and post-approval studies (phase IV). To find an optimal compound, many compounds – sometimes hundreds of thousands – must be screened. In the nonclinical stage of testing, proteomics, structure–function analysis, bioinformatics, and cell-based functional assays may be used to refine the compound. Once a lead compound has been identified, various steps are required to scale-up synthesis in order to produce enough of the candidate drug for nonclinical and clinical studies. An appropriate formulation must also be developed for suitable administration in the target study population, e.g., tablet, liquid, patch, gel, intravenous. On average it may take up to 8 years to get to this stage and many compounds will fall by the wayside. Nonclinical testing in animals and in vitro assays is required to determine the pharmacology, metabolism, and safety of an investigational medicine before it can be studied in humans. The pharmaceutical company then files an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA) or European Medicines Agency. Approval of this application allows the investigational medicine to be studied in humans. The clinical development stage can then be undertaken. Clinical trials may take 2–3 years (or more) to complete. Provided the compound completes nonclinical and clinical studies successfully, it can be submitted to regulatory authorities for approval. Regulatory review can take 1-2 years. Overall, on average, successful launch of the new medicine takes an average of 10-15 years from compound identification.

Psychiatry pharmacological pipeline
Dr. Thomas Raedler, MD, University of Calgary, Calgary, AB

While multiple unmet therapeutic needs remain in psychiatry, many pharmaceutical companies have either discontinued or significantly reduced their drug-development programs for CNS-Disorders. Despite this worrisome trend, several new pharmacological agents, as well as modifications / new formulations of previously approved medications, have been approved over the past years. Examples include levomilnacipran, vilazodone and vortioxetine as antidepressants; Aripiprazole for prolonged release injectable suspension, bexpiprazole, caripirazine and paliperidone palmitate 3 month as antipsychotics; methylphenidate hydrochloride (Foquest™) as a long acting stimulant. Other medications have received new indications or are under review by Health Canada / FDA. Examples include different antipsychotics for use in MDD and bipolar depression, aripiprazole for prolonged release injectable suspension for bipolar disorder and lisdexamfetamine for binge-eating disorder. Some newly approved pharmacological agents have a completely novel mechanism of action (pimavanserin for psychosis; suvorexant for insomnia). Other novel antidepressants (esketamine, rapastinel) and antipsychotics (ITI-007, MIN-101) are currently in phase III clinical trials. This presentation will review these treatment options with a focus on novel pharmacological treatment-options that are currently in development.
Pharmacology matters, or does it? an evaluation of generic and innovative medicines
Pierre Blier MD, PhD, Endowed Chair and Director, Mood Disorders Research Unit, Canada Research Chair in Psychopharmacology, Professor, Departments of Psychiatry and Cellular & Molecular Medicine, University of Ottawa, Institute of Mental Health Research

Treatment resistance in psychiatric disorders is very common and failing to get patients into full remission and maintaining wellness are solid predictors of relapse. Patients may be prescribed medications over quite a wide range of doses that may engage different receptors or transporters based on their affinity for these neuronal elements. Given that levels of multiple generic medications are allowed to vary from 80 to 125% of the brand level, there can be significant variations in drug exposure that may alter the effectiveness of generic medications. Result from controlled studies will be presented. Clinicians must take into account such variations when managing lack of response to treatment, side effects, or loss of response.

Canadian research in neuroscience, mental health and addictions – where we are headed?
Dr. Anthony G. Phillips, PhD, FRSC, FCAHS, Department of Psychiatry, University of British Columbia, Vancouver, BC

Key elements necessary to ensure significant breakthroughs in gaining unique insights into the neural and psychosocial bases of mental ill-health including substance misuse and their translation into new and more effective diagnostics and therapeutics are now aligned. As with most strategic initiatives, funding is the key. Over the past 12 months, Canada has seen the most significant increase in over a decade in the base budget of the Canadian Institutes for Health Research (CIHR) for basic and clinical health research. The CIHR Institute for Neurosciences, Mental Health and Addiction will play an increasingly important role in leading key federal research initiatives, especially when linked to public health crises such as the Opioid Crisis. When coupled with the outstanding success of leading university-based neuroscience groups in the recent Canada First Research Excellence Funds competition, this lays the foundation for a major nation-wide neuroscience and mental health research network. Complementing these significant investments by the current federal government, are generous donations from the private sector. These include the $100 Million gift to CAMH to advance the understanding and treatment of mental ill-health and the welcome announcement by the Weston Brain Institute of a Canada Big Ideas program designed to have a sustained impact on the development of therapeutics for neurodegenerative diseases of aging with a budget of up to $20 million.

In addition to improved funding, Canada has a second ‘ace in the hole’, namely an unparalleled ability to work cooperatively to achieve key national research goals. Beginning immediately, we must create additional new partnerships between preclinical and clinical researchers, ideally with close alliances with the private sector. The opportunity to align these efforts with international initiatives such as the Kavali Foundation International Brain Initiative must also be a high priority. Following this prescription, we could achieve Mental Health for all within a decade.

Symposium 4: Cannabis and the brain: how Canadian research can lead the world
Cannabidiol enriched cannabis herbal extract in pediatric patients with refractory epileptic encephalopathy – the CARE-E study
Dr. Richard Huntsman, University of Saskatchewan, Saskatoon, SK

Laprairie R, Lim HJ, Tellez-Zentino J, Huntsman RJ

**Introduction:** Initial studies suggest pharmaceutical grade cannabidiol (CBD) can reduce the frequency of convulsive seizures and lead to improvements in quality of life in children affected by epileptic encephalopathies. Physicians show reluctance to recommend Cannabis extracts given the lack of high quality safety data concerning the potential of harm caused by other cannabinoids especially 9-tetrahydrocannabinol (9-THC) and a lack of pharmacokinetic data of the cannabinoids in children. In order to address these concerns, the Cannabidiol in Children with Refractory Epileptic Encephalopathy (CARE-E study was established.

**Methods:** 30 children with epileptic encephalopathy refractory to standard medical treatment and aged 1 to 10 years will be enrolled from 5 Canadian cities into an open label, dose-escalation phase 1 trial. The primary outcomes for the study are (i) to determine if the cannabidiol enriched Cannabis Herbal Extract is safe and well-tolerated for pediatric patients with refractory epileptic encephalopathy and (ii) to determine the effect of cannabidiol enriched Cannabis Herbal Extract on the frequency and duration of seizures. Secondary outcomes include: (i) determine if extracts alter steady-state levels of co-administered anticonvulsant medications, (ii) assess effects of extracts on patient’s quality of life, (iii) determine the relationship between dose escalation and steady state trough levels of bioactive cannabinoids, and (iv) determine the relationship between dose escalation and incidence of adverse effects.

**Results:** Preliminary results for the CARE-E study suggest that CBD enriched Cannabis Herbal Extract is both well tolerated and provides benefit in controlling seizures in children with refractory epileptic encephalopathy. Preliminary pharmacokinetic data will also be presented. **Discussion:** The design of a phase 1 trial of cannabidiol enriched Cannabis Herbal Extract in children with epileptic encephalopathy refractory to medical treatment will be presented along with the advantages and challenges in performing pediatric Cannabis based clinical research in Canada.

**Allosteric modulation of type 1 cannabinoid receptor in absence epilepsy**

Dr. Robert Laprairie, University of Saskatchewan, Saskatoon, SK

Robert B. Laprairie, Quentin Greba, Mariam Alaverdashvili, Michael Anderson, Andrew J. Roebuck, Wendie N. Marks, Pushkar M. Kulkarni, Terrance P. Snutch, Ganesh A. Thakur, John G. Howland

Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are a rodent model of childhood absence epilepsy that display frequent absence seizures and an anxiety-like phenotype in the elevated plus maze and increased acoustic startle response. The present experiment tested the effects of acute treatment with the type 1 cannabinoid receptor 1 (CB1R) positive allosteric modulator GAT211 (10 mg/kg) on absence seizures and the anxiety-like phenotype of GAERS and a non-epileptic control (NEC) strain. In the first experiment, adult male GAERS (n=4) were implanted with recording electrodes in sensorimotor cortex and hippocampus. After recovery from surgery, rats were well-habituated to a recording chamber and EEG was recorded twice for 3 h on separate days. Rats were treated (i.p.) with either vehicle or GAT211 1 h after recording was initiated. Initial analyses revealed that GAT211 treatment decreased the total duration of seizures for 1 h after treatment. In the second experiment, male (n=4) and female (n=4) GAERS and NEC were injected with either vehicle or GAT211 and then tested on a battery of behavioural tests including the elevated plus maze and acoustic startle. Vehicle-treated GAERS showed decreased open arm time on the elevated plus maze and increased startle compared to NEC. Importantly, GAT211 treatment normalized both behaviours in GAERS without significant effects in NEC. These results suggest that positive allosteric modulation of CB1R may be therapeutically effective target for ameliorating absence seizures and their comorbidities such as anxiety.
Cannabidiol dosing considerations in paediatric patients

Dr. Jane Alcorn, University of Saskatchewan, Saskatoon, SK

When conventional medicine fails, some caregivers turn to cannabis-based products to effect seizure control in their children (high cannabidiol, low THC products). Given the lack of randomized clinical trials, physicians face uncertainty with recommending an appropriate dosage regimen for paediatric patients, defaulting often to the adage “start slow, go slow, stay low”. Oral administration is a preferred route for chronic disease management and, therefore, onset and duration of action of an oral cannabis product will be determined by the absorption and disposition (ADME) processes acting on the dosage form. In children, growth and physiological changes alter drug absorption and disposition such that the dose requirement (normalized on a body weight basis) may change with paediatric age. I will highlight current understandings of the ontogeny of drug absorption and disposition processes and discuss how growth and maturation might alter cannabidiol pharmacokinetics and dosing requirements relative to the young adult.

Changes in CB1 receptor expression in Alzheimer disease, Parkinson’s disease, and depression autopsied samples

Dr. Darrell Mousseau, University of Saskatchewan, Saskatoon, SK

The expression of the type 1 cannabinoid receptor (CB1R) in depression as well as in neurodegenerative disorders such as Alzheimer disease (AD) and Parkinson’s disease (PD) suggest both mechanistic and adaptive responses to disease progression. The sex of the patient could be contributing to CB1R function. Mouse models of AD suggest that the CB1R inhibits production of the beta-amyloid peptide (Abeta) and regulates Tau phosphorylation (two features of the AD brain). We examined autopsied cortical, hippocampal, and cerebellar samples (AD and age-/sex-matched controls) and explored whether there was any correlation with plaque-associated Abeta levels as well as with pSer396-Tau (paired helical filaments) levels. Sex-dependent patterns were observed. Levels of the CB1R were also examined in cortical samples from patients with a diagnosis of depression or PD. The role(s) of the CB1R in these contexts will be discussed.

CCNP Next Generation Presentation 2

Rapid change in fentanyl prevalence in a community-based, high-risk sample

Dr. William Honer, University of British Columbia, Vancouver, BC

William G. Honer, MD, FRCPC, FCAHS, Jack Bell Chair in Schizophrenia, Professor and Head, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, V6T 2A1

The Hotel study is a 10-year longitudinal study of risk factors and health outcomes of people living in marginal housing or homelessness. The cohort provided an opportunity to assess the prevalence of fentanyl in a community-based sample, complementing previous studies relied on autopsy findings, or assays of seized drugs. Between March and July, 2017, 237 participants provided monthly urine samples for drug screens. Among opioid users (n=91) the prevalence of fentanyl detected in urine increased from 45% in March, to 100% by July. In participants also being prescribed opioid agonist therapy (n=57), 55% had urine samples positive for fentanyl. Concurrent with the greatest month-to-month increase in fentanyl-positive urine samples, overall police calls and deaths related to overdoses in the City of Vancouver also increased. There were six deaths over this period in the study participants, at least four were thought to be overdoses.
Rapid increases in the prevalence of a high potency opioid create great risk for overdose deaths, and as greater tolerance develops in the community, the risk of exposure in those prescribed opioid agonist therapy with lower potency drugs may also increase.

**CCNP Young Investigator Award Lecture**

**Fatty acid amide hydrolase: investigating potential brain-based biomarkers in post-traumatic stress disorder**

Dr. Isabelle Boileau, University of Toronto, Toronto, ON

Isabelle Boileau PhD, Duncan Green, Belinda Williams, Donald Richardson M.D., Jinhee Kim PhD, Nancy Lobagha PhD, Rachel F. Tyndale, PhD, Richard Bazinet PhD, Sylvain Houle MD PhD, Junchao Tong PhD, Stephen J. Kish PhD.

**Background:** Fatty Acid Amide Hydrolase (FAAH), the enzyme responsible for terminating the endocannabinoid anandamide’s signaling at the cannabinoid receptor, has been proposed to play a role in the expression of post-traumatic stress disorder (PTSD). It has been suggested, based on preclinical and recent imaging studies that the enzyme FAAH might modulate key neural circuitry implicated in ‘fear’ response. Our Aims were to test the hypotheses that (1) catabolic activity of the enzyme FAAH is increased in PTSD and; (2) related to activity in ‘fear’ related network (amygdala and ventromedial prefrontal cortex [vmPFC]).

**Methods:** Healthy subjects (n = 31; 36 years old) and individuals with PTSD (n = 7; 43 years old) participated in a positron emission tomography scan following injection of the FAAH probe [11C]CURB and completed a functional magnetic resonance imaging session during resting-state. Blood was collected to measure endocannabinoids and to genotype a FAAH polymorphism (rs324420, C385A) which affects [11C]CURB binding. FAAH activity ([11C]CURB) was investigated brain-wide, group differences were assessed statistically using ANOVAs and relationship between [11C]CURB in amygdala and resting-state connectivity was investigated with a seed-based (in amygdala) analysis.

**Results:** We found no evidence for elevated brain FAAH or reduced peripheral anandamide in PTSD. Instead we find that subjects with PTSD have significantly elevated levels of the major endocannabinoid 2-AG. Furthermore, in healthy controls we find a negative relationship between [11C]CURB binding in amygdala and coupling between amygdala and vmPFC.

**Conclusion:** These are the first preliminary data of endocannabinoid metabolism in living brain of individuals with PTSD. The multimodal imaging data in healthy controls point to the role of FAAH in modulating activity in ‘fear’ circuitry. Confirmation of these findings in a sample of subjects with PTSD may advance the development of imaging biomarker for subtypes of (i.e: fear-based) PTSD.

**Diet-induced obesity impairs outcome devaluation and alters excitability of the OFC**

Dr. Stephanie Borgland, University of Calgary, Calgary, AB

Lindsay Naef, PhD*, Lauren Seabrook, BSc*, Corey Baimel, PhD, Madelyn Ellis, Allap Kaur & Stephanie L. Borgland, PhD Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary

**Introduction:** To make an appropriate decision one must evaluate the appropriate value of the outcome based on current information. This goal directed behavior, updating the action based on the value of the outcome is mediated via the orbital frontal cortex (OFC). The OFC has previously been shown to be important in outcome guided behaviours and is essential for selecting goals
based on current, updated values of expected reward outcomes. Little is understood on how this neural circuit is impeded in diet-induced obesity. We tested the hypothesis that obese mice have impaired ability to devalue rewards and this may be due to alterations in the OFC.

**Methods:** Male C57BL6 mice were fed a high or low fat diet for 12-15 weeks. Mice were trained to lever press for sucrose on a random ratio 20 and then tested in the valued (prefed with water) or devalued (prefed with sucrose) state. In some animals we used whole cell patch clamp electrophysiology in lateral OFC brain slices from obese or lean mice.

**Results:** We found that unlike lean mice, obese mice had impaired outcome devaluation when pre-fed with the sucrose reward. This was not due to altered motivation for the sucrose reward as obese and normal weight animals performed similarly on a progressive ratio for sucrose. Using in-vitro electrophysiology we show that diet induced obesity reduces inhibitory tone onto OFC pyramidal neurons. To determine if decreased inhibitory input to pyramidal neurons leads to impairment in reward devaluation in normal weight animals, we expressed an inhibitory DREADDs in VGAT ires cre mice. Reducing inhibitory tone onto pyramidal neurons in normal weight animals induced deficits in selective satiety reward devaluation.

