CCNP 2015 – Overview of Events
Lord Elgin Hotel, Ottawa ON
June 9 – 12

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Dr. David Park, Director, Brain and Mind Research Institute, University of Ottawa

Dear Participants:

Welcome to the 38th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) at the Lord Elgin Hotel in Ottawa, ON. The local organizing committee including Shawn Hayley, Diane Lagace, Zul Merali, and David Park under the leadership of Paul Arnold (Chair) has done a fabulous job in organizing and supporting the meeting. The scientific program combines an excellent collection of basic science, clinical research, and translational approaches and represents the latest research findings from across Canada and beyond. I want to thank the many sponsors of this year's CCNP meeting and want to send a special thank you to Pfizer for their continued support of the annual CCNP awards. In addition, I would like to thank Rachelle Anderson for her help with the program and the logistics of the meeting.

Highlights of the program include a ECNP keynote address by Dr. Michel Hamon from the Université Pierre et Marie Curie, Paris, France, presentations by the 2015 CCNP Award winners, several excellent symposia including an India-Canada joint symposium chaired by Dr. Ridha Joober and the Presidential symposium that features leaders in the field of gut-brain research. Congratulations to the trainees who received W.G. Dewhurst travel awards and those selected to present their work in the next generation symposium.

I look forward to connecting with colleagues and trainees and to meeting new people. I hope you take this opportunity to share ideas and learn from each other in order to foster existing and new collaborations. Enjoy your time in our nation's capital city of Ottawa.

Sincerely,

Jane Foster

TABLE OF CONTENTS

Accreditation Information

Approval of this program by the Office of Continuing Education and Professional Development, University of Ottawa is pending.

OVERVIEW OF EVENTS

TUESDAY JUNE 9

13:00 – 17:00	CCNP Council Meeting (Laurier Room)
17:00 – 18:00	JPN Board Meeting (Laurier Room)
17:00 – 21:00	Registration (Pearson Room Foyer)
17:30 – 18:30	CCNP Reception (Pearson Room Foyer)
17:30 – 18:30	Speakers Reception (Bar Lounge) (speakers only)
18:30 – 19:30	ECNP Keynote Lecture: Dr. Michel Hamon (Université Pierre et Marie Curie, Paris, France) (Pearson Room) **40 years of research on serotonin receptors**

WEDNESDAY JUNE 10

07:30 – 08:00	Breakfast (Pearson Room Foyer)
08:00 – 17:00	Registration (Pearson Room Foyer)
08:00 – 9:00	Heinz Lehman Award Lecture: Dr. Derek van der Kooy (University of Toronto) (Pearson Room) **Motivational effects of nicotine**
9:00 – 9:30	Coffee Break (Pearson Room Foyer)
9:30 – 11:30	Presidential Symposium: **Microbiota and brain function – implications for neuroscience and psychiatry** (Pearson Room) Drs. Jane Foster (Chair & CCNP President, McMaster University), Rochellys Diaz Heijtz (Karolinska Institutet), Elaine Y. Hsiao (California Institute of Technology), Emeran Mayer (UCLA)
11:30 – 13:00	LUNCH/CCNP Business Meeting (All are welcome) (Lunch in Pearson Room Foyer/Meeting in Lady Elgin Room)
13:00 – 15:00	Symposium #1: **Altered Dopamine-D2 receptor function in addiction and schizophrenia** (Pearson Room)

Drs. Paul R. Albert (Chair, University of Ottawa), Bruno Giros (McGill University), Christoff Kellendonk (Columbia University), Marco Leyton (McGill University)

13:00 – 15:00 Symposium #2: **Using targeted lipidomics to understand the brain-heart relationship**
(Lady Elgin Room)

Drs. Steffany Bennett (Co-Chair, University of Ottawa), Krista Lanctôt (Co-Chair, University of Toronto), Zdenka Pausova (University of Toronto), Graham Mazereeuw (University of Toronto), Richard P Bazinet (University of Toronto), Hongbin Xu (University of Ottawa)

15:00 – 15:30 Coffee Break (Pearson Room Foyer)

15:30 – 16:30 **Next Generation Symposium** (Pearson Room)

Dr. Darrell Mousseau (Co-Chair, University of Saskatchewan), Dr. Ana Andreazza (Co-Chair, University of Toronto), Victoria Marsh (University of Toronto), Faranak Vahid-Ansari (University of Ottawa), Emily Hawken (Queen's University), Julian Chiarella (Queen's University)

16:30 – 18:30 Poster Session I (Laurier Room)

THURSDAY JUNE 11

07:30 – 08:30 Breakfast (Pearson Room Foyer)

08:00 – 17:00 Registration (Pearson Room Foyer)

08:30 – 09:30 Innovations Award Lecture: Dr. Marco Leyton (McGill University)
Individual differences in dopamine transmission: a potential vulnerability pathway to addiction
(Pearson Room)

09:30 – 10:00 Coffee Break (Pearson Room Foyer)

10:00 – 12:00 Symposium #3: **An integrative approach to finding biomarkers for depression**
(Pearson Room)

Drs. Sidney Kennedy (Chair, University of Toronto), Gustavo Turecki (McGill University), Ken Evans and Harriet Feilotter (Queen's University), Daniel Mueller (CAMH, University of Toronto), Ana Andreazza (University of Toronto)

10:00 – 12:00	Symposium #4: **Behavioural and neurobiological substrates of compulsive drug use: insights from rats to humans** (Lady Elgin Room) Drs. Anne-Noël Samaha (Chair, Université de Montréal), Éric C. Dumont (Queen's University), Sean Barrett (Dalhousie University), Isabelle Boileau (CAMH, University of Toronto)
12:00 – 14:00	Lunch and Poster Session II (Pearson Room Foyer; Laurier Room)
14:00 – 16:00	Symposium #5: **Major depression: a GABA-ergic disorder? A multilevel translational perspective** (Ontario Room) Drs. Georg Northoff (Co-Chair, University of Ottawa), Etienne Sibille (Co-Chair, University of Toronto), Georg Northoff (IMHR, University of Ottawa), Jeff Daskalakis (CAMH, University of Toronto), Gerard Sanacora (Yale University)
14:00 – 16:00	Symposium #6: **Harnessing neuroinflammatory processes to treat neurodegeneration** (Quebec Room) Drs. Shawn Hayley (Chair, Carleton University), Francesca Cichetti (Laval University), David Stellwagen (McGill University), George Robertson (Dalhousie University)
17:00 – 19:00	Mentee/Mentor Mixer (St. Laurent Room)
18:00 – 19:00	Cocktails (Pearson Room)
19:00 – 22:00	Banquet (Pearson Room)

FRIDAY JUNE 12

07:30 – 08:30	Breakfast (Ontario Room Foyer)
08:30 – 11:00	Registration (Ontario Room Foyer)
08:30 – 9:30	Young Investigator Award Lecture: Dr. Sherif Karama (McGill University) (Ontario Room) **Cigarette smoking and thinning of the brain's cortex**
09:30 – 10:00	Coffee Break (Ontario Room Foyer)

10:00 – 12:00	Symposium #7: **Involvement of Astroglial cells in the antidepressant response and in mood disorders** (Ontario Room) Drs. Bruno Guiard (Co-Chair, University of Toulouse), Nasser Haddjeri (Co-Chair, University of Lyon), Naguib Mechawar (McGill University), David Stellwagen (McGill University)
10:00 – 12:00	India-Canada Joint Symposium: **Refining the role of genes in increasing risk for neurodevelopmental disorders** (Quebec Room) Drs. Ridha Joober (Chair, McGill University), Sarojini Sengupta (McGill University), John P John (Bangalore University, India), V. Ganesan (Bangalore University, India), Sherif Karama (McGill University)
12:00	Closing Remarks (Ontario Room)
15:00 – 16:00	**uOttawa-BMRI Plenary Lecture: Dr. Eric Nestler** (New York, USA) (University of Ottawa)

Tuesday, June 9, 2015

13:00 – 17:00 CCNP Council Meeting (Laurier Room)

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17:00 – 21:00 Registration (Pearson Room Foyer)

17:30 – 18:30 CCNP Reception (Pearson Room Foyer)

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18:30 – 19:30 **ECNP Keynote Lecture: Dr. Michel Hamon** (Université Pierre et Marie Curie, Paris, France)
40 years of research on serotonin receptors (Pearson Room)

ECNP KEYNOTE LECTURE ABSTRACT
40 YEARS OF RESEARCH ON SEROTONIN RECEPTORS

Michel D. Hamon
Faculté de Médecine Pierre et Marie Curie Site Pitié-Salpêtrière
91 Boulevard de l'Hôpital
75634 Paris cedex 13
France

Since the discovery of its chemical identity more than 60 years ago, serotonin (5-HT) was shown to exert multiple effects in both the animal and vegetal words. In mammals, its multiple actions are mediated through the activation of numerous receptors encoded by some fifteen specific genes. However, several decades of research were needed before reaching this status of knowledge. In the early ages, receptors were postulated entities only, and their existence and functional properties were inferred from the capacity of drugs to exert opposite effects as expected from agonists versus antagonists. The concept of autoreceptors mediating the inhibitory action of 5-HT on its own release was in fact postulated from such studies. Binding assays with radiolabeled agonists and antagonists then allowed the visualization and quantification of their molecular targets, and the very first demonstration of 5-HT receptor heterogeneity. Appropriate ligands were thus available for the exploding application of molecular biology methods, which led not only to the cloning and sequencing of 5-HT receptors already identified pharmacologically and biochemically, but also the discovery of other unsuspected receptor types. Specific antibodies raised against sequence domains then became remarkable tools for thorough characterization of cell phenotypes expressing the various receptor types. Today, molecular genetic approaches allow controlled changes in the expression of a given receptor type within a specific cell phenotype, and open new avenues toward thorough knowledge of the multiple physiological implications of this fascinating 5-HT.

Wednesday, June 10, 2015

07:30 – 08:00 Breakfast (Pearson Room Foyer)

08:00 – 17:00 Registration (Pearson Room Foyer)

08:00 – 9:00 **Heinz Lehman Award Lecture** (Pearson Room)
Dr. Derek van der Kooy (University of Toronto)
Motivational effects of nicotine

09:00 – 9:30 Coffee Break (Pearson Room Foyer)

09:30 – 11:30 **Presidential Symposium** (Pearson Room)

Microbiota and Brain Function – Implications for Neuroscience and Psychiatry

Chair: Dr. Jane Foster, President, CCNP

09:30 – 10:10 Dr. Rochellys Diaz Heijtz (Karolinska Institutet, Sweden)
Early life gut-microbiome-brain interactions: implications for neurodevelopmental disorders

10:10 – 10:50 Dr. Elaine Y. Hsiao (California Institute of Technology)
Uncovering microbial modulators of neuroactive molecules

10:50 – 11:30 Dr. Emeran Mayer (UCLA)
Gut microbiome brain interactions in humans

11:30 – 13:00 **LUNCH/CCNP Business Meeting** (All are welcome) (Lunch in Pearson Foyer/Meeting in Lady Elgin Room)

13:00 – 15:00 **Symposium 1** (Pearson Room)

Altered Dopamine-D2 receptor function in addiction and schizophrenia

Chair: Dr. Paul R. Albert (University of Ottawa)

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Transcriptional regulation of dopamine-D2 receptors in schizophrenia

13:30 – 14:00 Dr. Bruno Giros (McGill University)
Deciphering the role of dopamine in learning and memory

14:00 – 14:30 Dr. Christoff Kellendonk (Columbia University)
Upregulation of dopamine D2 receptors in the nucleus accumbens indirect pathway enhances motivational behavior but does not reduce alcohol consumption

14:30 – 15:00 Dr. Marco Leyton (McGill University)
Dopamine D2 receptors and addictions: PET studies in humans

13:00 – 15:00 **Symposium 2** (Lady Elgin Room)

Using targeted lipidomics to understand the brain-heart relationship

Co-Chairs: Drs. Steffany Bennett (University of Ottawa) and Krista Lanctôt (University of Toronto)

13:00 – 13:30 Dr. Zdenka Pausova (University of Toronto)
Circulating lipidome and pre-clinical cardiometabolic disease in adolescence

13:30 – 14:00 Dr. Graham Mazereeuw (University of Toronto)
The pro-inflammatory second messenger lipidome, cognitive deficits, and depression in older adults with coronary artery disease

14:00 – 14:30 Dr. Richard P Bazinet (University of Toronto)
Regulating brain fatty acid levels: Uptake and rapid metabolism