**Conclusion:** We find that diet-induced obesity decreases inhibitory tone onto pyramidal neurons in the OFC and this is associated with deficits in outcome devaluation.

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**Symposium 5: Neurostimulation: clinical applications and mechanisms of action**

**Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D)**

*Dr. Fidel Vila-Rodriguez,* University of British Columbia, Vancouver, BC

- Vila-Rodriguez, Fidel, MD; Blumberger, Daniel M, MD, MSc; Thorpe, Kevin E, MMath; Feffer, Kfir, MD; Noda, Yoshihiro, MD; Giacobbe, Peter MD; Knyahnytska, Yuliya, MD; Kennedy, Sidney H, MD; Lam, Raymond W, MD; Daskalakis, Zafiris J, MD, PhD; Downar, Jonathan, MD, PhD.

**Symposium:** "Mechanisms of rTMS" Background Treatment-resistant major depressive disorder (TRD) is common and repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for TRD. The goal of the study was to establish the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in adults with treatment-resistant depression.

**Methods:** RCT, non-inferiority. Participants were aged 18–65 years, were diagnosed with a current treatment-resistant major depressive episode or could not tolerate at least two antidepressants in the current episode, and had an HRSD-17 score of at least 18. Treatment was delivered open-label but investigators and outcome assessors were masked to treatment groups. Participants were treated with 10 Hz rTMS or iTBS to the left dorsolateral prefrontal cortex, administered on 5 days a week for 4–6 weeks. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score.

**Results:** 414 participants were randomized to receive 10Hz (205) and iTBS (209). HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group (adjusted difference 0·01, lower 95% CI -1·16; p=0·0011), which indicated non-inferiority of iTBS. The most common treatment-related adverse event was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208).

**Conclusion:** In patients with TRD, iTBS was non-inferior to 10 Hz rTMS for the treatment of depression. Both treatments had low numbers of dropouts and similar side-effects, safety, and tolerability profiles. By use of iTBS, the number of patients treated per day with current rTMS devices can be increased several times without compromising clinical effectiveness.
Repetitive transcranial magnetic stimulation in adolescents with treatment resistant depression

Dr. Frank MacMaster, University of Calgary, Calgary, AB

Frank P. MacMaster, PhD, Paul E. Croarkin, DO, T. Christopher Wilkes, MD, Quinn McLellan, MSc, Lisa Marie Langevin, PhD, Natalia Jaworska, PhD, Rose M. Swansburg, MSc, Yamile Jasaui, MSc, Ephrem Zewdie, PhD, Patrick Ciechanski, PhD, Adam Kirton, MD

Symposium: "Mechanisms of rTMS". Introduction: Major depressive disorder (MDD) is common in youth and treatment options are limited. We evaluated the effectiveness and safety of repetitive transcranial magnetic stimulation (rTMS) in adolescents and transitional aged youth with treatment resistant MDD.

Methods: This was a three-week, open-label, single center trial of rTMS at an outpatient clinic in a children’s hospital. 32 outpatients with moderate to severe, treatment-resistant MDD, aged 13 – 21 years participated. rTMS was applied to the left dorsolateral prefrontal cortex (DLPFC) using neuronavigation and administered for 15 consecutive weekdays (120% rest motor threshold; 40 pulses over 4 seconds [10 Hz]; inter-train interval, 26 seconds; 75 trains; 3000 pulses). The primary outcome measure was change in the Hamilton Depression Rating Scale (Ham-D). Treatment response was defined as a greater than 50% reduction in Ham-D scores. Safety, tolerability, and biomarkers were also examined.

Results: rTMS was effective in reducing MDD symptom severity (t = 8.94, df = 31, p < 0.00001). We observed 18 (56%) responders (= 50% reduction in Ham-D score) and 14 non-responders to rTMS. Fourteen subjects (44%) achieved remission (Ham-D score = 7 post-rTMS). There were no serious adverse events (i.e. seizures). Mild to moderate, self-limiting headaches (19%) and mild neck pain (16%) were reported. Participants ranked rTMS as highly tolerable. The retention rate was 91% and compliance rate (completing all study events) was 99%. Non-responders to rTMS had thicker DLPFC gray matter and elevated glutamate as compared to responders.

Conclusion: Our single center, open trial suggests that rTMS is a safe and effective treatment for youth with treatment resistant MDD. Furthermore, it identifies potentially predictive biomarkers of response.

Theta burst stimulation in treatment of youth depression

Dr. Faranak Farzan, Simon Fraser University, Burnaby, BC

Faranak Farzan, Prabhjot Dhani, Sravya Atluri, Yuliya Knyahnytska, Darren Courtney, Stacey Shim, Paul Croarkin, Daniel Blumberger, and Zafiris Jeff Daskalakis

Symposium: "Mechanisms of rTMS" Introduction: Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved non-invasive treatment for adult treatment-resistant depression (TRD) but studies in youth are sparse. Our objective was to assess the therapeutic potential of a brief form of rTMS in youth TRD and examine its influence on frontal inhibitory functioning.

Methods: We conducted an open label two-week clinical trial of Theta Burst Stimulation (TBS) from 2016 to 2017. Intermittent TBS was applied to left dorsolateral prefrontal cortex (DLPFC) and continuous TBS was applied to right DLPFC in twenty youth TRD. We used longitudinal EEG and TMS-EEG to monitor impact of TBS at rest and during Go/NoGo inhibitory control task. Depressive symptoms were assessed by the HRSD and The Children’s Depression Rating Scale, revised-version (CDRS-R) at baseline, during (week-1), and post week-2.

Results: Twenty TRD youth (9F, age range: 16-24 yr) were enrolled. All patients received and tolerated at least 6 daily TBS treatments with no adverse events. 18 subjects received all 10 treatments. Despite the brief daily sessions (10 min) and treatment duration (2-week), there was a significant improvement in depressive symptoms from baseline to treatment 5 (p<0.001) and treatment 10 (p<0.0001). Eight patients had more than 40% reduction in their depressive
symptoms at the end of treatment 10, four were responders with at least 50% reduction, and two of these patients hit remission (HRSD = 7). Pilot EEG were well tolerated, and data indicated a significant excessive DLPFC activation in NoGo trials in youth TRD (p<0.001). This excessive DLPFC activation was reduced (p = 0.04) after 10 daily TBS treatment. Pilot TMS-EEG data also reflected GABAB inhibition deficits in DLPFC in TRD youths.

**Conclusion:** TBS may be a feasible treatment for youth treatment resistant depression, and it may exert its effect by modulating frontal inhibitory functions.

**Neurophysiological mechanisms of rTMS efficacy in treatment resistant depression**

**Dr. Zafiris Daskalakis, University of Toronto, Toronto, ON**

**Symposium:** "Mechanisms of rTMS". Background: Little is known about the neurophysiological pathology of depression and how repetitive transcranial magnetic stimulation (rTMS) may affect neurophysiological markers such as cortical inhibition (CI) and cortical excitation (CE) in depression.

**Methods:** The TMS-Evoked Potential (TEP) waveform was assessed on 30 subjects with depression (21 subjects undergoing active rTMS treatment and 9 undergoing sham rTMS) through global mean field analysis (GMFA) and regional waveform analysis.

**Results:** Patients who received active rTMS demonstrated a significant decrease in N45 amplitude and a significant decrease in N100 amplitude whereas no change was seen with sham treatment. A decrease in N100 amplitude correlated with decreasing symptoms after active rTMS. Baseline TEP predicted presence or absence of suicidal ideation with 91.7% sensitivity.

**Conclusions:** Our results reinforce TMS-EEG measures of cortical inhibition as a potential biomarker of response to brain stimulation therapy in TRD. The most noteworthy changes occurred in the DLPFC, a region previously associated with the pathophysiology of depression.
Symposium 6: New approaches for treatment of mental illness

**Regulation and behavioral implications of clock gene expression in the striatum**

**Dr. Shimon Amir**, Concordia University, Montréal, QC

Shimon Amir, Nuria de Zavalia, Konrad Schöttner, Pavel Solis, Margo Button

Circadian clock genes are expressed throughout the mammalian brain and play critical roles in the regulation of normal rhythmic brain processes and behaviors. Furthermore, recent studies have suggested an important role of clock genes in several disorders, including major depression, bipolar disorder, anxiety, drug addiction, and alcohol use disorder. The aim of the talk is to discuss recent findings on the regulation and behavioral/pathological implications of clock gene expression in the striatum using mice with selective deletion of the core clock gene, Bmal1 from the striatal circuit.

**CRF receptor1 regulates anxiety behaviour via sensitization of 5-HT2A receptor signaling**

**Dr. Stephen Ferguson**, University of Ottawa, Ottawa, ON

Stephen Ferguson, Tier I CRC in Brain & Mind, University of Ottawa Brain & Mind Research Institute, Professor, Department of Cellular and Molecular Medicine, Rm 3230E, Roger Guindon Hall, University of Ottawa, 451 Smyth Rd, Ottawa, ON, K1H 5M8

CRF1 and 5-HT2AR are expressed in the same neurons in the prefrontal cortex and pre-activation of CRF1 increases 5-HT2AR signaling as a consequence of increasing 5-HT2AR expression at the cell surface via an interaction with an unknown PDZ containing protein. Mutation of the PDZ interacting motif of both the CRF1 and 5-HT2AR or a Tat-tagged peptide mimicking the CRF receptor PDZ binding motif prevents CRF-dependent increases in 5-HT2AR signaling. CRF pretreatment of mice also sensitizes 5-HT2AR-mediated anxiety behaviours.

**When SSRI’s don’t work: altered 5-HT1A autoreceptor gene repression results resistance to chronic SSRI treatment**

**Dr. Paul Albert**, University of Ottawa, Ottawa, ON

Paul R. Albert, Ph.D., Faranak Vahid-Ansari, Ph.D., Valerie Turcotte-Cardin, M.Sc. Ottawa Hospital Research Institute (Neuroscience), UOttawa Brain and Mind Research Institute, Ottawa, Ontario, Canada

**Introduction**: Selective serotonin reuptake inhibitors (SSRIs) are the first line treatment of clinical depression. However, chronic treatment is required and 50% of patients fail to remit. SSRI’s increase serotonin (5-HT) neurotransmission, but the reasons for resistance to SSRI treatment remain unclear. The 5-HT1A autoreceptor, a primary negative regulator of 5-HT activity, may be involved. Brain imaging studies correlate the level of 5-HT1A autoreceptors with resistance to SSRI treatment. A promoter polymorphism that causes over-expression of 5-HT1A autoreceptors is associated with major depression and SSRI resistance.

**Methods**: We present the cF1ko mouse model with selective deletion in adult 5-HT neurons of a key 5-HT1A repressor, Freud-1/CC2D1A. We also introduce the 1AcKO mice, with adulthood...
deletion the 5-HT1A autoreceptor itself. These mice were characterized for 5-HT1A autoreceptors, anxiety- and depression-like behavior and for response to chronic SSRI (fluoxetine).

**Results:** In cF1ko mice, 5-HT1A autoreceptor expression and function was increased. Oppositely, 5-HT content and neuronal activity in the dorsal raphe were reduced. The cF1ko mice displayed increased anxiety- and depression-like behavior that was resistant to chronic fluoxetine treatment. The behavior effect in cF1ko mice was reversed if the 5-HT1A autoreceptor was also deleted. By contrast, 1AcKO mice show no behavioral changes, but sub-chronic SSRI treatment induced anxiety-like behavior.

**Conclusion:** These clinically relevant mouse models implicate 5-HT1A autoreceptor expression in anxiety, depression and response to SSRIs. These models of SSRI resistance may be useful to test new pharmacological and brain stimulation treatments. Supported by CIHR.

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**Novel approaches for early optimized treatment for clinical depression**

**Dr. Pierre Blier**, University of Ottawa, Ottawa, ON

Major depressive disorder may result in progressive alterations in brain morphometry and circuit function. Early optimized treatment, using measurement-based care and targeting symptom domains most distressful to patients, may lead to functional recovery. Controlled clinical studies indicate that implementing modifications of treatment regimens every two weeks, and using more than one medication at a time to target complementary mechanisms of drugs on monoamine neural elements, can help decrease long delays before achieving remission.

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**CCNP Next Generation Presentation 3**

**Modeling opioid maintenance therapy in rats: effects of chronic buprenorphine and the biased mu-opioid receptor agonist TRV130 on relapse to oxycodone seeking**

**Dr. Jennifer Bossert**, National Institute on Drug Abuse, Virginia Commonwealth University, Richmond, VA, USA

Jennifer M. Bossert¹, Jennifer K. Hoots¹, S. Stevens Negus², Bruce E. Blough³, and Yavin Shaham¹¹Behavioral Neuroscience Branch, IRP/NIDA/NIH ²Dept. of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA ³Center for Drug Discovery, Research Triangle Institute, Research Triangle Park, NC

**Background:** High relapse rates perpetuate opioid addiction and are a major obstacle in addressing the current opioid epidemic. Maintenance therapy with opioid agonists (buprenorphine, methadone) is an effective treatment for opioid addiction. Here, we establish an experimental procedure in rats trained to self-administer the prescription opioid oxycodone to compare the efficacy of an established treatment (buprenorphine) with that of a newer biased mu-opioid receptor (MOR) agonist, TRV130.

**Methods:** We trained rats to self-administer oxycodone (0.1 & 0.05 mg/kg/infusion; 7 d/dose, 6-h/d) in Context A where infusions were paired with a discrete tone-light cue. We implanted Alzet osmotic pumps containing vehicle, buprenorphine (3, 6, or 9 mg/kg/d; n=11-16), or TRV130 (3, 6, or 9 mg/kg/d; n=13-14) and performed three tests: (1) responding for drug-paired discrete cues under extinction conditions in a non-drug context (Context B), (2) context-induced reinstatement of oxycodone seeking in Context A after extinction in Context B, and (3) reacquisition of oxycodone self-administration in Context A.

**Results:** Chronic buprenorphine significantly decreased responding for drug-paired discrete cues
in Context B under extinction conditions and reacquisition of oxycodone self-administration in Context A; chronic buprenorphine also decreased context A-induced reinstatement of oxycodone seeking but this effect did not reach statistical significance. Chronic TRV130 significantly decreased oxycodone seeking or taking on all three relapse measures.

**Conclusions:** We introduce a rat model to study the effect of agonist-based maintenance therapy on relapse to prescription opioid seeking. We showed that chronic buprenorphine significantly decreased oxycodone seeking provoked by exposure to oxycodone-associated discrete cues and by exposure to oxycodone itself, demonstrating the predictive validity of the model. More importantly, we showed that chronic TRV130 significantly decreased oxycodone seeking using multiple measures of relapse. We propose that biased MORs should be considered as a novel opioid agonist maintenance treatment for addiction to prescription opioids and heroin.

**Rapid assessment of choice between fentanyl and liquid food in rats: effect of reinforcer magnitude and immunoantagonism**

*Dr. E. Andrew Townsend*, Virginia Commonwealth University, Richmond, VA, USA

E. Andrew Townsend¹, S. Stevens Negus¹, S. Barak Caine², Morgane Thomsen³, Kim Janda⁴, and Matthew L. Banks¹ ¹Virginia Commonwealth University, Richmond, VA, USA; ²McLean Hospital, Belmont, MA, USA; ³Psychiatric Center Copenhagen, Copenhagen, Denmark, ⁴Scripps Research Institute, La Jolla, CA, USA

**Introduction:** The aim of this work was to develop a drug self-administration procedure in rats that permitted within-session assessment of choice between fentanyl and liquid food.

**Methods:** Rats (n=18; 9 females, 9 males) initially responded under a concurrent FR5:FR5 schedule of fentanyl (0-10 µg/kg/inj) and liquid food (18% Ensure) reinforcement during daily 2h sessions. Once choice was stable, the concentration of liquid food was manipulated across sessions (0-100%). A distinct cohort of rats (n=6; 3 females, 3 males) was administered an anti-fentanyl vaccine and its effects on choice were monitored across subsequent weeks.

**Results:** Under baseline conditions, rats dose-dependently increased choice for fentanyl over 18% liquid food. Increasing the liquid food concentration decreased choice for fentanyl. Finally, vaccination resulted in a decrease in fentanyl choice accompanied by an increase in food choice, with a maximally-detectable decrease in fentanyl choice observed at week 4.

**Conclusions:** These results show feasibility of training a within-session fentanyl vs. food choice procedure in rats. The observed sensitivity of opioid choice to manipulations of an alternative, non-drug reinforcer provides evidence of the generality of this procedure to other choice procedures used in previous human and nonhuman primate drug self-administration studies. Furthermore, the observed vaccine effects provide evidence that an anti-fentanyl vaccination can decrease the reinforcing effects of fentanyl.

*Symposium 7: Sex, stress and mental health*

**Sex-specific estrogogenic neurophysiology in homeostasis brain circuits**

*Dr. Eric Dumont*, Queen’s University, Kingston, ON

Eric C. Dumont, PhD. Biomedical and Molecular Sciences (Biology, Psychiatry), Center for Neuroscience Study, Queen’s University, Kingston, Ontario, Canada. James Gardner Gregory. Center for Neuroscience Study, Queen’s University, Kingston, Ontario, Canada.

**Introduction:** The Bed nucleus of the Stria Terminalis (BNST) is a crucial coordinating node of
the neural circuits of homeostasis and, consequently, seems to contribute to maladaptive manifestations of chronic stress, including anxiety-related eating disorders. The BNST is rich in sex hormones and their receptors and is one of the most sexually dimorphic brain region in mammals. A better understanding of sex hormones neurophysiology in the BNST might help elucidate the neural mechanisms underlying chronic stress-associated mental illnesses which are unequivocally sex-specific.

**Methods:** We used brain slice electrophysiology to investigate the effects of estradiol on synaptic transmission in the oval(ov) subregion of the anterior BNST in adult male and female Long-Evans rats. Groups of rats, males and females, were gonadectomized to determine the influence of circulating sex hormones on estrogenic neurophysiology and monitored the estrus cycle in females using vaginal swabbing.

**Results:** Estradiol was a robust modulator of inhibitory synaptic transmission in the rat ovBNST, being 100 times more potent in females compared to males. Neuroactive estradiol was locally-synthesized through synaptic activity-dependent aromatization of testosterone. Consistent with a the key role of the ovBNST in energy homeostasis, a caloric challenge (24-hr food deprivation) significantly affected the neuromodulatory effects of estradiol and its local synthesis, in a sex-dependent fashion. The neuromodulatory effects of estradiol in the ovBNST were unaffected by gonadectomy and independent of the estrus cycle.

**Conclusion:** Our study suggests that sex is determinant in the neuromodulatory effects of estradiol in a key region of the brain circuits regulating energy homeostasis. These data may be an important stepping stone to understand the neural mechanisms of anxiety-related eating disorders such as anorexia and bulimia nervosa.

**Sex differences in the hypothalamic-pituitary adrenal (HPA) axis and stress habituation**

**Dr. Victor Viau,** University of British Columbia, Vancouver, BC

**Victor Viau,** PhD, Cellular and Physiological Sciences, The University of British Columbia, Vancouver, BC, Canada

**Introduction:** Males and females display different neuroendocrine and behavioral outcome responses to chronic stress exposure. However, few studies have explored sex differences in stress HPA axis habituation, defined as a reduction in glucocorticoid responses to the same stimulus repeated in a predictable manner. As the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) provides a stimulatory tonus to the HPA axis, we hypothesized that the normal decline in corticosterone responsiveness to repeated stress would be met by a decrease in 5-HT stimulatory control.

**Methods:** To make inroads on this possibility, here we compared the capacity of adult male and female Sprague-Dawley rats to show adaptive neuroendocrine responses during repeated restraint stress exposure, in addition to changes in central nervous system markers of 5-HT activity.

**Results:** Evidence will be provided to underscore that despite showing similar neuroendocrine profiles, stress habituation is met by distinct, underlying changes in 5-HT synthesis and 5-HT 1A receptor gating in adult male and female rats. Thus, within the raphe nucleus, the principle source of 5-HT in the brain, only females showed a reduction in tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of 5-HT. However, only males showed increases in the expression of the presynaptic 5-HT 1A receptor, which normally diminishes excitability of 5-HT raphe neurons.

**Conclusion:** While these underlying mechanisms to decrease 5-HT signaling may well serve adaptive neuroendocrine responses in males and females, they may also be relevant to sex differences in vulnerability to anxiety and depressive disorders.
Pubertal probiotic treatment promotes resilience to stress-induced mood disorders
Dr. Nafissa Ismail, University of Ottawa, Ottawa, ON

Dr. Nafissa Ismail, School of Psychology, uOBMRI, University of Ottawa, Ottawa, Ontario, Canada.

Puberty is a critical period of development during which sexual maturity is reached. It is also an important period during which the brain is remodeled and reorganized, making it a sensitive and vulnerable period to environmental stress. Pubertal exposure to an immune challenge results in an enduring decrease in behavioral responsiveness to estradiol as measured both in reproductive and non-reproductive behaviors, such as depression-like behavior in mice. The objective of this presentation is to discuss age and sex differences in immune response and the impact of the gut-brain axis on this response. Our results show that exposure to an immune challenge induces important age and sex differences in immune response, thermoregulation, cytokine mRNA, c-Fos and TH expression. Exposure to probiotics during puberty alters immune response differently in males and females and appears to prevent enduring changes in depression-like behavior, especially in the males. These findings propose potential mechanisms through which exposure to an immune challenge can cause enduring alterations in reproductive and non-reproductive behaviors and possible preventative measures.

Sex differences in the role of orexins in mediating habituation to repeated stress and stress-induced changes in sleep and cognitive function
Dr. Seema Bhatnagar, University of Pennsylvania, Philadelphia, PA, USA

Laura Grafe and Seema Bhatnagar

Introduction: Women are twice as likely as men to suffer from stress-related psychiatric disorders, such as PTSD and depression. However, the biological basis of these sex differences is unknown. Key features of these disorders include sleep disturbances, Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation, and cognitive deficits. The neuropeptides orexins, known to underlie arousal, the stress response, and attention, are altered in anxious and depressed patients. In the studies discussed here, we used rat models to examine the role of orexins in producing sex differences in responses to stress, and in behavioral consequences of stress exposure including cognitive flexibility and sleep microarchitecture.

Methods: We used adult male and female rats. Rats were exposed to 5 days of 30min restraint exposure. In some experiments, we examined cortically-mediated cognitive flexibility to assess behavior and used telemetry devices to assess sleep microarchitecture before during and after 5 days of repeated restraint exposure.

Results: Female rats had increased orexin expression and activation compared with males, which was associated with impaired HPA habituation to repeated stress and subsequent cognitive deficits. We then showed that inhibiting orexin neurons (via Designer Receptors Exclusively Activated by Designer Drugs; DREADDs) during repeated restraint decreased activation in the PVN, decreased basal corticosterone levels, and improved subsequent cognitive function in females. Repeated restraint stress caused sleep disruptions in female rats but not male rats. Specifically, REM sleep duration and bouts were suppressed in females after repeated restraint stress. We are currently using DREADDs to inhibit orexins throughout repeated restraint to see if we can reverse these stress-induced sleep disturbances in females.

Conclusions: These results indicate that orexins mediate a number of important sex differences that are stress related and that are disrupted in stress-related psychiatric diseases. Thus, targeting orexins may impact a range of psychiatric symptoms in a sex-specific manner.
Symposium 8: Antidepressant effects of ketamine: synaptic mechanisms and network dynamics

Roles of the location of NMDA receptors in the antidepressant effects of ketamine
Dr. Tak Pan Wong, McGill University, Montréal, QC

Yiu Chung Tse, Joëlle Lopez, Alex Moquin, Shui-Ming Alice Wong, Dusica Maysinger & Tak Pan Wong

Although antagonists for NMDA receptor (NMDAR) such as ketamine exhibit antidepressant effects, the contribution of NMDARs to those effects remain debatable. NMDARs can be found inside and outside synapses. While extrasynaptic NMDARs (exNMDARs) have been implicated in the computation of synaptic currents and neuronal death, their contribution to depression-related behavior remains unknown. Using the chronic social defeat model, a mouse model of depression, we compared synaptic (sNMDAR) and extrasynaptic NMDAR function in the hippocampus of nonstressed control mice and mice that are resilient or susceptible to chronic social defeat. In addition, we examined the impact of ketamine and memantine, which respectively decreases and increases mouse susceptibility to chronic social defeat, on sNMDAR and exNMDAR function. We found that the susceptibility of mice to chronic social defeat is related to low hippocampal exNMDAR function. In addition, ketamine, which is a fast-acting antidepressant, enhanced the ratio of exNMDAR and sNMDAR function by preferentially blocking sNMDAR currents. However, memantine, which preferentially inhibited exNMDAR currents, enhanced mice susceptibility to chronic social defeat. Finally, using drugs that selectively enhanced exNMDAR but not sNMDAR currents reduced mice susceptibility to chronic social defeat. An antidepressant effect of ketamine may be related to restoring the ratio between sNMDAR and exNMDAR function in the hippocampus.

Critical roles of glutamatergic receptors and synaptic plasticity in ketamine antidepressant actions
Dr. Yu Tian Wang, University of British Columbia, Vancouver, BC

Yu Tian Wang, Lily Aleksandrova and Anthony Phillips

Accumulating evidence implicates dysfunction within the glutamatergic system and a dysregulation of synaptic plasticity in the pathophysiology of depression. The recent discovery that a single intravenous infusion of ketamine (a non-selective NMDA R antagonist) at a subanesthetic dose had robust, rapid and sustained antidepressant effects in individuals with treatment-resistant depression has inspired tremendous interest in investigating the molecular mechanisms mediating ketamine’s clinical efficacy as well as increased efforts to identify new targets for antidepressant action. Using Wistar-Kyoto (WKY) rats, an inbred strain of rats shown greatly increased susceptibility to stress, we have recently investigated the potential roles of synaptic plasticity, particularly the long-term potentiation at the hippocampal CA1 glutamatergic synapses, in mediating ketamine’s antidepressant effects. Our results suggest that WKY rats exhibited a significant impairment in LTP, and that ketamine may exert its anti-depressant effects at least in part by restoring the LTP via both NMDA receptor dependent and independent mechanisms. Our studies may aid the development of a new generation of much-needed superior antidepressant agents.
Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced synaptogenesis
Dr. Conor Liston, Cornell University, New York, NY, USA

Conor Liston, MD, PhD, Brain and Mind Research Institute and Department of Psychiatry, Weill Cornell Medicine, New York, NY, USA

Introduction: Depression is a fundamentally episodic form of mental illness, yet the neurobiological mechanisms underlying the induction and remission of depressive episodes over time are not well understood.

Methods: We used two-photon microscopy, calcium imaging, and novel optical probes to investigate how prefrontal cortical synaptic remodeling contributes to behavioral state transitions during chronic stress and after antidepressant-dose ketamine treatment.

Results: We show that the induction of depression-related behavior is associated with clustered, branch-specific elimination of postsynaptic dendritic spines on prefrontal projection neurons ($P=0.004$, Wilcoxon), mediated in part by a mineralocorticoid receptor-, transcription-dependent signaling process. Antidepressant-dose ketamine reverses these effects by selectively rescuing eliminated spines ($P=0.001$, Wilcoxon) and restoring coordinated activity in multicellular ensembles that predict motivated escape behavior ($t=4.34, P<2e-5$). Using behavioral interventions and a photoactivatable driver of Rac1 signaling to bidirectionally modulate the survival of newly formed spines, we show that unexpectedly, ketamine-induced synapse formation is required for the long-term maintenance of selected antidepressant behavioral effects ($P=0.002$, Wilcoxon), but not for their induction.

Conclusion: These results define a previously unappreciated, causal role for prefrontal synaptogenesis in sustaining antidepressant effects on selected depression-related behaviors and suggest new avenues for optimizing interventions aimed at enhancing and maintaining remission after ketamine treatment.

Cortical glutamatergic functional hyperconnectivity after chronic stress and selective network effects of subanesthetic ketamine
Dr. Alexander McGirr, University of Calgary, Calgary, AB

Human depression is associated with glutamatergic dysfunction and alterations in resting state network activity. Using the chronic social defeat mouse model of depression, we characterize how mesoscale glutamatergic networks are altered after chronic stress, and in response to the rapid acting antidepressant, ketamine. Transgenic mice (Ai-85) expressing iGluSnFR (a recombinant extracellular glutamate sensor) underwent chronic social defeat or a control condition, while spontaneous cortical activity was longitudinally sampled. After chronic social defeat, we observe network-wide glutamate functional hyperconnectivity in defeated animals, also confirmed with voltage sensitive dye imaging in an independent cohort. Subanesthetic ketamine has unique effects in defeated animals, inducing large global cortical glutamate transients, and an elevated subanesthetic dose results in sustained global increase in cortical glutamate. Twenty-four hours after ketamine, normalization of depressive-like behaviour in defeated animals is accompanied by reduced glutamate functional connectivity strength. Altered glutamate functional connectivity in this animal model confirms the central role of glutamate dynamics as well as network-wide changes after chronic stress and in response to ketamine.
**Poster Session I – Friday, June 29, 2018**

**13:00 – 14:00 – HSBC Hall/Overflow**

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**Sex differences in stress habitation modulate pre- and post-synaptic 5-HT1A receptor function**


Most of the basic research examining behavioural and neural responses to stress has focused on males, despite sex differences. Serotonin (5-HT) is a neurotransmitter system implicated in stress and is sexually dimorphic. Considering that 5-HT is regulated by 5-HT 1A receptors, we hypothesized that habitation to stress affects 5-HT 1A receptor function differently in males and females. Male and female SD rats were exposed to a single or repeated restraint stress (2hr daily for 5 consecutive days) or no stress. Animals were then injected with the 5-HT 1A receptor agonist, 8-OH-DPAT, using hypothermia and corticosterone responses as physiological indices for changes in pre- and postsynaptic 5-HT 1A receptor function, respectively. Males and females habituated to the stress and showed significantly lower (45% and 40%, respectively) corticosterone on the fifth day of restraint. Habitation increased hypothermia in males, but not females, suggesting higher pre-synaptic 5-HT1A receptor function. Restraint and 8-OH DPAT agonism increased corticosterone in both males and females, suggesting changes in post-synaptic 5-HT 1A receptor transduction. GTP?S[35] and 8-OH[3] DPAT binding assays were performed to confirm changes in 5-HT1A receptor transduction and number. These data suggest that habitation to stress increases pre-synaptic 5-HT 1A receptor function and levels in males, but not females. This uncovers an important mechanism for stress habitation that occurs in males, but not females and elucidates why females have a higher risk of mood and anxiety disorders.

**Changes in biological rhythms and mood from pregnancy to postpartum in women with comorbid mood and anxiety disorders**

Anastasiya Slyepchenko¹,²; Benicio N. Frey, MD, MSc, PhD ¹,²,³ ¹ McMaster Integrative Neuroscience Discovery and Study, McMaster University, Hamilton, ON, Canada; ² Women’s Health Concerns Clinic, St. Joseph’s Healthcare Hamilton, Hamilton, ON, Canada; ³ Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada.

**Background:** Although changes in sleep and biological rhythm disruptions occur as part of mood episodes and precede mood episodes, current knowledge regarding the role of biological rhythms in mood disorders, and associated anxiety, during the perinatal period is limited. Here, investigated whether subjective and objective measures of biological rhythms and sleep differ in euthymic women with bipolar and major depressive disorders, with and without anxiety comorbidities during pregnancy and postpartum.

**Methods:** Seventy-eight women (N=17 mood, N=31 mood with comorbid anxiety, N=30 controls) completed 15-day actigraphy and the Biological Rhythms Interview of Assessment in Neuropsychiatry during third trimester of pregnancy, 1-3 weeks and 6-12 weeks postpartum. Depression (Edinburgh Postnatal Depression Scale), anxiety (Generalized Anxiety Disorder-7), seasonality (Seasonal Pattern Assessment Questionnaire) and sleep (Pittsburgh Sleep Quality Index) were assessed. The study was conducted from 2015-2018 at the Women’s Health Concerns Clinic at St Joseph’s Healthcare Hamilton.