14:30 – 15:00 Dr. Hongbin Xu (University of Ottawa)
Mining the circulating glycerophospholipidome for primary determinants of Alzheimer's Disease

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15:00 – 15:30 Coffee Break (Pearson Room Foyer)

15:30 – 16:30 **Next Generation Symposium** (Pearson Room)

Co-Chairs: Drs. Darrell Mousseau (University of Saskatchewan) and Ana Andreazza (University of Toronto)

15:30 – 15:45 Victoria Marshe (University of Toronto)
Association of il-1b, il-2, il-6, tspo and bdnf gene variants with response to treatment with duloxetine and placebo in patients with major depression

15:45 – 16:00 Faranak Vahid-Ansari (University of Ottawa)
Post-stroke depression in a new focal ischemic mouse model is reversed by chronic fluoxetine treatment and involves brain region-specific fosb induction

16:-00 – 16:15 Emily R. Hawken (Queen's University)
Brain-derived estradiol controls hunger state-dependent plasticity of gaba synapses

16:15 – 16:30 Julian Chiarella (Queen's University)
Frontal-limbic brain development in depressed adolescents with various levels of childhood abuse: a preliminary study

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16:30 – 18:30 Poster Session I (Laurier Room)

Wednesday, June 10, 2015
Abstracts for Oral Presentations

Heinz Lehmann Award Lecture

Motivational effects of nicotine
Derek van der Kooy

Nicotine produces rewarding and aversive motivational effects in humans and other animal species. We report that the mammalian ventral tegmental area(VTA) represents a critical neural substrate for the mediation of both the rewarding and aversive properties Of nicotine. We demonstrate that direct infusions of nicotine into the VTA produce rewarding and aversive motivational effects. While the rewarding effects of higher doses of nicotine were not attenuated by dopamine (DA) receptor blockade, blockade of mesolimbic DA signaling with either systemic or intra-nucleus accumbens (NAc) neuroleptic pretreatment potentiated the sensitivity to nicotine's rewarding properties over a three-order-of-magnitude dose range. Furthermore, the behavioural effects Of lower doses of intra-VTA nicotine were reversed, switching the motivational valence of nicotine from aversive to rewarding. Our results suggest that blockade of mesolimbic DA signaling Induced by neuroleptic medication may block selectively the aversive properties of nicotine, thus increasing the vulnerability to nicotine's rewarding and addictive properties by inducing a unique, drug-vulnerable phenotype. The rewarding effects of acute nicotine are due to direct effects on VTA GABA neurons, whereas the acute aversive effects are due to direct effects on VTA dopamine neurons. In animals chronically treated with nicotine and in withdrawal there is a large up regulation of CRF in the VTA which underlies the dopaminergic motivational effects of nicotine in these chronically treated animals.

Presidential Symposium - Microbiota and Brain Function – Implications for Neuroscience and Psychiatry

Early life gut-microbiome-brain interactions: implications for neurodevelopmental disorders
Rochellys Diaz Heijtz, PhD, Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Environmental influences during early life can have a profound impact on brain development and later life structure and function. One such environmental factor is the gut microbiota (the microorganisms that inhabit our intestines) that over evolutionary time has adapted to coexist with mammals. A growing number of studies have recently revealed that the gut microbiota has much wider effects on host physiology and development than originally believed, including the early-life programming of brain circuits involved in the control of emotions, motor activity, and cognitive functions. We have previously shown that adult mice raised under germ-free (GF) conditions display increased motor activity and decreased anxiety-like behavior compared to mice with normal gut microbiota (specific-pathogen-free, SPF). These mice also showed alterations in synaptic-related proteins (e.g., synaptophysin and PSD-95). Recently, we found that adult GF mice also exhibit increased social approach. Interestingly, we discovered that some of the behavioral traits of GF mice emerge only after puberty. These findings in mice suggest that the gut microbiota may also influence the development of the human brain and affect mental health later in life. However, the cellular and molecular mechanisms mediating interactions between the gut microbiota and the developing brain remain poorly understood. This presentation will cover recent findings supporting the hypothesis that one of the mechanisms mediating these

interactions involves gut-derived microbial molecules–mediated activation of pattern-recognition receptors of the innate immune system within the brain. Finally, the implications for neurodevelopmental disorders associated with both gastrointestinal problems and neuroinflammation (e.g., autism) will be considered.

Uncovering microbial modulators of neuroactive molecules

Jessica Yano, Kristie Yu, Gregory P. Donaldson, Gauri G. Shastri, Phoebe Ann, Liang Ma, Cathryn R. Nagler, Rustem F. Ismagilov, Sarkis K. Mazmanian and Elaine Y. Hsiao

Introduction: There is growing evidence that the microbiota fundamentally regulates the development and function of the nervous system, but the mechanisms underlying indigenous microbe-nervous system interactions are largely unknown. We explore fundamental interactions between the indigenous microbiota and mammalian host that regulate the bioavailability of neuroactive molecules, including neurotransmitters and neuropeptides.
Methods: We utilized germ-free and gnotobiotic mice to investigate microbial effects on serotonin metabolism by imaging, qPCR and metabolomics. To evaluate dependence on serotonin biosynthesis, mice were treated with the small molecular inhibitor of tryptophan hydroxylase, PCPA. To investigate effects on host physiology, we measured intestinal transit, neuronal activation, and platelet activation/aggregation by flow cytometry and imaging. In vitro culture assays were used to screen for serotonergic microbial metabolites. Positive candidates were tested ior the ability to promote serotonin in vivo.
Results: We reveal that a striking ~60% of peripheral serotonin (5-hydroxytryptamine, 5-HT) is regulated by host-microbe interactions. We identify a limited microbial consortium that sufficiently and reversibly modulates host serotonin biosynthesis in specific cell subtypes of the gastrointestinal tract, and that corrects enteric and hemostatic abnormalities related to serotonin deficiency in germ-free and genetically-altered mice. We further identify particular microbial metabolites that confer this serotonergic effect of gut microbes, suggesting direct metabolic signaling of particular gut microbes to host cells to induce serotonin biosynthesis.
Conclusions: Our findings reveal a molecular mechanism by which a limited bacterial consortium from the mouse or healthy human microbiota modulates host serotonin levels and serotonin-related disease phenotypes in mice.