**Results:** During pregnancy and postpartum, women with a history of mood disorders and anxiety...
disorders had worsened subjective sleep, biological rhythms, mood and anxiety than controls. Women with mood disorders had less poor subjective sleep, and mood than those with comorbid anxiety. Actigraphy data analysis revealed differences in sleep efficiency between groups during pregnancy. 1-3 weeks postpartum: euthymic women with mood disorders had lower interdaily stability than controls. 6-12 weeks postpartum: women with mood and anxiety disorders had lower weekend intradaily variability than controls. Light exposure differences during rest and sleep were found between women with mood disorders with and without anxiety comorbidities (all p<0.05). **Conclusions:** Women with a history of mood disorders with anxiety disorders experienced worsened subjective sleep and biological rhythms in pregnancy and the postpartum period. Women with a history of mood disorders without comorbidities did not differ from controls in depressive symptoms and sleep quality during pregnancy and 1-3 weeks postpartum.

**Pharmacogenomics and depression symptom improvement: treatment by primary care physicians or psychiatrists**

Julie-Anne Tanner, PhD (¹,²), Paige E. Davies, MSc (²), Lisa C. Brown, PhD (³), Nicholas C. Voudouris, MD (⁴), Bryan M. Dechairo, PhD (⁵), and James L. Kennedy, MD, MSc, FRCPC, FRSC (¹) Affiliations: (¹) Tanenbaum Pharmacogenetics Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, ON, Canada. (²) Assurex Health Ltd., Toronto, ON, Canada. (³) Assurex Health, Mason, OH, USA. (⁴) Thornhill Medical Centre, Toronto, ON, Canada.

**Introduction:** Major depressive disorder is a significant health burden worldwide. Multiple failed medication trials are associated with decreased probability of achieving remission, highlighting the need for optimizing treatment selection for depression. We aimed to compare the utility of pharmacogenomic (PGx) testing in the treatment of depression between primary care and psychiatric care settings.

**Methods:** We conducted a sub-analysis of a naturalistic, prospective study examining PGx guidance in psychiatric medication decisions (IMPACT study, impact.camhx.ca/en/home.php). In a large patient sample (N=2025), selected for moderate-to-severe depression (Beck Depression Inventory, BDI, score >17) at baseline, who received combinatorial PGx testing, we compared symptom improvement, response, and remission between patients treated by primary care physicians (PCPs) and psychiatrists. Symptom improvement was quantified as the percent change in BDI score from baseline to end of study (8-12 weeks). Medication congruence with the combinatorial PGx test guidance was compared between patients treated by different healthcare providers.

**Results:** Psychiatrists were prescribers for 57% of patients. At end of study, symptom improvement was significantly greater in patients treated by PCPs (32%) compared to psychiatrists (24%, P<0.0005). The same relationship between physician type and symptom improvement was observed for subgroups of senior patients (=65 years, P=0.03) and those younger than 65 (P<0.001). Response and remission rates were also higher in the PCP group; patients treated by PCPs had 1.4 and 1.7 times greater odds of responding and remitting, respectively, compared to psychiatrists (P<0.0005). There was no significant difference in congruence with the combinatorial PGx test among PCPs and psychiatrists (88% and 85%, respectively) (P>0.1).

**Conclusions:** Following combinatorial PGx testing, patients with depression exhibited greater symptom improvement when treated by PCPs than psychiatrists. Expanding on findings from previous double-blind controlled trials, the current study supports the use of this treatment approach in a larger patient population and primary care treatment settings.
Chronic desipramine treatment reverses anxiety and depression phenotypes in a mouse model of fluoxetine resistance

Faranak Vahid-Ansari1 Mireille Daigle1 Paul R. Albert1 1OHRI (Neuroscience), UOttawa Brain and Mind Research Institute, Ottawa, ON, CA

Introduction: Serotonin-1A (5-HT1A) autoreceptors negatively regulate 5-HT tone. Increased 5-HT1A autoreceptors have been associated with major depression and SSRI resistance. To model this, we generated the cF1ko mice, in which the repressor Freud-1 is deleted in adult 5-HT cells (Vahid-Ansari et al., 2017). The cF1ko mice have increased 5-HT1A autoreceptor levels and function, and a fluoxetine-resistant anxiety/depression phenotype. Here we examine changes in brain activity in the cF1ko mice. We also address whether cF1ko mice respond to desipramine, a tricyclic antidepressant that targets the noradrenaline system.

Methods: Co-immunofluorescence for FosB/GAD67 or /VGluT1-3 was used to detect brain-wide chronic activity of GABAergic or glutamatergic neurons, respectively. A separate cohort of cF1ko mice was treated chronically with desipramine, and examined using validated behavioral tests. These included the elevated-plus maze, open-field, novelty-suppressed feeding, forced-swim and tail-suspension tests.

Results: The cF1ko mice had reduced FosB+ cells (GABA and glutamate) in several corticolimbic areas. These included hippocampal-CA2/3, lateral-septum, medial-prefrontal cortex, entorhinal-cortex, with no change in nucleus accumbens or hippocampal-dentate gyrus. In the cF1ko dorsal raphe, FosB+/5-HT cells were reduced, while FosB+/vGlut3 neurons increased, with no significant change in FosB+/GABA neurons. Chronic desipramine treatment reversed the depression/anxiety phenotype of cF1ko mice to wild-type levels.

Conclusion: These findings implicate presynaptic Freud-1 in 5-HT1A autoreceptor regulation in vivo and in mediating fluoxetine-resistant depression and anxiety. The induction of 5-HT1A autoreceptors in cF1ko mice was associated with global changes in the corticolimbic circuitry implicated in depression and anxiety. In contrast to fluoxetine, chronic desipramine treatment reversed the cF1ko behavioral phenotype. These results suggest that SSRI-resistance may be overcome by targeting other neurotransmitter systems, or SSRI-resistant cells directly. In summary, the cF1ko mice provide a clinically relevant genetic model of SSRI-resistance to test new treatment strategies. Supported by HSF-CPSR (FVA) and CIHR (PRA).

Developing new tools to study β-Glucocerebrosidase as a biomarker in Parkinson’s Disease

Maa O. Quartey, Daniel Tesolin, Shusheng Wang, Morshed Chowhury, Jennifer Nyarko, Christopher Phenix, and Darrell D. Mousseau.

Introduction: Parkinson’s disease (PD) affects an estimated 5.1% of Canadians, with direct and indirect costs to society and the healthcare system estimated at $202 M and $245 M, respectively. A diagnosis of PD is confirmed post-mortem, with the presence of a-synuclein aggregates in neurons (i.e. Lewy Bodies). The symptoms of PD emerge only after approximately 50-60% of dopaminergic neurons have been lost, which makes early intervention difficult. It is important to develop and employ preferably non-invasive techniques to detect and monitor changes in the relevant brain molecules at the earliest time-point possible. The risk of PD is known to increase in families with Gaucher’s Disease, which is linked to mutations in the GBA1 gene that encodes the hydrolytic enzyme, β-glucocerebrosidase (GCase). In addition, almost 7% of PD patients carry mutations in the GBA1 gene, which supports the involvement of GCase in the etiology of PD. GCase is now a high-priority therapeutic and diagnostic target for PD.

Methods: We have prepared a chlorofluorescein-labeled conduritol aziridine derivative that is a potent activity-based probe of GCase. Western blotting, SDS-PAGE, and confocal microscopy.
were used to determine the specificity and selectivity of the fluoroprobe for GCase in various protein and tissue/cell preparations. Results and Discussion: The novel activity-based probe efficiently labeled GCase both in vitro (mammalian cell lysates) and in vivo (fixed mammalian cell lines). A screen (Western blotting) of autopsied human brain samples revealed a variety of GCase isoforms (possible splice variants) and we are currently testing our activity-based probe to determine which isoform(s) is/are ‘active’ in PD brain extracts. These preliminary studies using fluorescent derivatives will serve to guide the design of F-18 labeled conduritol aziridines intended to image GCase in vivo using positron emission tomography (PET).

**Sex-specific effects of amphetamine in adolescence on DCC regulation, dopamine development, and cognitive maturation**

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**Introduction:** Drug use during adolescence enduringly increases later vulnerability to develop addiction. In male mice, early adolescence is a critical period when exposure to amphetamine, at doses equivalent to those abused by humans, downregulates expression of the guidance cue receptor DCC in dopamine neurons and leads to long-term changes in dopamine connectivity and behavior. However, the effects of early adolescent amphetamine exposure in female mice on DCC expression, dopamine connectivity, and behavior remain unknown.

**Methods:** We treated male and female mice with a regimen of amphetamine (4 mg/kg) or saline during early adolescence (PND 22±1 - 31±1). Six weeks after treatment, when all mice were adults, we measured behavioral inhibition, motivation, open field behavior, and assessed the organization of dopamine connectivity in the medial prefrontal cortex (mPFC). In a separate cohort of female mice, we assessed DCC expression in ventral tegmental area (VTA) samples with qPCR one week after amphetamine treatment.

**Results:** Adult males that received amphetamine early in adolescence showed impaired behavioral inhibition, increased risk taking-like behavior, and an inability to adapt to changing reward contingencies. However, the behavior of adult females exposed to amphetamine during early adolescence did not differ from their saline-treated littermates. In contrast to our previous findings in male mice, amphetamine did not alter VTA DCC expression in females one week after treatment in early adolescence, indicating that DCC expression is regulated by amphetamine in a sex-specific manner.

**Conclusions:** Our data show for the first time that amphetamine exposure regulates VTA DCC expression not only in an age-dependent, but also in a sex-specific manner. Amphetamine exposure during early adolescence in males disrupts DCC-mediated development of dopamine connectivity and leads to cognitive impairments that are associated with addiction vulnerability. In females, however, the exact same amphetamine regimen does not lead to these molecular and behavioral changes.

**Reduced cerebrovascular reactivity among adolescents with bipolar disorder**

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**Background:** Cardiovascular disease (CVD) is excessive and premature among individuals with bipolar disorder (BD). Cerebrovascular reactivity (CVR), reflecting vasodilatory capacity of cerebral blood vessels in response to vasoactive substances, is a marker of cerebrovascular
health. Despite informative findings in other diseases, CVR has not previously been examined in BD.

Methods: Twenty-five adolescents with BD and 25 age and sex-matched psychiatrically healthy controls (HCs) completed six 15-second breath-holds (BHs) during functional magnetic resonance imaging (fMRI) at 3-Tesla. CVR was determined by comparing blood-oxygenation-level dependent (BOLD) signal change between epochs of rest and breath-hold challenge. Voxel-wise and lobar region-of-interest contrasts were analyzed. Body mass index (BMI) was examined as a potential confound.

Results: In voxel-wise analyses, CVR in the posterior cingulate gyrus and periventricular white matter was lower in BD vs. HC. There was also a significant main effect of BMI on CVR. After controlling for differences in BMI, additional between-group CVR differences were observed in the temporal poles, supramarginal gyrus, and lingual gyrus. There were no regions in which CVR was significantly greater in BD vs. HC. CVR was not associated with mood symptoms.

Conclusions: This preliminary study provides evidence of cerebrovascular dysfunction in BD, including regions known to be susceptible to cerebrovascular dysfunction and/or disease. These findings warrant additional research on the causes and consequences of cerebrovascular dysfunction in early-onset BD.

A comparison of schizophrenia relapse rates of 3 paliperidone formulations, once-daily, once-monthly and once every-3-month: post-hoc analysis from 3 randomized controlled trials


Introduction: Relatively lower rates of relapse and delayed time to relapse may be expected in patients discontinuing longer acting injectable (LAI) treatment relative to their shorter acting equivalents. In this post hoc analysis, we evaluated the percentage of patients with schizophrenia experiencing relapse, time to relapse and secondary parameters (Positive and Negative Syndrome Scale [PANSS] total score, Clinical Global Impression-Severity [CGI-S] and Personal and Social Performance [PSP] scale scores) between the active and placebo arms of three different formulations of paliperidone (oral paliperidone extended release [paliperidone ER], paliperidone palmitate once monthly [PP1M] LAI, and paliperidone palmitate three monthly [PP3M] LAI).

Methods: Data from three similarly designed, randomized, double-blind, placebo-controlled relapse prevention studies in adult patients with schizophrenia (DSM-IV-TR criteria) were separately analyzed. Patients stabilized during an open-label stabilization phase with either paliperidone ER, PP1M or PP3M were then randomized to receive either placebo (analogous to non-adherent patients in the real world) or the same active treatment used during stabilization phase (analogous to adherent patients).

Results: A total of 922 patients were included (active treatment, 473; placebo, 449). Lowest percentage of patients experiencing relapse were observed with PP3M followed by PP1M and paliperidone ER in both the active treatment (PP3M, 9% < PP1M, 18% < paliperidone ER, 22%) and placebo (PP3M, 29% < PP1M, 48% < paliperidone ER, 52%) groups. The post discontinuation median time to relapse (95% CI) was significantly longer (P<0.0001) in the placebo group and was not estimable in the active treatment group. Patients receiving active treatment remained stable while worsening in terms of change from baseline in all secondary endpoints was observed in patients discontinuing the active treatment.
**Conclusion:** The lower percentage of relapse observed with PP3M versus PP1M and paliperidone ER in the placebo group could be advantageous to non-adherent patients, as this mimics real-world scenario where patients discontinue their active antipsychotic treatment suddenly.

**A national survey on the socio-demographics and disease burden of Canadians with treatment resistant depression**

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**Introduction:** Treatment Resistant Depression (TRD) is associated with significant morbidity. With limited Canadian data on the TRD population, this survey aimed to better understand the severity and impact of TRD in Canadian patients.

**Methods:** A 25-minute on-line survey was conducted in October/November 2017 using a national consumer panel. The target sample size was 200. Eligible subjects reported being treated by a physician for depression for at least two years, had been prescribed a minimum of 2 antidepressants in the past, were currently taking at least two medications for depression and were still experiencing continuous or intermittent depressive symptoms.

**Results:** The mean respondent age was 51. 65.3% were female and 62.5% received a diagnosis of MDD more than 10 years ago. Respondents reported being prescribed an average of two antidepressants and nearly half were taking 1 other psychotropic medication for depressive symptoms. Respondents answered the Patient Health Questionnaire (PHQ-9) and the mean score was 14.2. 28.9% scored 15-20 (major depression, moderate) and 22.8% scored greater than 20 (major depression, severe). Respondents reported that symptoms made it very or extremely difficult to do work or schoolwork, (47.3) to take care of things at home (48.4%), and to get along with other people (34.0). Among the 31 respondents in full time employment, 55.3% missed at least one day of work in the past 30 days (median time lost = 3 days). 56.5% reported having thoughts of death or self-harm several days or more in the last two weeks. On a scale of 1 (not well at all) to 10 (very well) on how well they are coping with their depression, the mean rating was 5.8.

**Conclusions:** A large percentage of individuals prescribed antidepressants for depressive disorders receive polypharmacy, report clinically significant depressive symptoms, and manifest significant psychosocial and workplace related functional consequences.

**A national survey on treatment and resource utilization of Canadians with treatment resistant depression**

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**Introduction:** The aim of this survey was to review treatments and resources utilized by Canadian individuals with Treatment Resistant Depression (TRD), and their satisfaction with care received.

**Methods:** A 25-minute on-line survey was conducted in October/November 2017 using a national consumer panel. The target sample size was 200. Eligible subjects reported being treated by a physician for depression for at least two years, had been prescribed a minimum of 2 antidepressants in the past, were currently taking at least two medications for depression and were still experiencing continuous or intermittent depressive symptoms.

**Results:** 57.5% of respondents were managed by a general/family practitioner and 38.9% were managed by a psychiatrist. 68.5% saw their health care provider 4 times a year or more. 62.5%
were diagnosed over 10 years ago, and since diagnosis, 53.5% had visited an emergency room at least once and 41.8% had been admitted to hospital at least once for depression. Among the previously hospitalized respondents, 26.5% had been admitted to hospital in the past 12 months. On average, respondents were currently taking two anti-depressants and two other psychotropic medications. Awareness of somatic treatments was highest for electroconvulsive therapy (59.7%) and low for rTMS (17.6%) or deep brain stimulation (17.6%). Usage (past or current) of any somatic treatment was 16.3% in the sample. On a scale of 1 (highly dissatisfied) to 10 (highly satisfied) with current therapy, the mean rating was 6.5. A low percentage of patients accessed resources other than a physician to obtain information related to depression or its treatments. Family member/friend (46.3%) and mental health organization resources (40.2%) were the most frequently mentioned.

**Conclusions:** TRD patients are high utilizers of pharmacological treatments and utilize services across multiple healthcare settings. Individuals with TRD do not report a high level of satisfaction with existing treatments.

The impacts of actual and perceived acute nicotine administration on resting state functional connectivity between the insula and the nucleus accumbens, anterior cingulate cortex, and amygdala in dependent smokers

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**Introduction:** Drug administration effects in humans involve both pharmacological and psychological components. However, studies that aim to examine such effects tend to attribute them exclusively to the pharmacological properties of the drug administered.

**Methods:** A balanced placebo design was used to examine the relative impacts of perceived and actual nicotine administration on smokers’ neural responses. 26 tobacco dependent smokers (12 women) were randomly assigned to receive either a nicotine inhaler (4mg deliverable) or a nicotine-free inhaler across two sessions following a minimum of 3 hrs of tobacco abstinence. Instructions regarding the inhaler’s nicotine content (told nicotine vs. told nicotine-free) and flavour (mint vs. citrus) differed across sessions. Resting state functional connectivity between subregions of the insula (anterior & posterior) and a priori identified regions of interest (nucleus accumbens, anterior cingulate cortex (ACC), and amygdala) was measured using magnetic resonance imaging before and after inhaler administration.

**Results:** Both nicotine administration and the belief that nicotine had been administered independently altered functional connectivity between the anterior insula and the ACC but these effects were in opposite directions. Specifically, actual nicotine administration was associated with a relative decrease, and perceived administration with a relative increase, in coupling between the anterior insula and the ACC. In contrast, functional connectivity between the anterior insula and the nucleus accumbens was significantly reduced by actual nicotine administration only. Finally, perceived, but not actual, nicotine administration was related to reduced coupling between the posterior insula and the amygdala.

**Conclusions:** Findings indicate that both pharmacological and non-pharmacological factors impact nicotine-related neural effects and highlight the importance of explicitly considering non-pharmacological factors when examining drug mechanisms of action in humans.

The association between 5-HTTLPR and obsessive-compulsive symptoms in women during the perinatal period

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Introduction: Women are susceptible to developing obsessive-compulsive symptoms (OCS) in the postpartum period, with symptoms centered on mothering abilities and the infant’s well-being. The serotonin transporter polymorphism, 5-HTTLPR, has been shown to be associated with obsessive-compulsive disorder in the general population. We investigated whether 5-HTTLPR is associated with OCD in perinatal women and if the 5-HTTLPR genotype status predicts severe obsessive-compulsive symptoms postpartum.

Methods: 77 women (n=17 OCD) were seen during the 2nd-3rd trimester of pregnancy. All women completed a CIDI-Venus interview, behavioural questionnaires and a blood sample collection. 44 women returned 3-6 months postpartum and recompleted the Perinatal Obsessive-Compulsive Scale (POCS), and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) questionnaire. Genotyping the 5-HTTLPR was completed using PCR-RFLP. Chi-square test examined the association of allele and genotype frequencies with OCD diagnosis. Logarithmic regression models determined whether 5-HTTLPR genotype predicted perinatal OCS severity, with high scores classified as total score =15 on POCS or Y-BOCS.

Results: There was no significant association of 5-HTTLPR genotype or allele status with OCD diagnosis. Controlling for age and weeks postpartum, 5-HTTLPR genotype and diagnosis predicted whether women had high POCS scores postpartum, but not Y-BOCS. Specifically, women with OCD (OR 35.2, 95% CI [3.56, 1046.9] and the functional La/La genotype vs. SS genotype (OR 114.1, 95% CI [2.59, 27700]) were more likely to have higher scores on the POCS.

Conclusion: 5-HTTLPR did not associate with OCD; however, women with OCD and the La/La genotype had a higher likelihood of having more severe mothering- and infant-related OCS in postpartum women.

Venlafaxine ameliorates cognitive impairments and brain myelin deficits in a cuprizone induced demyelination animal model

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Introduction: Depression and cognitive dysfunction are commonly seen in multiple sclerosis (MS). MS is characterized by myelin loss, oligodendrocyte apoptosis and consequent axonal damage. The strategies improving oligodendrocytes survival and development may be neuroprotective. Venlafaxine, a serotonin noradrenaline reuptake inhibitor (SNRI) has recently been shown to exert potent neuroprotective effects through multiple mechanisms in addition to its well-established effects on neurotransmitter levels. However, it is unclear whether this neuroprotective benefits can mitigate the demyelination-induced oligodendrocyte loss and what effect it might have on oligodendrocyte development. Therefore, we investigated the impact of Venlafaxine in an acute cuprizone mouse model of demyelination.
**Methods:** We studied the effects of venlafaxine on oligodendrocyte and myelin loss, as well as the promotion of survival, proliferation and differentiation of oligodendrocyte lineage cells in vivo. Three groups of C57BL/6 mice (n=15 per group) were subjected to six weeks feeding with 0.2% cuprizone. Two of these groups received venlafaxine at doses of 5mg/kg and 20 mg/kg for the six weeks while one group was untreated. Three other groups of C57BL/6 (n=10/group) mice served as controls. The working memory and depression-like behaviours were assessed using Y-maze and tail/ forced swim tests respectively. Mice brains were harvested after euthanasia and processed for immunohistochemistry.

**Results:** We found that Venlafaxine treatment at 20 mg/kg significantly (p<0.05) improved percentage spontaneous alternation (a measure of working memory) in the cuprizone-fed mice compared to untreated cuprizone fed mice. We also found out that venlafaxine significantly (p<0.05) protected against myelin protein loss, astrogliosis, microgliosis, oligodendrocyte loss, and it prevented an increase in oligodendrocyte progenitor cells number in cuprizone-fed mice compared to the untreated cuprizone fed mice.

**Conclusion:** Therefore, this study provides evidence that venlafaxine improves cognitive behaviours and protects against white matter damage in a demyelination mouse model.

**Association between inflammatory markers and neurocognitive flexibility among adolescents with and without bipolar disorder**

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**Introduction:** Peripheral inflammatory markers are elevated among adolescents and adults with bipolar disorder (BD), particularly during symptomatic episodes. In adults with BD, inflammatory markers are negatively associated with neurocognitive functioning. This relationship has not been investigated in BD adolescents.

**Methods:** Participants were 13-20 years old, 63 with BD (31 symptomatic hypomania and/or depression, 32 euthymic) and 60 HC. Diagnoses were confirmed using the K-SADS semi-structured interview. Serum levels of three pro-inflammatory markers (interleukin (IL)-1, IL-6, and tumor necrosis factor) and an anti-inflammatory marker (IL-10) were measured using commercial ELISA kits. Neurocognitive flexibility was assessed via the CANTAB intra/extradimensional shift (IED) task. Multivariate linear regression controlled for IQ and lifetime ADHD.

**Results:** IL-1ß, IL-6, TNF and IL-10 protein concentration levels did not differ by diagnosis. Significant interactions were observed: within symptomatic BD adolescents, but not asymptomatic BD or HC adolescents, lower IL-16/IL-10 ratio was significantly associated with more errors prior to the extra-dimensional shift (p=0.028). Similarly, among symptomatic BD adolescents, but not asymptomatic BD or HC adolescents, lower IL6/IL10 ratio was associated with significantly more
trials to complete the IED task (p=0.035). The models accounted for 11.5% and 11.8% of variance in neurocognitive flexibility, respectively.

**Conclusion:** Anti-inflammatory predominance was unexpectedly associated with better neurocognitive flexibility among symptomatic BD adolescents, but not among euthymic adolescents or HCs. Prospective, repeated measure studies are warranted to verify the direction of these findings.

**Association of cannabis use with brain structure in adolescents with bipolar disorder**

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**Introduction:** Little is known regarding the association of cannabis use with brain structure in adolescents with bipolar disorder (BD). Therefore, we set out to examine this topic in a well-characterized sample of adolescents with BD and healthy control (HC) adolescents.

**Methods:** Participants included 114 adolescents (n=54 BD, n=60 HC), ages 14-20 years; of these, 37 participants (n=29 BD, n=8 HC) reported lifetime use of cannabis. FreeSurfer-processed T1-weighted images, based on 3T MRI, yielded measures of cortical thickness, surface area (SA), and volume. Vertex-wise analyses complemented region of interest (ROI; amygdala, hippocampus, ventro-lateral prefrontal cortex (vlPFC), ventro-medial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC)) analyses. General linear models (GLM) covaried for age and sex. For volume and SA analyses only, intracranial volume was added as an additional covariate.

**Results:** ROI analysis revealed a significant diagnosis x cannabis interaction such that cannabis use was associated with greater reduction in vlPFC SA (F=6.333, p=0.013) in BD versus HC. Vertex-wise analysis revealed a significant diagnosis x cannabis interaction such that cannabis use was associated with greater reduction in pars orbitalis (p=0.024) and rostral middle frontal (p=0.036) SA, middle temporal volume (p=0.003), and banks of superior temporal sulcus thickness (bankssts) (p=0.014) in BD versus HC.

**Conclusion:** These preliminary cross-sectional, retrospective findings suggest that the association between cannabis use and brain MRI phenotypes is moderated by BD diagnosis. Further studies are necessary to determine the direction of the observed association, and whether these associations also relate to neurocognitive dysfunction and/or symptom burden.

**The neuroimaging phenotypes of CACNA1C rs1006737 in adolescents with BD and HCs of European descent**

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Department of Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, Canada. 7 Tanenbaum Centre for Pharmacogenetics, Centre for Addiction and Mental Health, Toronto, Canada. 8 Department of Psychiatry, University of Toronto, Toronto, Canada.

**Introduction:** CACNA1C rs1006737 is a genome-wide association study supported gene that has been implicated in structural brain differences in adults with bipolar disorder (BD) and/or healthy controls (HCs). Regions implicated include the ventromedial prefrontal cortex (vmPFC), ventrolateral prefrontal cortex (vlPFC), anterior cingulate cortex (ACC), putamen, and amygdala. However, no prior study has examined associations between rs1006737 and brain structure in adolescents.

**Methods:** Seventy-one adolescents (14-20 years; 38BD, 33HC) of European descent underwent 3-Tesla Magnetic Resonance Imaging (MRI). T1-weighted images were processed using FreeSurfer. ROI and whole-brain vertex-wise analyses examined cortical volume, surface area (SA), and thickness, as well as subcortical volume. General linear models included main effects of diagnosis and rs1006737, and an interaction term, controlling for age, sex, and total intracranial volume.

**Results:** Vertex-wise analysis found significant diagnosis-by-rs1006737 interactions for prefrontal and occipital brain structure such that BD A-carriers were found to have greater SA relative to BD non-carriers, while HC A-carriers had reduced SA relative to HC non-carriers. ROI analysis found an interaction in the ACC such that BD A-carriers were found to have greater SA relative to BD non-carriers, while no significant difference was found in HCs. Main effects of rs1006737 were found on ACC SA from ROI analysis, and occipital SA from vertex-wise analysis, such that A-carriers had larger SA relative to non-carriers in both regions.

**Conclusion:** The current study identified neurostructural intermediate phenotypes relevant to the impact of CACNA1C rs1006737 on adolescent BD. Further investigation is warranted into the neural, neurovascular, and neurocognitive relevance of rs1006737 associations with BD-specific elevations in regional cortical SA.

The effect of chronic altered lighting conditions on motor coordination, cognitive functions and wheel running in aged mice

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**Introduction:** Brain ageing leads to the degradation of many brain systems, including the suprachiasmatic nucleus, the mammalian master clock. We investigated the link between circadian disruption and neurological ageing, hypothesizing that chronic exposure to altered light cycles would exacerbate aging-related behavioural deficits.

**Methods:** Three groups of mice were aged for one year under different lighting conditions aimed to mimic modern light exposure: 1) 12 hours light and 12 hours dark (12L:12D), 2) 12 hours light and 12 hours dim light (12L:12dimL) or 3) week day 9 hours light and 15 hours dark and weekend 15 hours light and 9 hours dark (irregularL:D). All aged mice and a young mice cohort were then subjected to a 12L:12D cycle and tested on behavioural measures.

**Results:** Compared to each aged group, young mice had significantly higher forelimb strength (p<.01) and in the elevated plus maze, less anxiety-like behaviour (p<.05). When comparing all aged groups to one another, the 12L:12D mice had significantly less vertical activity (p<.01). All groups performed similarly in the balance beam, Morris Water Maze and prepulse inhibition of acoustic startle. Running wheel behaviour under 12L:12D showed that young mice were significantly more active over 24h than 12L:12dimL and 12L:12D groups (p<.05) but not the irregularL:D group. When comparing all three aged groups, there was a significant effect of light
condition, with the irregularL:D group significantly more active over 24h than the 12L:12D group (p<.05). The 12L:12dimL and 12L:12D groups (p<.01), but not the irregularL:D group, took longer than young mice to re-entrain following a 6-hour advance of the light:dark cycle. **Conclusion:** These data show that year-long lighting alterations result in slight behavioural differences between the aged mice conditions. This is evidence that normal aging can be shaped by chronic aberrant lighting to produce phenotypic differences.

**Comparison of paliperidone palmitate 1-month vs 3-month long-acting injectables for negative symptom improvement**

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**Background:** Negative symptoms of schizophrenia are key predictors of long-term disability. This post hoc analysis compared improvement in negative symptoms in patients on paliperidone palmitate 3-month (PP3M) and PP 1-month formulation.

**Methods:** Data from a randomized double-blind (DB), phase-3 study in patients with schizophrenia (DSM-IV-TR) were analyzed. After screening (3 wks), patients entered 17-wk open-label (OL) phase to receive flexible dose PP1M (day 1 [150 mg], day 8 [100 mg], wks 5, 9 and 13 [50, 75, 100, or 150 mg]) and entered a 48-wk DB phase and randomized (1:1) to receive either PP1M or PP3M. Positive and Negative Syndrome Scale scores (PANSS) for PP1M vs PP3M were assessed.

**Results:** Of 1429 enrolled, 1016 randomized to receive PP3M (n=504) or PP1M (n=512) in DB phase. Majority of patients were men and white (both 55%), with mean (SD) age of 38.4 (11.86) yrs. At baseline, the mean (SE) negative subscale total was 23.2 (0.12), indicating a moderate-to-severe level of negative symptoms. Negative subscale and negative symptoms factor scores showed continuous improvements throughout OL and DB phases: mean (SD) at OL baseline and DB endpoint for total negative subscale score and symptom factor score were 23.2 (4.60) and 15.9(4.99) and 14.9(4.81), both R2:0.16, respectively. The mean (SD) PANSS negative subscale score changes from DB baseline for PP1M vs PP3M were similar over time (mean change from baseline to DB endpoint was -1.4 [3.67], R2:0.06 vs -1.4 [3.63], R2:0.05).

**Conclusion:** PP3M and PP1M demonstrated consistent and similar efficacy in patients with moderate to severe negative symptoms of schizophrenia over observed timepoints, including patients with predominantly negative symptoms. This indicates that long-acting therapies are associated with continued improvement in negative symptoms over time. Treatment with long-acting injectables for longer than a year was associated with greatest improvements in negative symptoms.

**Randomized, double-blind study of flexibly-dosed intranasal esketamine plus oral antidepressant vs. active control in treatment-resistant depression**

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**Background:** About 30% of patients with major depressive disorder (MDD) fail to achieve remission despite treatment, and are considered to have treatment-resistant depression (TRD).