Gut microbiome brain interactions in humans

Emeran A Mayer MD,PhD, Oppenheimer Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA

Tremendous progress has been made in recent years to characterize the bi-directional interactions between the central nervous system, the enteric nervous system and the gastro-intestinal tract. More recently, a series of provocative pre-clinical studies have suggested that the gut microbiota play a prominent role in these interactions. A possible role has been implicated in the development of brain systems involved in emotional, nociceptive, social and ingestive behaviours, stress responsiveness and brain neurotransmitter systems. In addition, studies in adult animals have revealed the modulatory effect of microbiota changes (induced by probiotics, antibiotics and fecal microbial transplantation) on some of these behaviors. There are multiple parallel pathways between the gut and the brain, which could mediate gut microbiota to brain signalling, and which allow the brain to alter microbial composition and function.
At the moment, limited information is available to suggest if and how these findings might translate to healthy humans, or to disease states involving the brain, or the brain gut axis. Available information comes from studies demonstrating associations between altered microbial composition and metabolites and disease states involving the brain gut axis (including irritable bowel syndrome, colicky babies), as well as studies demonstrating brain changes in response to alterations of the gut microbiota. It remains to be determined what role gut microbial influences

play during human brain development, and to what degree they can influence the function of the adult and aging brain. This presentation will assess what's been learned so far and where next steps might take us.
Dr Emeran Mayer is a Professor in the Departments of Medicine, Physiology and Psychiatry at the David Geffen School of Medicine at UCLA, Executive Director of the Oppenheimer Center for Neurobiology of Stress, and Co-director of the CURE: Digestive Diseases Research Center at UCLA. He has 30 years' experience in the study of clinical and neurobiological aspects of how the digestive system and the nervous system interact in health and disease. He has published over 320 peer reviewed articles, co-edited four books, and organized several interdisciplinary symposia in the area of visceral pain and mind body interactions. His current research focuses on the role of the gut microbiota in brain gut interactions in health, chronic visceral pain and obesity.

Symposium 1 - Altered Dopamine-D2 receptor function in addiction and schizophrenia

Transcriptional regulation of dopamine-d2 receptors in schizophrenia
Paul R. Albert, Ph.D., Ottawa Hospital Research Institute, University of Ottawa, Ottawa ON

Hyperactivity of the dopamine system is implicated in schizophrenia, and antipsychotic drugs antagonize dopamine-D2 receptors. Recent genome-wide association of the DRD2 gene with schizophrenia suggests polymorphisms that alter its transcription are associated with schizophrenia. We have identified the rs2734836 A/G polymorphism in intron2 of DRD2 that reduces binding and repression by the transcription factor Freud-1/CC2D1A, leading to increased D2 receptor expression. In addition, suppression of Freud-1 using siRNA led to increased D2 receptor expression, while over-expression of Freud-1 reduced D2 receptor levels. Since it is predicted to increase D2 receptors, we hypothesized that this DRD2 polymorphism may be associated with schizophrenia. Schizophrenia and major depression subjects and matched controls were genotyped for rs2734836 and the D2-Taq1A (rs1800497) polymorphisms, and while neither showed significant association in these cohorts, the two polymorphisms were in strong linkage dys-equilibrium. This suggests that previous association of D2-Taq polymorphism with schizophrenia and addiction may be in part due to transcriptional dys-regulation of Freud-1 repression at the rs1800497 polymorphism. Recent data suggest that a nearby polymorphism is part of a haplotype associated with alcoholism. Further investigation of additional functional polymorphisms that alter D2 receptor expression in schizophrenia and addiction may reveal clearer associations. Supported by CIHR and OMHF.

Deciphering the role of dopamine in learning and memory
Bruno Giros, PhD, Douglas Hospital Research Center, McGill University, Montreal, QC

The role of Dopamine (DA) in the regulation of cognitive functions, from attention and novelty detection to learning and memory, pointed to question its role in the physiopathology of schizophrenia. At the synaptic level, long-term potentiation (LTP) and depression (LTD) are believed to underlie memory processes in the hippocampus (HP). With genetic and pharmacological methods, we looked at the implication of DA in HP plasticity and memory processes in situations of normal and excessive DA levels. We first assess that blocking D2Rs or genetically removing them in the mouse temporal HP resulted in same impairments in LTP and LTD. It was accompanied by increased DA release, increased sprouting of DA fibers and deficits in spatial and recognition memory. Specific deletion of the presynaptic D2R was sufficient to

reproduce LTD deficit and memory impairments. Then, we infused GBR12935, a specific blocker of the dopamine transporter (DAT), to induce chronic excess of DA in the HP. After two weeks of DAT blockade in temporal CA1, mice exhibited severe deficits in novel-object recognition (NOR) and object-place recognition (OPR) and a drastic decrease in DA fibers. Local or systemic pretreatment with sulpiride abolished the NOR deficit. In vitro electrophysiogical recordings in temporal CA1 revealed that GBR impairs LTD in a D2R-dependent manner. Altogether, this work suggests that D2R blockade is a positive asset in case of preexisting DA hyperactivity but precipitates deficits in the healthy HP. It will help refining APD pharmacological profile toward cognitive functions of the HP.

Upregulation of dopamine d2 receptors in the nucleus accumbens indirect pathway enhances motivational behavior but does not reduce alcohol consumption

Eduardo Gallo, Mike Salling, Bo Feng, Neil Harrison, Jonathan A. Javitch, Christoph Kellendonk, Departments of Psychiatry & Pharmacology, Columbia University, New York State Psychiatric Institute, New York

Introduction: Brain imaging studies in humans have implicated an important role for ventral striatal dopamine D2Rs in motivational behavior and high D2Rs levels have been proposed to be protective in several forms of addiction.
Methods: I. Using viral methods in combination with the Cre/loxP system we upregulated D2Rs selectively in the indirect pathway of the adult nucleus accumbens core (NAc). II. We analyzed the impact of D2R upregulation in an operant progressive ratio task to assess motivational behavior towards seeking a natural food reward. III. We tested the mice in two models of free-choice alcohol drinking: the continuous and intermittent access models. IV. Using slice electrophysiology we further analyzed how D2R upregulation affects striatal circuit function.
Results: We found that upregulation of D2Rs in the NAc enhances the motivation to work for food. Increased motivation is associated with decreased lateral inhibition from the indirect to the direct pathway. Stimulating direct pathway function using pharmacogenetic tools is sufficient to increase motivation. In contrast, D2R upregulation does not affect voluntary alcohol drinking. Conclusion: Our data suggest that increased D2R function in the NAc enhances motivation to work for natural rewards via disinhibiting direct pathway activity. This imbalance in striatal circuit function does not protect against excess alcohol intake.