**Methods:** This was a Phase 3, double-blind, active-controlled, multicenter study (NCT02418585). The study enrolled adults with moderate-to-severe, non-psychotic, recurrent or persistent depression, and history of non-response to =2 antidepressants in the current episode of depression, with 1 of them assessed prospectively. Non-responders were randomized (1:1) to flexibly-dosed esketamine nasal spray (56 or 84 mg twice weekly) and a new oral antidepressant or placebo nasal spray and a new oral antidepressant. The primary efficacy endpoint – change from baseline to endpoint (day 28) in Montgomery-Asberg Depression Rating Scale (MADRS) total score – was assessed among patients who received =1 dose of (intranasal and oral) study medication by mixed-effects model using repeated measures.

**Results:** 435 patients were screened, 227 randomized, and 197 completed the double-blind period. Change (LS mean [SE] difference vs. placebo) in MADRS total score with esketamine nasal spray and oral antidepressant was superior to oral antidepressant and placebo nasal spray at day 28 (-4.0 [1.69], 95% CI: -7.31, -0.64; 1-sided p=0.010); likewise, clinically meaningful improvement was observed with esketamine nasal spray plus oral antidepressant at earlier time points. Remission rate (MADRS total score =12) at day 28 was 52.5% (53/101) and 31.0% (31/100) for the respective groups. The most common adverse events reported for the esketamine plus oral antidepressant group were dysgeusia, nausea, vertigo, and dizziness.

**Conclusions:** Robust efficacy of esketamine nasal spray and superiority to an active comparator were demonstrated on the primary efficacy endpoint result. More than half of the esketamine-treated TRD patients achieved remission by the 4-week endpoint. Favorable safety and tolerability of esketamine reported in this study suggest a positive benefit-risk profile of esketamine nasal spray.

**Behavioral assessment of cocaine self-administration in HIV-1 transgenic rats compared to F344 wildtypes**

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**Introduction:** Use of the HIV-1 Tg (Tg) rat model is valuable to increased understanding of HIV-associated neurocognitive disorders (HAND), including substance use disorders. Behavioral studies using experimenter-administered drugs have demonstrated Tg rats are more sensitive to cocaine because of the HIV-1 Tat protein action on dopamine transporter binding, but the few studies using self-administration have shown mixed behavioral results and unclear acquisition trajectories.

**Methods:** Adult male Tg and WT rats were fitted with intravenous catheters and given 7 self-administration sessions at 0.1 mg/kg/infusion cocaine on an FR1 schedule. We then attempted several approaches designed to boost self-administration in these rats. Session 8 was an auto-shaping session designed to prompt an association between drug and active lever. Sessions 9 and 10 were self-administration sessions (FR1 with 0.1 mg/kg cocaine). Sessions 11-17 were FR1 at 0.3 mg/kg/infusion. Sessions 18-20 were returned to 0.1 mg/kg/infusion, and sessions 21-27 were at 0.08 mg/kg/infusion. Sessions 28-35 were VR3 at 0.08 mg/kg/infusion. Sessions 36-42 were FR1 at 0.08 mg/kg/infusion, and sessions 43-50 were at 0.04 mg/kg/infusion.
Results: Evidence of robust acquisition of cocaine self-administration emerged in WT rats following the autoshaping session. These rats maintained significantly greater levels of cocaine intake than Tg rats throughout the remainder of training. Tg rats maintained very low levels of cocaine intake until session 36 (returned to FR1 at 0.08 mg/kg/infusion). At this point, wide variation of individual differences emerged in this cohort.

Conclusion: There are dramatic differences in cocaine self-administration by Tg compared to WT, even after implementing some behavioral ‘tricks’ to increase consumption. This outcome appears consistent with suggestions that Tg rats are more sensitive to cocaine and a full disclosure of the pattern of self-administration acquisition that we observed should aid other researchers interested in investigating comorbidities between HAND and substance use disorders.

Deficits in N-acetylaspartate in frontal white matter in euthymic bipolar disorder: relationship with peripheral inflammation

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Introduction: Bipolar Disorder (BD) is a severe mental disorder associated with increased morbidity and mortality. While the pathophysiology of BD remains to be determined, white matter abnormalities are among the most consistent neuroimaging findings in this disorder, and are suggestive of dysconnectivity. The underlying cellular and molecular mechanisms are unknown, although our prior post-mortem studies have revealed alterations in axonal and glial function. To better understand the etiology and pathophysiology of white matter abnormalities in BD we used proton spectroscopy (1H MRS) to quantify concentrations of brain metabolites, and examined the relationship between brain metabolite levels and markers of peripheral inflammation.

Methods: 1H MRS was performed on euthymic BD patients (n=24) and community controls (n=20), with similar age and sex distributions. MRS voxels were located predominantly in the left/right frontal white matter. Spectra were analyzed using LCModel and absolute concentrations were obtained using the unsuppressed internal water signal method, in conjunction with tissue fractions obtained from tissue segmentation and corresponding relaxation times. Concentrations of the cytokines interleukin (IL) -1ß, -6, -8 and -10, interferon-gamma, and tumour necrosis factor-alpha (TNF-alpha) were quantified in plasma.

Results: N-acetylaspartate (NAA), as measured by MRS, was lower in both left and right frontal white matter in euthymic BD subjects, relative to controls. In addition, levels of the cytokines IL-8 and IL-10 were higher in plasma in the BD group. Brain NAA levels were negatively correlated with plasma IL-8, IL-10 and TNF-alpha levels in the full cohort.

Conclusion: Deficits in NAA in BD may indicate altered axonal integrity in this disorder. Correlations with peripheral cytokines suggest that axonal integrity is lower in individuals with higher levels of peripheral inflammation, potentially elucidating a mechanism underlying white matter pathology in this disorder.

Interaction of phenelzine with human MAO-B reveals unexpected mechanistic insights

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Introduction: Phenelzine (ß-phenylethylhydrazine; PLZ) is a non-selective irreversible monoamine oxidase (MAO) inhibitor used to treat major depressive disorder and a variety of anxiety disorders. PLZ is oxidised by MAO predominantly to phenylethylidenehydrazine (PEH)
which, though a reversible inhibitor of MAO, irreversibly inactivates other enzymes. Irreversible inhibition of MAO by PLZ is thought to occur through occasional generation of an alternative product, phenylethyldiazene (PEDz), which presumably alkylates the flavin cofactor in situ. PLZ thus acts both as a substrate and as a suicide inhibitor of MAO. We have examined the interaction of PLZ with human MAO-B in an attempt to understand better the process that leads to formation of PEDz rather than PEH.

**Methods:** Activity versus PLZ of purified human MAO-B, expressed in Pichia pastoris yeast, was measured spectrophotometrically through peroxidase-coupled or aldehyde dehydrogenase-coupled assays, and versus benzylamine through direct photometric measurement of benzaldehyde. Concentrations of PLZ, PEH and hydrazine, a PEH hydrolysis product, were determined by liquid chromatography combined with mass spectrometry.

**Results:** Oxidation of PLZ by MAO-B resulted in almost stoichiometric release of PEH, a competitive, reversible MAO-B inhibitor, accompanied by time-dependent irreversible enzyme inactivation. The latter effect was not due to hydrazine. As PLZ concentration increased, the number of turnovers required prior to enzyme inactivation increased such that very high PLZ concentrations could not completely inactivate the enzyme. At the same time, the half life for inactivation of MAO-B was shorter at higher enzyme concentrations.

**Conclusions:** These observations suggest direct catalytic formation of an inhibitory species, presumably PEDz, which appears to dissociate from the active site before returning to inactivate MAO-B. This might be explained if the reduced flavin must first be reoxidised prior to alkylation. Binding competition of PEDz with PLZ/PEH, or allosteric influences on active site chemistry, may further impact the irreversible inactivation step.

**Intravenous ketamine: dissociative experience and antidepressant response**

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**Introduction:** In recent years, the most striking breakthrough in the treatment of major depressive disorder has been the discovery of the rapid antidepressant effect of ketamine, a glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist. When administered intravenously at sub-anesthetic doses, a single ketamine infusion can produce rapid but transient reductions in depressive symptoms. Repeated infusions have been shown to prolong the antidepressant effects. Dissociative side effects such as out of body experiences or distorted visual/auditory perception are common throughout ketamine infusions and recent studies have shown that dissociation during ketamine infusions correlates with antidepressant response.

**Methods:** Forty-one participants with treatment-resistant depression completed a single-centre trial of intravenous ketamine. Participants first received a single ketamine infusion administered during a randomized, double-blind cross-over with midazolam (an active control). Following relapse of depressive symptoms, participants received six open-label ketamine infusions administered thrice-weekly over two weeks. Depressive symptoms were evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS), and in a subset of twenty-two participants, dissociative symptoms were evaluated using the Clinician-Administered Dissociative States Scale (CADSS).

**Results:** Participants had a significantly larger decrease in MADRS scores 24 hours after the ketamine infusion compared to midazolam (p = 0.005). As anticipated, participants exhibited higher levels of dissociation (higher total CADSS scores) following ketamine infusion compared to midazolam (p < 0.006). Dissociative effects of ketamine were significantly correlated with antidepressant response at 24 hours post-infusion (r=0.46; p < 0.03). Following repeated infusions, change in total CADSS scores pre-
and post-infusion were smaller than with the first infusion (p=0.001), indicating the dissociative effects of ketamine attenuate with repeated infusions.

**Conclusion:** A single ketamine infusion elicited rapid antidepressant effects which were sustained with repeated administration. Initial dissociative side effects of ketamine were associated with antidepressant response. However, dissociation decreased following repeated infusions despite increasing therapeutic benefits.
**Differential Effects of High and Low Doses of Amphetamine in Adolescence on Dopamine and Behavioral Development**

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**Introduction:** The miR-218/DCC signaling pathway is fundamental to the adolescent development of the mesocorticolimbic dopamine circuitry. In adolescent mice, exposure to 4 mg/kg of amphetamine, a dose that reaches plasma levels similar to those achieved by abused doses in humans, dysregulate miR-218/DCC expression in dopamine neurons, disrupting in turn mesocortical dopamine connectivity and cognitive processing in adulthood. However, amphetamine drugs are commonly prescribed to treat neurodevelopmental conditions. Here we investigated whether low doses of amphetamine, comparable to those used in therapeutic settings, regulate the DCC pathway and dopamine development.

**Methods:** In all the experiments we used male C57BL/6 mice that received a low dose of amphetamine (0.5 mg/kg, i.p.) or saline, once every other day, for a total of 5 injections, from PND 22 ± 1 to PND 31 ± 1. First, we measured miR-218, Dcc mRNA, and DCC protein in the Ventral Tegmental Area (VTA) one week after treatment. Second, we allowed a separate cohort to reach adulthood (PND 75 ± 15) in order to assess behavioral flexibility and behavioral control using the attentional set shifting (ASST) and the Go/No Go tasks. Finally, we performed stereological analyses to quantify mesocortical dopamine connectivity and organization in adulthood.

**Results:** 1) Low doses of amphetamine in adolescence increased VTA DCC protein expression, without altering miR-218 or Dcc mRNA levels. 2) In comparison to saline groups, amphetamine-treated mice exhibited a small but significant improved performance across the ASST task and greater overall efficiency in the Go/No Go task. 3) There were no detectable group differences in mesocortical dopamine connectivity.

**Conclusion:** Low doses of amphetamine in adolescence lead to different, even opposite dopamine and behavioral effects in adulthood compared to high drug doses. These differences are likely to result from the opposite regulation that these doses exert on miR-218/DCC signaling in the VTA.
Beta-Actin expression correlates with monoamine oxidase activity in a sex- and region-dependent manner in the Alzheimer disease brain

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Introduction: Changes in the cytoarchitecture contributes to the loss of synaptic integrity during the aging process and is exacerbated in diseases with cognitive impairment such as Alzheimer disease (AD). Cognitive impairment often accompanies clinical depression and, not surprisingly, depression is now an acknowledged risk factor for AD. The two forms of monoamine oxidase (i.e., MAO-A and MAO-B) are thought to contribute to the pathology in both disorders and have been implicated in the regulation of cytoarchitectural proteins.

Methods: MAO-A and MAO-B activities were measured in autopsied cortical and hippocampal brain samples obtained from control and late-onset AD donors. Western blotting and densitometry were used to examine protein expression of both MAO isoforms as well as levels of cytoarchitectural proteins such as beta-actin, beta-tubulin, and the microtubule-associated protein Tau. Transient expression of MAO-A and MAO-B in glial and neuronal-like cells were used to examine the importance of each isoform in regulating the cytoarchitectural proteins.

Results: The most robust findings were correlations between the activities of the MAO isoforms and the beta-actin protein. Both MAO-A and MAO-B activities are positively correlated with beta-actin protein levels in the hippocampus of control female (but not male) donors. This correlation is lost with a diagnosis of AD. In contrast, there is no correlation between MAO isoforms and beta-actin expression in control donors, but there is a negative correlation between MAO-A activity and beta-actin protein in the male AD cortex, and between MAO-B and beta-actin in the female AD cortex. Expression studies in cell cultures confirm an influence of MAO-A activity on beta-actin expression.

Conclusion: These data support both region- and sex-dependent influences of MAO isoforms on cytoarchitectural changes in the AD brain and could inform on the improvement of disease management in the clinical context.

DCC gene network in the prefrontal cortex predicts brain volume and impulsivity in healthy children

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Introduction: The axon guidance receptor DCC is involved in organization of the mesocorticolimbic dopamine connectivity during adolescence and has been associated with psychopathologies involving prefrontal cortex (PFC) dysfunction. Here, we created a polygenic score1 based on the DCC co-expression gene network and hypothesized that discrete differences in behavior and brain structure will emerge according to an individual’s genotype expression.

Methods: Followed from birth to 12 years of age with multiple behavioral measures (n=260; 131 females), 64 of the healthy volunteers (n=64; 33 females) underwent magnetic resonance imaging
(MRI) and had genetic data collected using genotype sequencing (Psychip/Psycharray). Based on the assumption that coherent gene networks are represented by co-expressed genes, we obtained (from postmortem genetic databases) single nucleotide polymorphisms (SNPs) in genes co-expressed with DCC, with region (PFC) and age (1.5 to 11 y.o.) specificity. Then, using GTEx regression model of the gene expression we used the slope coefficient as the weight for alleles. The polygenic expression score is created by combining the estimated effects of alleles for the SNPs that each subject carries.

**Results:** We show that the DCC co-expression based polygenic score predicts morphological aspects of a healthy child's brain. Specifically, children with high polygenic score have significantly smaller brain volumes (p=0.016, F=6.22), when adjusted for age, sex and ethnicity. Volumetric thalamus measures are smaller in children with high co-expression scores (p=0.032, F=4.86) and are especially evident in boys (p=0.030, F=4.99). As for behavioral outcomes, CANTAB Stop Signal test reveals substantial impulsivity of the high polygenic score group (p=0.034, F=4.55).

**Conclusion:** DCC genetic mutations have been shown to impact brain development, structure and connectivity. However, using this novel genomic approach we reveal that variations in the gene expression of the DCC gene network also predict individual differences in brain structure that are apparent at an early age of a healthy population.

**Increased susceptibility to SKF 83959-induced anxiety in female rats is correlated to theta frequency oscillations within the nucleus accumbens**

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**Introduction:** The mechanisms underlying increased female susceptibility to develop anxiety disorders are not well understood. Neuronal oscillations are critical to proper brain functioning, and dysregulation of this activity within the reward circuitry has been linked to anxiety. In this study, sex differences in neuronal oscillations within the nucleus accumbens (NAc) of rats was assessed and correlated to anxiety responses induced by the dopamine agonist SKF 83959.

**Methods:** Anxiety-like behaviour in male and female rats was examined in the elevated plus maze (EPM) following administration of three escalating doses of SKF 83959 (0, 0.1, 0.25 mg/kg s.c., every other day), doses previously shown in male rats to be sub-threshold for inducing anxiety. During each test, recordings from NAc were obtained to evaluate oscillatory activity at specific frequencies in this region.

**Results:** showed that in the female, but not male, rats the highest dose of SKF 83959 induced anxiety-like behaviour as evidenced by significantly reduced EPM open arm time (p<0.01). SKF 83959 administration suppressed NAc low frequency power in both the delta (1-4 Hz, p<0.001) and theta range (>4-12 Hz, p<0.001) in female animals only with no significant effects observed in the male rats. Furthermore, correlation analysis revealed for each sex a linear relationship between SKF 83959-induced changes in NAc theta power and anxiety-like responses.

**Conclusions:** Together these findings indicate that female rats are more susceptible to the anxiogenic effects of SKF 83959 and highlight a potential relationship between anxiety and low frequency oscillations in NAc.

**Differential regulation of cortical and striatal neural oscillatory activity by the antipsychotics haloperidol and asenapine maleate in a model system of schizophrenia**

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**Introduction:** Synchronous neural oscillations are critical to normal cognitive functioning and their dysregulation has been demonstrated both in schizophrenia patients and in model systems of
schizophrenia. Typical antipsychotics are largely ineffective at combatting the cognitive symptoms of the disorder, whereas atypical antipsychotics have been proven more effective. This suggests that these drugs may differentially regulate neural oscillations in brain regions associated with cognition.

**Methods:** The effectiveness of the typical antipsychotic haloperidol (HAL, 1.0 mg/kg i.p.) and the atypical antipsychotic asenapine maleate (AM, 0.15 mg/kg, i.p.) at restoring cortical and striatal oscillatory deficits in the methylazoxymethanol acetate (MAM) rat model system were evaluated. Pre-pulse inhibition was also used to assess sensory gaiting deficiencies prior to, and following, the experimental protocol. Local field potentials from the prefrontal cortex (PFC) and caudate putamen (CPu) were obtained at baseline and following 14 days of drug administration in awake, freely moving animals.

**Results:** MAM rats exhibited PPI deficits that were improved following HAL or AM treatment. MAM rats exhibited increased beta frequency power in both the PFC and CPu with no differences in CPu-PFC coherence. In CPu, HAL or AM increased theta power in MAM and control rats whereas only AM normalized the beta power elevation in MAM rats. In PFC, only AM increased theta power and normalized beta power in the MAM rats. HAL, but not AM, increased gamma power in both CPu and PFC.

**Conclusions:** These findings indicate that while typical and atypical antipsychotics exert similar effects on neural function in CPu, newer generation antipsychotics are more effective in normalizing aberrant oscillatory function in PFC. It is hypothesized that enhanced striatal gamma synchronization following HAL may contribute to the drug’s motor side effects.

**Network-level changes of brain function in patients with bipolar disorder and major depressive disorder during working memory task**

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**Introduction:** Working memory (WM) impairment has been proved to be a common and core feature of mood disorder. The network-level mechanisms are still unclear with default mode network (DMN), frontoparietal network (FPN) and bottom-up (sensory) abnormalities arousing high suspicion. This study aimed to explore the network-level changes of brain function among groups of major depressive disorder (MDD) and bipolar disorder (BD) and healthy controls (HC) during working memory process.

**Methods:** A total of 434 participants, including 93 BD, 179 MDD and 162 HC, was included and tested by Two-back task during MRI scan. In addition to analyses of task-based activation and deactivation patterns across the brain, independent component analyses (ICA) were performed with the calculation of network engagement (beta weights) and between-network interaction.
(functional network connectivity, FNC) based on load contrast 2-back > 0-back.

**Results:** Both groups of patients performed worse in the task (F=8.155, p=0.000) and presented higher activation in left middle temporal gyrus (MTG) than HC (p<0.05, FWE corrected), but no significant difference between BD and MDD was found. In term of ICA analyses, the engagement of FPN was significantly different among three groups (F=6.491, p=0.002) with MDD>BD>HC pattern. FNC of SN-VN (visual network, VN; salience network, SN) and FPN-DMN were significantly different among groups. BD group showed less SN-VN anti-correlation compared to MDD [Cohen's d (p value): 0.41(0.002)] and HC [d(p)=0.28(0.04)] and more FPN-DMN anti-correlation compared to HC group [d(p)=-0.33(0.01)].

**Conclusion:** Our observations suggest that in both MDD and BD, recruitment of task-positive regions is excessive but not efficient to increase working memory performance. In BD, bottom-up inputs from visual to the salience network may be aberrant, in turn leading to a stronger dissociation between FPN and DMN. We conclude that disruption in the bottom-up sensory-salience interaction is likely to be specific to the pathophysiology of bipolar disorder.

**What determines social functional improvement in patients with major depressive disorder? A neuroimaging study**

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**Introduction:** 59.3% patients with the major depressive disorder (MDD) have severe social functional impairments, and functional improvement often lags behind the improvement in depressive symptoms. However, it is still unclear what determines the deficits and outcomes of social function in MDD patients. Our primary objective of this study was to investigate the biomarkers of social function in patients with MDD using structural magnetic resonance imaging (MRI).

**Method:** 3T anatomical MRI was obtained from 109 MDD patients, with 46 in high-functioning (high-SF, Sheehan Disability Scale (SDS) rating < 18) and 63 in low-functioning (low-SF, SDS score = 18) groups, and 163 healthy controls (HC) at baseline. 33 patients were followed up for 12 weeks. Voxel-based morphometry (VBM) was performed to locate brain regions with significant grey matter (GM) changes in relation to social functioning of MDD patients.

**Results:** Right parahippocampal (PHG) volume was significantly reduced in low-SF MDD subjects compared to high-SF MDD subjects (p<0.05, FDR correction). In correlation analysis, right PHG volume was lower in patients with higher scores in SDS and lower total, psychological and work/school condition scores in quality of life scale. High-SF patients with MDD had greater right PHG volume than both low-SF patients and HCs, indicating that increased right PHG volume may be an effective compensation in patients with high-SF. Over 12 weeks of follow-up, SF improved in both low and high-SF group though the groups continued to differ in their SF; but both groups had no changes in PHG volume, indicating that lower PHG volume is a stable, trait-like marker for low-SF.
Conclusion: Greater GM volume (GMV) of the right parahippocampal gyrus (PHG) marks and predicts better social functional ability and quality of life in patients with MDD. Treatment strategies that produce a morphological effect on this region may have favorable functional consequences in patients with MDD.

d-Govadine ameliorates working memory impairments induced by deficient prefrontal cortex GABA function

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Deficient prefrontal cortex (PFC) GABA function is thought to contribute to working memory impairments observed in schizophrenia and other psychiatric disorders. Pharmacological reduction of PFC GABA activity induces reproducible delayed-response working memory impairments in rodents, suggesting that this approach could be used to test compounds that may ameliorate PFC GABA-related working memory impairments. d-govadine is a recently characterized tetrahydroprotoberberine that promotes mesocortical dopamine release and enhances working memory in intact rats performing a delayed-response radial maze task. Furthermore, stimulation of PFC dopamine D1 receptors increases GABAergic inhibition of PFC pyramidal cells, which may reverse deficits in PFC GABA signalling. Here, we tested the hypothesis that d-govadine or D1 receptor stimulation could mitigate working memory impairments induced by PFC GABA hypofunction. Male rats were trained on an operant delayed-response task prior to implantation with bilateral cannulae in medial PFC. The task consisted of a sample phase in which one lever is extended, and a choice phase in which the rat must select the opposite lever, separated by a variable delay (1-24s). On test days, rats were pre-treated with either saline, d-govadine (0.5-1.0 mg/kg) or SKF 81297 (0.03-0.3 mg/kg) prior to receiving infusions of saline or the GABA-A receptor antagonist, bicuculline (50 ng). Reducing PFC GABA activity caused delay-independent working memory impairments that were ameliorated by pre-treatment with both doses of d-govadine, in a manner similar to certain doses of SKF81297. d-govadine did not affect performance when administered with PFC saline infusions. In a separate experiment, intra-PFC bicuculline impaired performance of a reference/working memory radial maze task, and this effect was attenuated by SKF81297 and d-govadine. These results further highlight the therapeutic potential of d-govadine in the treatment of schizophrenia-related cognitive impairment, and suggest that these effects may be mediated in part by facilitation of D1 receptor activity.

Small vessel pulsatility in white matter as a putative marker of early cerebrovascular risk in adolescent bipolar disorder

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Introduction: Bipolar disorder (BD) is associated with premature onset of cardiovascular disease. Hypertension and obesity are risk factors that cause arterial stiffness, leading to higher microvascular pulsatility and stress on capillaries. Cerebral microvascular damage appears as white matter hyperintensities (WMH) and is common in adult BD. This study uses blood oxygenation level dependent (BOLD) magnetic resonance imaging (MRI) to identify small vessel pulsatility index (SPI) in adolescent BD. Based on reported elevated SPI in white matter (WM) in small vessel disease (SVD), we predict similar findings in BD.
Methods: Thirty-eight adolescents with BD, ages 13-20, and 38 age-matched healthy controls were scanned using a 3 Tesla Philips scanner to obtain T1-weighted and BOLD images. BOLD data were preprocessed using CONN toolbox. SPI was calculated as the percentage of temporal coefficient of variation of BOLD signal in WM, and between-group differences were investigated. Body mass index (BMI), blood pressure and global functioning were also measured.

Results: We found higher SPI in periventricular and deep WM regions in BD compared to controls (p < .05). BMI correlated with SPI in both groups (r = .34). Pulse pressure correlated with SPI in controls (r = .33), while global functioning correlated with SPI in BD (r = -.41). Conclusion: We found elevated SPI, reflecting early microvascular dysfunction in WM among adolescents BD, in regions overlapping those where WMH are commonly reported in adult BD. Prospective studies are warranted, combining functional MRI with structural connectivity imaging to examine the link between SPI and impaired functioning in adolescent BD.

Antioxidant defence in schizophrenia and bipolar disorder: a meta-analysis of MRS studies of anterior cingulate glutathione

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Background: Glutathione [GSH] is a major intracellular antioxidant that disposes peroxides and protects neurons and glial cells from oxidative stress. In both schizophrenia and bipolar disorder, atypical levels of GSH has been demonstrated, particularly in the anterior cingulate cortex (ACC), though no consistent results have emerged due to limitations in sample size. Method: We reviewed all 1H-MRS studies reporting GSH values for patients satisfying DSM or ICD based criteria for a primary psychotic disorder (SCZ) or bipolar disorder (BPAD) in comparison to a healthy controls (HC) group in the Anterior Cingulate Cortex (ACC) published until February 2018. A random-effects model was used to calculate the pooled effect size using metaphor package. A meta-regression analysis of moderator variables was also undertaken. Results: The literature search identified 17 studies published between 2000 and February 2018 with a total sample size of 536 controls, 551 patients with schizophrenia or bipolar disorder. In schizophrenia, there are no significant differences in ACC GSH in patients compared to HC (N=12; RFX SMD =0.20; 95% CI [0.02 to 0.38]; p=0.026; heterogeneity p = 0.19). In bipolar disorder, there were highly significant differences in the ACC GSH, with patients having higher GSH concentrations than HC (N=6; RFX SMD = 0.28, 95% CI [-0.09 to -0.47]; p=0.003; heterogeneity p = 0.95).

Discussion: We report a small, but significant reduction in GSH concentration in the ACC in schizophrenia, and a similar sized increase in bipolar disorder. Schizophrenia and bipolar disorder have notably different patterns of redox abnormalities in the ACC. Reduced ACC GSH may confer a schizophrenia-like clinical phenotype, while an excess favouring a bipolar disorder-like profile. Larger head-to-head comparisons are warranted to confirm this proposition.

Characterizing cerebral venous oxygenation in adolescents with bipolar disorder using trust MRI

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**Introduction**: Altered cerebral blood flow (CBF) is evident in both adolescents and adults with bipolar disorder (BD). The effect of these changes on the brain’s oxygen homeostasis is unclear. Cerebral venous oxygenation (Yv) is an important physiological measure that provides information on how much oxygen has been consumed by the brain. This study uses the T2-relaxation-under-spin-tagging (TRUST) magnetic resonance imaging (MRI) technique to quantify and compare Yv between adolescents with and without BD. Due to previously reported CBF alterations in BD and increased cardiovascular risk, we hypothesize that adolescents with BD will have lower Yv.

**Methods**: Sixty adolescents (13-20 years old) with BD (type I, II or NOS) and 67 healthy controls (HC) were scanned using a 3 Tesla Philips scanner to acquire TRUST images. In a subset of participants (n=47 BD, n=50 HC), both baseline and post-exercise TRUST scans were obtained to examine the effects of a single bout of moderate-intensity aerobic exercise on Yv. Yv was estimated by a mono-exponential model in MATLAB, by calculating the T2 relaxation of the venous blood in the sagittal sinus.

**Results**: There was no significant difference in baseline Yv between the BD and HC group. We found a significant correlation between Yv and age (r = -0.21). In the subset group that engaged in exercise, there was no significant effect of aerobic exercise on Yv.

**Conclusion**: Although Yv was found to be similar between groups, previous evidence of CBF alterations in BD suggests that the relationship between Yv and cerebral metabolic rate (CMRO2) should also be investigated. Combining TRUST with other MRI modalities measuring CBF will provide additional insight on oxygen homeostasis in the brain.

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**Fractalkine signaling in bipolar disorder and schizophrenia: relationship with microglial activation**

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**Introduction**: While the pathophysiology underlying bipolar disorder (BD) and schizophrenia (SCZ) has not yet been clearly established, evidence suggests that alterations in immune function may contribute. However, the degree to which immune activation impacts brain function remains to be determined. Microglia, the brain's resident immune cells, mount the neuro-immune response and are critical in shaping synaptic connectivity. Fractalkine signaling plays a critical role in the management of microglial function, including modulation of microglial activation and regulation of synaptic pruning and plasticity. We previously identified a significant reduction in microglial activation in BD and hypothesize that diminished microglial activation may be associated with alterations in fractalkine signaling.

**Methods**: Levels of the fractalkine receptor CX3CR1 and the fractalkine-regulating protein ADAM10 were quantified in postmortem brain in BD, schizophrenia, and controls by immunoblotting. Correlations between CX3CR1, ADAM10, measures of microglial activation, and additional immune and synaptic proteins were examined.

**Results**: We observed a modest reduction in CX3CR1 protein expression in both BD and SCZ groups relative to controls, which trended towards significance. We also observed a statistically significant correlation between CX3CR1 expression and microglial activation, as well as levels of the synaptic protein SNAP25.

**Conclusion**: Our results suggest that fractalkine-CX3CR1 signaling contributes to altered microglial activation and modification of synaptic connectivity in BD and SCZ, further implicating immune dysfunction in these disorders. Further investigation of mechanisms underlying immune dysregulation in BD and SCZ is critical for informing future therapeutic interventions targeting the immune system in these disorders.
The impact of childhood trauma on in vivo brain measures of histone deacetylases in adulthood: A pilot study

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Introduction: Exposure to childhood trauma (CT) is a risk factor for many psychiatric disorders. CT can alter gene expression through epigenetic mechanisms, potentially altering brain development. Histone deacetylases (HDACs) are important epigenetic regulators. Animal studies have demonstrated that HDACs are strongly implicated in CNS development, and HDAC activity can be modified by early trauma. However, little is known about how HDACs are associated with CT in humans. In the present study, we characterize brain regional densities of class-I HDACs in adults with and without CT, using positron emission tomography (PET) and the novel tracer, [11C]Martinostat (Wey et al., 2016).

Methods: 20 volunteers (10 with high CT, 10 with low CT) from a longitudinal cohort followed since childhood will be tested; 5 low CT cases have been studied so far. Participants undergo a 90-minute PET scan following [11C]Martinostat injection (370 MBq), MRI, and behavioral assessments. CT status is defined as scoring in the highest vs. lowest 10% of results on an index combining several childhood adversity factors, including exposure to child abuse. Primary outcome measures are regional specific uptake volumes of [11C]Martinostat computed from 60-90 minutes after tracer injection (rSUV60-90min).

Results: Our 5 initial cases show higher rSUV60-90min values within the putamen (3.53 ± 0.84), thalamus (3.36 ± 0.93), and cingulate cortex (3.37 ± 0.75) than within the hippocampus (2.44 ± 0.71) and amygdala (2.51 ± 0.61). Signal was higher than background in all grey matter regions examined with moderate regional and inter-individual variations, suggesting that [11C]Martinostat has imaging properties appropriate to test our hypotheses throughout the brain.