Dopamine d2 receptors and addictions: pet studies in humans

Marco Leyton, Department of Psychiatry, McGill University, Montreal, Quebec, Canada
Tel. 514-398-5804, marco.leyton@mcgill.ca

Low striatal dopamine D2 receptor availability in people with substance use disorders (SUD) is one of the best-replicated findings in biological psychiatry (27 / 31 studies). The origin of this decrease and its neurobiological and behavioral consequences remain unclear. Low D2 receptors could be a pre-existing trait or a consequence of extensive drug exposure. They could reflect changes to post-synaptic dopamine transmission or pre-synaptic autoreceptor inhibition. To investigate these possibilities, we measured D2 receptor availability, as assessed by positron emission tomography with [11C]raclopride and [18F]fallypride, in healthy controls, people at risk for addictions, and people with a current SUD. The results suggest that striatal D2 receptors are unaltered in high-risk individuals prior to developing an addiction. In people with a current severe SUD, individual differences in midbrain D2 levels are associated with differences in drug cue-induced striatal dopamine release and self-reported craving. Mediation analyses suggest that the effect on craving was mediated by striatal dopamine release. Together, these results suggest that low striatal D2 receptors in people with SUDs are most commonly the consequence of extensive drug use. Low D2 receptors in the midbrain could reflect drug-induced effects or pre-existing traits, potentially increasing susceptibility to cue-induced phasic dopamine release and incentive

motivational responses to drug-related cues.

Symposium 2 - Using targeted lipidomics to understand the brain-heart relationship

Circulating second-messenger glycerophophocholines and cardiovascular risk factors in a population-based sample of adolescents

Simon Czajkowski[1], Michal Abrahamowicz[2], Gabriel Leonard[3], Michel Perron[4], Louis Richer[5], Suzanne Veillette[4], Daniel Gaudet[6], Yun Wang[7], Hongbin Xu[7], Graeme Taylor[7], Tomas Paus[8], Steffany Bennett[7] and Zdenka Pausova[1], [1]the Hospital For Sick Children, University of Toronto, Toronto, Canada; [2]Department Of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada; [3]Montreal Neurological Institute, McGill University, Montreal, Canada; [4]Department of Human Sciences, Université du Québec à Chicoutimi, Chicoutimi, Canada; [5]Department Of Psychology, Université du Québec à Chicoutimi, Chicoutimi, Canada; [6]Community Genomic Centre, Université de Montréal, Chicoutimi, Canada; [7]Neural Regeneration Laboratory, Ottawa Institute of Systems Biology, University of Ottawa, Ottawa, Canada; [8]Rotman Research Institute, University of Toronto, Toronto, Canada

Circulating second-messenger glycerophosphocholines (smgpcs), including lysophosphatidylcholines and platelet-activating factors, are low-abundance plasma phospholipids that modulate atherosclerosis and inflammation. As such, smgpcs may be involved in the etiology of cardiovascular disease (cvd), a leading cause of morbidity and mortality in Canada. Cvd is a slow progressing disease culminating by ischemic heart disease or stroke in middle-to-late adulthood; it may emerge as early as during childhood and adolescence. In the present study, we investigated whether circulating smgpcs are associated with classical cvd risk factors – excess body fat, elevated blood pressure, insulin resistance and low-grade inflammation – in a community-based sample of adolescents. We studied a large population-based sample of Canadian adolescents (n=1029, 52% females, aged 12 to 18 years), as part of the saguenay youth study. We used targeted serum lipidomics with front-end separation by liquid chromatography coupled to mass spectrometry to identify and quantify circulating smgpcs within the 450-600 da range. In all participants, we also measured: (i) adiposity with magnetic resonance imaging (as visceral fat) and multi-frequency bioimpedance (as whole-body fat); (ii) blood pressure beat-by-beat for five minutes under standard clinical conditions; and (ii and iv) serum fasting insulin (as an index of insulin resistance) and c-reactive protein (as an index of low-grade inflammation) in blood samples drawn at 8:00-9:00 a.m. After overnight fast, associations between smgpcs and the above cvd risk factors were examined with multivariate mixed linear model. Within the 450-600 da range, we identified a total of 81 smgpcs that varied by the length and saturation of their fatty acyl residues and by the type of linkage of these residues to the glycerol backbone. Over 30 of them were associated with multiple cardiometabolic risk factors ($p<6x10^{-4}$). Most of these associations were inverse and involved mainly 'medium' molecular mass smgpcs. Tthere were also some positive associations and these involved predominantly 'low' or 'high' molecular mass smgpcs. Most strongly inversely associated smgpcs were pc(20:6/0:0), pc(o-18:6/2:0) and pc(16:0/2:0); lysophosphatidylcholine pc(20:6/0:0) and platelet-activating factor pc(o-18:6/2:0) were inversely associated with both whole-body fat and c-reactive protein, whereas the lysophosphatidylcholine pc(16:0/2:0) was inversely associated with both visceral fat and blood pressure. The most strongly positively associated smgpc was lysophosphatidylcholine pc(14:1/0:0), and this smgpc was positively associated with both visceral fat and fasting insulin. Tthus, in a population-based sample of adolescents, circulating smgpcs are strongly associated with multiple cvd risk factors, with some of these associations indicating 'protective' and other 'adverse' involvement of these smgpcs. Elucidating molecular pathways that regulate these smgpcs in the context of cvd may provide useful pharmaceutical targets.

The pro-inflammatory second messenger lipidome, cognitive deficits, and depression in older adults with coronary artery disease

Graham Mazereeuw MSc[1,2,5], Nathan Herrmann MD[2,3], Steffany AL Bennett PhD[4,5], Hongbin Xu PhD[4,5], Paul I Oh MD[2,6], Krista L Lanctôt PhD[1,2, 3, 5, 6]

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Introduction: Cognitive deficits and depressive symptoms are highly prevalent in coronary artery disease (CAD) patients and increase vulnerability to Alzheimer's disease (AD); however, underlying disease-mechanisms remain unclear. Here, we show how pro-inflammatory lipid second messengers, such as platelet activating factors (PAFs), may be mechanistically relevant markers of cognitive deficits and depressive symptoms in CAD patients, offering a new direction for research into underlying mechanisms of AD.
Methods: This cross-sectional study included CAD (50% stenosis in a major coronary artery) patients. Cognitive performance was assessed using a standardized battery for vascular cognitive impairment. The presence of a depressive episode (DSM-IV criteria) and depressive symptom severity (Hamilton Depression Rating Scale) were assessed. History of a previous depressive episode was determined through patient report. Plasma PAF abundance was measured from fasting blood using electrospray ionization mass spectrometry in precursor ion scan. The PAF PC(O-18:0/2:0) is well-characterized and was used as a proof-of-concept species.

Results: 24 CAD patients (age=60.3±9.4, 70.8% male, 65.2% depressed, 45.8% history of depression) were included. Greater plasma PC(O-18:0/2:0) abundance significantly correlated with poorer global cognition in all patients ($r=-0.45$, $p=.03$), but most strongly in those with depression ($r=-0.59$, $p=.02$). PC(O-18:0/2:0) also significantly correlated with depressive symptom severity among those without a history of depression ($r=0.66$, $p<.01$), independently of cognitive performance. Several additional PAFs were associated with depressive symptom severity and cognitive deficits in exploratory analyses.
Conclusion: These preliminary findings support PAFs as pro-inflammatory lipid mediators that may influence depressive symptoms and cognitive deficits in a population at risk for AD.

Regulating brain fatty acid levels: uptake and rapid metabolism
Dr. Richard P Bazinet, University of Toronto

The brain is especially enriched with the polyunsaturated fatty acids (PUFA) docosahexaenoic acid (DHA) and arachidonic acid, while being virtually devoid of other PUFA such as eicosapentaenoic acid (EPA). It has been suggested that the plasma supply to the brain regulates brain PUFA levels and replace PUFA consumed in the brain. Candidate plasma pools that supply the brain with PUFA include the plasma unesterified pool, PUFA esterified to lysophosphatidylcholine or the uptake of PUFA-containing lipoproteins via lipoprotein receptors into endothelial cells of the blood brain barrier. This paper will present recent studies that have examined the role of lipoprotein receptors and the kinetics of candidate plasma pools which supply the brain. Upon presenting evidence that the plasma unesterified pool is a major source of brain PUFA, especially for DHA, I will describe how rapid metabolism also maintains very low levels of certain PUFA, such as EPA. Because fatty acid uptake into the brain can be imaged, we can estimate brain PUFA, including DHA, requirements. A better understanding of how PUFA

enter and are metabolised within the brain could lead to new approaches to target the brain as well as new insights into brain function in health and disease with fatty acid imagining.

Mining the circulating glycerophospholipidome for primary determinants of Alzheimer's Disease

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The emerging field of neurolipidomics seeks to understand how dynamic changes in membrane composition regulate brain cell function and how these changes can be used a biomarkers to predict disease outcome and track disease fate. Commonly conceptualized as undulating fields of identical molecules, neuronal membranes are, in fact, made up of hundreds of chemically and molecularly diverse lipid species. For the first time, significant technological advances in high performance liquid chromatography (LC), electrospray ionization (ESI), and matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) are enabling membrane composition to be profiled comprehensively at the molecular level. Coupled with subcellular fractionation and careful consideration of extraction protocols that enrich for different phospholipid families, species that vary by only one double bond, a single methylene group, or carbon chain linkage can now be quantified directly in synaptic preparations. These advances are allowing for discovery of novel biomarkers of disease transition, progression, and fate and new mechanistic insight into the determinative roles of lipid metabolism in neurodegenerative disease. Yet, as with imaging biomarkers, accuracy and reproducibility are fundamentally dependent on how lipid biomarkers are measured. Here, we ask whether changes in phosphocholine (PC) membrane predict transition from a pre-symptomatic to symptomatic state distinguish normal elderly from mild cognitive impairment (MCI) and AD and we describe challenges in harmonization of protocols, analyses, and lipid identification required for replication of biomarker results obtained in through neurolipidomic investigations.

Next Generation Symposium

Association of il-1b, il-2, il-6, tspo and bdnf gene variants with response to treatment with duloxetine and placebo in patients with major depression

Victoria S. Marshe*[1,2], MSc Candidate; Malgorzata Maciukiewicz*[1], PhD, Arun K. Tiwari[1], PhD; Natalie Freeman[1], MSc; James L. Kennedy[1,3], MD MSc; Jane A. Foster[4], PhD; Sidney H. Kennedy[5], MD, MBBS, FRCPC; Daniel J. Müller, MD PhD[1,3] [1] Pharmacogenetics Research Clinic, Centre for Addiction and Mental Health, Toronto, ON, [2] Institute of Medical Sciences, University of Toronto, Toronto, ON [3] Department of Psychiatry, University Health Network, University of Toronto, Toronto, ON [4] Department of Psychiatry and Behavioral Neurosciences at McMaster

University, Hamilton, ON [5] Department of Psychiatry, Toronto General Hospital, University Health Network, Toronto, ON *shared first-authorship

Introduction: Major depressive disorder (MDD) is a prevalent psychiatric disorder treated with antidepressant medication such as duloxetine. In addition, placebo treatments have been shown to improve depressive symptoms in a subgroup of patients. This study examined the role of genetic variation of inflammatory markers (IL-1B, IL-2, IL-6, TSPO) including brain-derived-neurotrophic factor (BDNF) in response to duloxetine and placebo.
Methods: Twenty single nucleotide polymorphisms (SNPs) across IL-1B, IL-2, IL-6, TSPO and BDNF were genotyped in 215 patients receiving duloxetine and 235 patients receiving placebo for 8 weeks. Samples were obtained through a partnership between the Canadian Biomarker Integration Network for Depression (CAN-BIND) and Lundbeck. Interleukin SNPs ($r2 = 0.8$, MAF > 0.05) covered ~100% of the common genetic variation. For ANCOVAs, we used quantitative and binary response variables. Quantitative response was defined as percentage change in MADRS score from baseline to endpoint. Binary response versus non-response was defined by at least 50% of reduction of MADRS scores from baseline.
Results: Two SNPs, rs2066992 ($p=0.047$) and rs10242595 ($p=0.028$), in the IL-6 gene were associated with response to duloxetine after 6 weeks of treatment. IL-6 variant rs2066992 was also significantly associated with response to placebo after 6 weeks ($p=0.026$). When dichotomizing response into response vs. non-response, IL-6 variant rs10242595 was also found to be associated with response to duloxetine ($p=0.003$), but not placebo. Conclusion: SNPs across IL-6 may play a role in response to duloxetine and placebo. We have started GWAS analyses in these samples and results will be presented at the meeting.