Conclusion: [11C]Martinostat is a promising ligand to assess epigenetic enzymes in vivo in human brain. Further use of this ligand in individuals exposed to CT may contribute to our understanding of how this influences CNS development and can result in CT-related psychiatric disorders.

Chromosomal microarrays finger genes regulating dendritogenesis – potential implications for precision medicine in bipolar disorder and schizophrenia

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Introduction: Variation in genes involved in synaptic function has been robustly associated with risk of neurodevelopmental disorders (NDDs) and major psychiatric disorders (MPDs) such as bipolar disorder and schizophrenia. The therapeutic relevance of genes that regulate dendritogenesis to these disorders is less well appreciated.

Methods: Clinical chromosomal microarray screening using the Affymetrix Cytoscan HD platform was used to detect rare and novel copy number variants (CNVs) in patients with NDDs and MPDs. CNVs involving dosage-sensitive genes implicated in brain development and function were prioritized for analysis, using literature mining and databases such as DECIPHER, OMIM, GeneCards, SCZGR2, denovo-db, UniProt, the UCSC genome browser, and Ensemble. Relevant cellular pathways and gene networks, and their regulation by pharmacological agents were identified through literature mining and databases such as STRING, CTG, and GTEx. Case-based genotype-phenotype correlation was performed.

Results: Genes implicated in positively regulating dendrite growth and branching with predicted CNV-mediated gene dosage changes were identified. A patient with intellectual disability and severe refractory psychosis was found to have a proximal 16p11.2 chromosomal microduplication (conferring an 11-fold increase in schizophrenia risk). Duplication of the MAPK3 (map kinase 3) gene predicts attendant overexpression of ERK1 kinase, a positive regulator of dendritogenesis. The patient was being treated unsuccessfully with drugs which upregulate ERK1/2 kinases, including divalproex and clozapine (the antipsychotic with the strongest effects in this regard), thereby potentially worsening his psychiatric phenotype. Two patients with stress-induced manic psychotic episodes associated with prominent olfactory hallucinations had CNVs predicted to upregulate thrombospondin-1 (TSP-1) signaling. Gabapentin, which has mood-stabilizing effects, is a powerful antagonist of TSP-1 at its receptor (a2dd-1).

Conclusion: Genes that regulate dendritogenesis may be therapeutic targets in some patients with NDDs and major psychiatric disorders. In patients with pathological upregulation of ERK signaling, therapy for refractory psychosis may actually worsen rather than improving outcomes.

Improvement of smell and taste with discontinuation of buprenorphine/naloxone

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Introduction: Buprenorphine/naloxone, a partial opioid agonist, has been described to induce smell and taste aversion (Lonergan et al., 2011) and impairs chemosensation (Mizera et al., 2016). Discontinuation of buprenorphine resulting in enhancing smell and taste has not heretofore been described. Two such cases are presented.

Method: Case 1: A 36 year old, right-handed married male had a 10-year history of opioid abuse including fentanyl, acetaminophen/oxycodone and heroin. A few days prior to presentation he was on a variety of substances including 8 mg buprenorphine/2 mg naloxone every 12 hours, a fentanyl patch 100 mg every 48 hours, snorting heroin ½ gram each day, smoking marijuana daily and cigarettes one pack per day. He was undergoing withdrawal manifested by insomnia, fatigue, anxiety, and poor appetite.

Results: Case 1: Clinical Opiate Withdrawal Scale: 21 including diaphoresis with sweat streaming off face, constant rhinorrhea, lacrimation, vomiting, diarrhea, and frequent adventitious movements. After being placed on buprenorphine/naloxone sublingual 4 mg/1 mg twice a day, he observed a total absence of his ability to smell and taste. Within 2 days of suddenly discontinuing
buprenorphine/naloxone, his smells and taste returned to 50% of normal. Within a week of him restarting buprenorphine/naloxone, his ability to smell and taste disappeared again. **Discussion:** The use of opiates has been reported to alter taste (Schiffman, 2015) and reduce smell (Lotsch et al., 2012). Mizera specifically listed buprenorphine/naloxone as an origin for chemosensory loss (Mizera et al., 2016). However, the discontinuation of buprenorphine/naloxone has not previously been described to improve smell and taste. Maybe the reduction in olfactory function was partial and due to a reduction in specific G protein-coupled receptors (GPCRs) with reduced cAMP as the second messenger (Lotsch et al., 2012). Given the above, a trial of buprenorphine/naloxone in those with hyperosmia and hypergeusia may be warranted.

**Peripheral reelin administration rescues neurochemical alterations and depression-like behavior in a preclinical model of depression**

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**Introduction:** Chronic stress is a significant risk factor for the onset of depression. This can be further studied in animal models. We have shown that repeated corticosterone (CORT) treatment produces a behavioral phenotype of depression that is associated with deficient hippocampal neurogenesis, decreased hippocampal reelin levels, and larger serotonin transporter (SERT) protein clusters in peripheral lymphocytes that parallel changes seen in human depression patients. Our most recent data revealed that intrahippocampal infusions of reelin can normalize the alterations produced by CORT. Here we examined whether peripheral intravenous administration of reelin may have a similar antidepressant-like effect.

**Methods:** Rats received 21 days of daily CORT or vehicle injections along with either 3µg or 5µg of reelin every 5 or 10 days. Thereafter, they were subjected to the forced swim test to measure depression-like behavior. Brain sections were used to analyze the number of Reelin+ cells in the dentate subgranular zone (SGZ) and the paraventricular nucleus (PVN) as well as the number and complexity of newborn neurons in the granule cell layer. We also analysed SERT protein clustering in peripheral lymphocytes.

**Results:** Our results revealed that reelin reversed the CORT-induced increases in FST immobility, the downregulation of reelin in the SGZ, and the increase in size of SERT clusters. However, only 3µg every 10 days reversed the decreases in reelin expression in the PVN, and all doses failed to reverse the CORT-induced decrease in the number and complexity of dendritic processes of developing newborn neurons.

**Conclusion:** These novel findings show for the first time that peripheral reelin administration can normalize CORT-induced increases in depression-like behavior and the size of SERT protein clusters in peripheral lymphocytes and the decreases in hippocampal plasticity. Although additional mechanistic and pharmacokinetic studies are necessary, our data also open the possibility of developing reelin peptides with antidepressant activity.

**A human neuronal cell model for Neuroscience: gene expression profile of the SH-SY5Y cells using a microarray analysis**

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Background: It has been proposed that the differentiation of the human neuroblastoma cell line, SH-SY5Y, into cells with a neuronal profile may be a relevant model to study diseases that affect the central nervous system (CNS). Previous studies of our group demonstrate the feasibility of this model to investigate psychiatric disorders. Given that pathways involved in the differentiation process of SH-SY5Y cells are fundamental for the use of this model in neuroscience, this work aimed to characterize the gene expression profile of SH-SY5Y cells.

Methods: Neuronal differentiation of SH-SY5Y cells was induced by retinoic acid for seven days. Then, RNA was isolated and purified for microarray analysis (GeneChip PrimeView, Affymetrix). Differential expression and gene set enrichment analysis was performed to identify biological process associated with cell phenotypes (proliferative and differentiated cells).

Results: Microarray data generated in this study were deposited in Gene Expression Omnibus (GEO) repository (GSE71817). Genes associated with neuronal biological processes, such as synaptic transmission, regulation of neurotransmitter levels and membrane potential were enriched in the differentiated cell phenotype, while genes associated to cell proliferation and biosynthetic processes were enriched in the proliferative cell phenotype.

Conclusions: To the best of our knowledge, this is the first study that conducted a microarray analysis and characterized the gene expression profile of differentiated SH-SY5Y cells. Our findings reinforce the neuronal phenotype of this in vitro model and the relevance of using this model to study diseases that affect the CNS.

Cognitive performance and salivary cortisol levels in children

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Introduction: The cognitive impairment in students may cause unpleasant phenomena like stress. Stress has been associated with disturbed activation of the hypothalamic-pituitary-adrenal axis (HPA). However, studies are scarce about the relation between the cognitive performance and physiological stress in children. Thus, the aim of this study is to assess the correlation between the cognitive performance and the salivary levels of cortisol in school children.

Methods: This is a cross-sectional study that included children aged between 7 and 8 years old from public schools from Southern Brazil, selected by probability sampling. The cognitive performance of the students was analyzed through Wechsler Abbreviated Scale of Intelligence (WASI). In the same day of the cognitive assessment, we have collected saliva from children. The salivary cortisol levels were measured through Roche Commercial kit, using the electrochemiluminescence technique, expressed by ng/mL. The statistical analysis was performed in SPSS22, using Spearman correlation for the crude analysis, and linear regression for adjusted analysis.

Results: The sample included 543 children. There was a significant negative correlation (r=-0.189; p<0.001) between verbal intelligence quotient and salivary cortisol levels, and this
association was kept after adjusted for confounders (p=0.003). Thus, lower verbal intelligence quotient among students is associated to higher salivary levels of cortisol. There was no association between executive intelligence quotient and salivary cortisol levels in our sample, after adjusted for confounders (p=0.365).

**Conclusion:** The worse cognitive performance in the school environment, especially regarding verbal tasks, may be a source of stress for the children.

**The effects of drug therapy in depression depend on the location of network dysfunctions**

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**Introduction:** CAN-BIND is a multisite initiative in Canada that includes a 16-week protocol where patients with Major Depressive Disorder (MDD) are treated with a first-line antidepressant (escitalopram 10–20 mg/d) that, if clinically warranted after eight weeks, is augmented with an evidence-based, add-on medication (aripiprazole 2–10 mg/d).

**Methods:** EEG data analysis can provide an informative assessment of brain activity, however, reliable EEG related biomarkers of (MDD) and response to drug therapy are still missing. Network fragmentation was computed based on estimated dynamic cross-entropy (DCE). The method compared the area under the ROC curve in all brain regions estimated in 50 CAN-BIND patients at baseline, week 2 and week 8 of therapy. Linear mixed-effects models were used to determine the relationship between the drop of Montgomery–Åsberg Depression Rating Scale (MADRS), and changes of network fragmentation after two months of therapy. The model was corrected for confounding factors such as age and sex.

**Results:** The highest drop of MADRS score occurs when the focal injury on network activity is located in the left DLPFC at electrode F3: F(1, 17)= 7.13, p=0.016 and left temporal region at T7: F(1, 17)= 6.9, p=0.017. Patients with network dysfunctions at right parietal region at electrode P8, and left occipital regions at electrode O1 also benefit by drug therapy, however, the regression analysis does not show statistically significant values, P8: F(1,17)= 2.82, p= 0.11 , O1: F(1,17)= 2.76, p= 0.11. The administration of escitalopram increases the severity of depression if the network dysfunctions are located in the primary motor cortex, right hemisphere at electrode C4:F(1,17)=15.96, p=0.0009.

**Conclusion:** relevance/implications: The decrease of depression severity after drug administration depends on the location of network dysfunctions. Specifically, the topographic distribution of network dysfunctions is a predictor of treatment remission for depression.

**GLP-1 receptor agonists: a potential new therapeutic target for treatment of psychiatric disorders**

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Depression is one of the leading causes of disability worldwide and current antidepressant therapies have minimal efficacy for 30-50% of patients. Considering that many factors are associated with the pathophysiology of depression — including the immune system —, our aim was to evaluate the potential antidepressant-like effects of the acute treatment with EX-4, a glucagon-like peptide-1 (GLP-1) receptor agonist, in an animal model of inflammation induced by LPS. Male Wistar rats were injected with LPS (0.25 mg/kg i.p.) or saline and treated with three different doses of EX-4 (0.1, 0.3 and 0.5 µg/kg i.p.) or saline at three different time points. Animals were submitted to the open field and the modified forced swim test (FST; 5h and 28h after LPS injection, respectively). Following the euthanasia by decapitation, the blood was collected, and the brain was removed. IL-6, TBARS and BDNF levels were measured in the serum and hippocampus. LPS injected rats exhibited significant body weight loss (p<0.0001), decreased locomotor activity (p<0.006), higher serum levels of TBARS (non-significant) and significant decreased serum levels of BDNF (p<0.02), when compared to saline injected animals. IL-6 serum levels were only detected in LPS injected animals. Also, no changes were observed in those same parameters in the hippocampus of LPS injected animals when compared to the saline group. Depressive-like behaviour was no longer observed in the FST at 28h after LPS injection. Overall, the different doses of EX-4 did not improve sickness-behaviour and neither the serum levels of the parameters analyzed under this schedule of treatment. However, given evidence on its antioxidant, neuroprotective and potential anti-inflammatory properties, GLP-1 receptor agonists are still considered as a promising opportunity to further identify a new therapeutic target for depression.

Early growth response 3 and brain-derived neurotrophic factor in a shared biological pathway: potential targets for novel therapeutics in bipolar disorder

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Introduction: Bipolar disorder (BD) is a severe psychiatric disorder involving complex interactions between genes and environmental factors. Using gene network-based approach, we have shown that the regulatory unit of early growth response gene 3 (EGR3) was repressed in post-mortem prefrontal cortex of BD patients. EGR3 mediates critical neurobiological processes, and has the potential to translate environmental stimuli into long-term changes in brain. Here we aimed to summarize findings about EGR3 and Brain-Derived Neurotrophic Factor (BDNF), which has been consistently related to BD, to investigate potential molecular links between them.

Methods: A review of the literature was performed focused on (1) the EGR3 pathway and (2) findings indicating that changes in BDNF are a consistent feature in BD. We summarized evidence supporting the link between EGR3 and BDNF in a shared biological pathway and its potential contribution to BD pathophysiology.

Results: A growing body of data from our group and others has shown that peripheral BDNF levels are reduced during mood episodes and also with illness progression. Lower BDNF levels observed in BD may influence the reduced EGR3 levels in this illness since EGR3 expression is induced by BDNF. Considering that EGR3 regulates the expression of the neurotrophin receptor p75NTR and may also indirectly induce BDNF expression, we also suggest that reduced EGR3 expression could contribute to lower BDNF levels associated with BD.

Conclusion: With this perspective study, we propose a feedback-loop involving EGR3 and BDNF reinforcing a dysfunctional pathway in BD. This process could impair neuroplasticity and resilience, ultimately leading to increased vulnerability to stress, and underlying neuroprogression. Thus, we suggest an interesting link between EGR3 and BDNF in BD, and this pathway could provide potential targets for follow-up studies to clarify the interaction between environment and
genetic factors that influence BD, and for the development of novel therapeutics.

**Cues enhance the pro-addictive power of motor impulsivity**

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The cues featured in human gambling enhance the addictive potential of play. Our group has modeled this phenomenon in rats using the cued rat gambling task (crGT), a variant of our original rat gambling task (rGT). In the crGT, audiovisual cues are presented with each win, and compared to the rGT, animals become riskier and exhibit greater motor impulsivity. The cues associated with drug use likewise become powerful incentive stimuli, evoking within individuals a desire drugs, facilitating the transition to addiction. Given the comorbidity between drug addiction and gambling disorder, we primarily wondered whether cue-induced risky choice and impulsivity would impact the self-administration of cocaine. We also asked if cocaine self-administration modulated the ongoing expression of these traits. We trained male Long-Evans rats to stability in either the rGT or crGT before implanting them with jugular catheters and allowing them to self-administer cocaine for 10 days. crGT rats were significantly riskier and more impulsive than rGT rats. For crGT rats, impulsivity was positively correlated with cocaine seeking, whereas no correlation was observed in the rGT group. These findings suggest that exposure to reward cues may make individuals more impulsive as well as potentiate the pro-addictive power of trait impulsivity. Both groups exhibited reductions in state impulsivity following cocaine self-administration; this is consistent with the therapeutic efficacy of psychostimulants against disorders of impulse control. Cocaine-induced decreases in impulsivity were not associated with ongoing decreases in cocaine seeking, which remained coupled to baseline impulsivity. While risky decision making was not associated with increased cocaine seeking/taking, a history of self-administration did cause an increase in risky choice in rats already risky at baseline. As individuals become risker, they become more prone to maladaptive cost/benefit decision making. It is therefore possible that risky decision making does not directly influence the acquisition of drug use.
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