Post-stroke depression in a new focal ischemic mouse model is reversed by chronic fluoxetine treatment and involves brain region-specific fosb induction

Faranak Vahid-Ansari, PhD candidate[1,4] Diane C. Lagace, PhD[1,2,3,4] Paul R. Albert, PhD[1,2,3,4] [1]Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada [2]Ottawa Brain and Mind Institute, Ottawa, Ontario, Canada [3]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada[4]Canadian Partnership for Stroke Research

Introduction: Post-stroke depression (PSD) is a prevalent and disabling disorder, yet the evidence regarding its etiology/effectiveness of treatment remains inconclusive. Suitable animal models are required to study the biological basis of PSD and the discovery of novel therapeutic targets.
Methods: We have established a new mouse model of PSD using microinjection of endothelin-1 targeting the left medial prefrontal cortex (mPFC) that results in a consistent small lesion and a robust anxiety/depression phenotype. We treated PSD mice for 4 weeks with exercise (free access to running wheel) or serotonin specific reuptake inhibitor (SSRI, fluoxetine 18 mg/kg, po) comparing common treatments given to PSD patients. In order to begin to identify changes in cellular activity associated with the SSRI treatment, we examined number of cells expressing Fos-B, which is a marker of chronic neuronal activation implicated in plasticity.
Results: The behavioral phenotype persists at least 6 weeks following the injury making this model ideal to study clinically relevant recovery interventions, their effects on behavior and corresponding neuronal activity. Chronic treatment with fluoxetine alone reversed the anxiety/depression phenotype. Chronic SSRI induced a significant Fos-B elevation expressing cells in the right (contralateral) side of the brain in regions including mPFC, nucleus accumbens, septum, basolateral amygdala and serotonin neurons of the dorsal raphe. Conclusion: Thus overall treatment with SSRI was sufficient to reverse the anxiety phenotype and activate discrete brain areas. Future work is now aiming to dissect how these regional changes may be involved in the effects of SSRI PSD treatment.

Brain-derived estradiol controls hunger state-dependent plasticity of gaba synapses
Emily R. Hawken, Ph.D, James Gardner Gregory, Éric C. Dumont, Ph.D.

The Bed Nucleus of the Stria Terminalis (BNST) is heavily involved in feeding and anxiety-related behaviors. Furthermore, the oval Bed Nucleus of the Stria Terminalis (ovBNST) is one of the most sexually dimorphic regions of the brain, containing both estrogen and androgen receptors. This study investigated how estrodial (E2) in the ovBNST modulates synaptic transmission and contributes to hunger states and risk-reward trade offs. We combined brain slice neurophysiology and behavioral pharmacology in Long Evans rats. ovBNST GABAA-IPSC were electrically-evoked at 0.1 Hz. E2 (1nM): GABA plasticity was induced by 5 mins of either low-frequency stimulation (LFS) or exogenous application of E2 and other E2 receptor agonists. Rats were either naïve (fully sated), subjected to food restriction (24hr) or food restriction (FR) followed by refeed (40 mins) and then underwent brain slice neurophysiology. Other groups were tested for exploratory activity in the open-field test and novelty-induced suppression of feeding while receiving intra-ovBNST microinjections of saline or estrogen receptor (ERa/ß) antagonist ICI 182780, 30 mins before paradigm. LFS produced long-term potentiation (LTP>150%) of ovBNST GABAA-IPSCs in naïve animals. FR unmasked long-term depression (LTD) but refeed reinstated LTP. Furthermore, ICI 182780 mimicked the effects of FR. Exogenous E2 produced a 60-80% increase of GABAA-IPSCs but only the ERa agonist PPT produced an increase in GABAA-IPSCs. Microinjections of the ERa/ß antagonist ICI 182780 modulated feeding behavior in high-risk situations. Conclusion: Our data show increased GABA transmission in the ovBNST may be a satiety signal that is modulated by E2 and influences risk-taking behavior.

Frontal-limbic brain development in depressed adolescents with various levels of childhood abuse: a preliminary study
Julian Chiarella, B.Sc [1], Lyndall Schumann, M.Sc [1], Cherine Fahim, Ph.D. [2], Jennifer Thunem, B.Sc. [1], Sarosh Khalid-Khan, MD [3], Moshe Szyf, Ph.D. [4], Anita Peter [3], Beverly Blaney [3], Jennifer Gillies, M.Sc [1], Kate Harkness, Ph.D [1], & Linda Booij, Ph.D [1], [2]. [1] Department of Psychology, Queen's University, Kingston[2] CHU Sainte-Justine, University of Montreal, Montreal [3] Hotel Dieu Hospital, Queen's University, Kingston [4] Department of Pharmacology, McGill University, Montreal

Introduction: Our understanding of the pathophysiology of depression in adolescence is incomplete: little is known about how childhood abuse relate to alterations in early brain development, reflected in structural and functional differences in brain areas involved in emotion processing and cognitive control. The objective of this pilot study was to examine associations among childhood abuse and frontal-limbic brain development in depressed adolescents.
Methods: Seventeen depressed adolescents were carefully assessed using the Childhood Experience of Care and Abuse interview and for symptomatology. They underwent a 3T (f)MRI scan. Peripheral DNA methylation was also assessed, with an emphasis on SLC6A4 methylation, given its role in brain development and based on previous work in adult patients (Booij et al., 2015).
Results: Structurally, there was decreased anterior cingulate GM density in patients with a childhood history of abuse. Notably, there was also increased superior temporal gyrus GM density, increased WM density, and decreased corpus callosum WM density (pFWE all < .005), compared to those without a history of abuse. First analyses of the methylation data showed a positive association between SLC6A4 methylation and aspects of frontal-limbic functional brain development.
Conclusions: The stress associated with childhood abuse may alter early brain development in adolescence, shown by chronic superior temporal activation and density that impairs the anterior cingulate, developmental deficits in age-appropriate pruning, and/or delays in myelination. DNA methylation may underlie some of these alterations. We are currently following these adolescents to determine whether cognitive therapy can reverse some of these brain and epigenetic changes.

Thursday, June 11, 2015

07:30 – 08:30 Breakfast (Pearson Room Foyer)

08:00 – 17:00 Registration (Pearson Room Foyer)

08:30 – 09:30 **Innovations Award Lecture** (Pearson Room)
Dr. Marco Leyton (McGill University)

Individual differences in dopamine transmission: a potential vulnerability pathway to addiction

09:30 – 10:00 Coffee Break (Pearson Room Foyer)

10:00 – 12:00 Symposium 3 (Pearson Room)

An integrative approach to finding biomarkers for depression

Chair: Dr. Sidney Kennedy (University of Toronto)

10:00 – 10:20 Dr. Ana Andreazza (University of Toronto)
DNA mutations and redox modulations

10:20– 10:50 Dr. Daniel Mueller (CAMH, University of Toronto)
Genetic variation of inflammatory markers (IL-1beta, IL-2, IL6, TSPO) and BDNF in response to treatment with duloxetine and placebo

10:50 – 11:30 Dr. Ken Evans and Dr. Harriet Feilotter (Queen's University)
Cell free circulating biomarkers in depression

11:30 – 12:00 Dr. Gustavo Turecki, McGill University
MicroRNAs as peripheral biomarkers of antidepressant response

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10:00 – 12:00 Symposium 4 (Lady Elgin Room)

Behavioural and neurobiological substrates of compulsive drug use: insights from rats to humans

Chair: Dr Anne-Noël Samaha (Université de Montréal)

10:00 – 10:30 Dr. Anne-Noël Samaha (Université de Montréal)
How fast and how often: the pharmacokinetics of cocaine use determine the later motivation to self-administer the drug\

10:30 – 11:00 Dr. Éric C. Dumont (Queen's University)
Neurophysiological dysregulation underlying compulsivity in rats

11:00-11:30 Dr. Sean Barrett (Dalhousie University)
Factors that impact measures of tobacco reinforcement in human laboratory models

11:30 – 12:00 Dr. Isabelle Boileau (CAMH, University of Toronto)
Investigating the D3 dopamine receptor and its relationship to addiction-relevant behavioral endophenotypes: positron emission tomography imaging with [11C]-(+)-PHNO

12:00 – 14:00 Lunch and Poster Session II (Pearson Room Foyer; Laurier Room)

14:00 – 16:00 Symposium 5 (Ontario Room)

Major depression: a GABA-ergic disorder? A multilevel translational perspective

Co-Chairs: Drs. Georg Northoff (University of Ottawa) and Etienne Sibille (University of Toronto)

14:00 – 14:30 Dr. Georg Northoff (IMHR, University of Ottawa)
GABA and glutamate in default-mode network in depression

14:30 – 15:00 Dr. Jeff Daskalakis (CAMH, University of Toronto)
What can ECT and rTMS tell us about GABA In depression?

15:00 – 15:30 Dr. Gerard Sanacora (Yale University)
Chronic stress alters rates of GABA synthesis, and reduces expression of GAD67 and other GABA-related genes in the PFC of the rat

15:30 – 16:00 Dr. Etienne Sibille (CAMH, University of Toronto)
Somatostatin neurons as new targets for GABA-related deficits in depression

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14:00 – 16:00 Symposium 6 (Quebec Room)

Harnessing neuroinflammatory processes to treat neurodegeneration

Chair: Dr. Shawn Hayley (Carleton University)

14:00 – 14:30 Dr. Francesca Cichetti (Laval University)
The role of hematogenous transport of pathological proteins in neurodegenerative diseases

14:30 – 15:00 Dr. David Stellwagen (McGill University)
Tumor necrosis factor as a modulatory of synaptic plasticity and its relevance for neuronal recovery

15:00 – 15:30 Dr. George Robertson (Dalhousie University)
The role of inflammation processes on mitochondrial mechanisms in neurodegeneration

15:30 – 16:00 Dr. Shawn Hayley (Carleton University)
The LRRK2-interferon pathway as a target for neuroprotection and neurorecovery

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17:00 – 19:00 Mentee/Mentor Mixer (St. Laurent Room)

18:00 – 19:00 Cocktails (Pearson Room)

19:00 – 22:00 Banquet (Pearson Room)

Thursday, June 11, 2015
Abstracts for Oral Presentations

Innovations Award Lecture

Individual differences in dopamine transmission: a potential vulnerability pathway to addiction

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Altered dopamine neurotransmission has long been implicated in the susceptibility to and development of addictions. However, our understanding of how this occurs remains poor, and direct evidence in humans has been lacking. Here, we discuss recent developments from studies using functional neuroimaging and methods for manipulating dopamine transmission. These studies suggest that, in healthy humans, compulsively abused drugs across a range of pharmacological classes increase extracellular dopamine levels in the striatum. These effects on dopamine transmission do not influence drug-induced euphoria, but they do increase the ability of reward-related cues to elicit and sustain approach and desire. The magnitude of these dopamine responses varies markedly from person to person. This variability has been associated with differences in personality traits, cortical thickness, serotonergic tone, autoreceptor mediated inhibitory feedback, and past drug exposure. Following repeated drug use, the dopamine responses can become progressively larger (sensitized) and conditioned to environmental cues. Both of these effects are seen first within the ventral limbic striatum and then, as drug exposure increases, in the dorsolateral striatum. Finally, impulsive individuals at risk for addictions exhibit altered drug-induced dopamine responses. Both increases and decreases have been observed, potentially related to the presence *vs*. absence of drug related cues. Together, these studies parallel and extend features identified in animal models, and raise the possibility that one biological vulnerability trait for addiction is susceptibility to labile dopaminergic and appetitive responses to reward-related cues.

Symposium 3 - An integrative approach to finding biomarkers for depression

Micrornas as peripheral biomarkers of antidepressant response

Juan Pablo Lopez, Raphael Poujol, Vanessa Lariviere, Jennie P Yang, Volodymyr Yerko, Carl Ernst, Sidney H Kennedy and Gustavo Turecki, Department of Psychiatry, McGill University

There is significant variability in antidepressant treatment outcome, and approximately 30-40% of patients with major depressive disorder (MDD) do not present adequate response after several antidepressant trials. The objective of the CAN-BIND study is to identify molecular biomarkers of response to antidepressant treatment. Here, we focus our investigation on microRNAs (miRNAs) because they are emerging as promising biomarkers in psychiatric disease. We investigated RNA from blood samples collected from placebo-controlled clinical trials of antidepressants conducted by Lundbeck. We conducted miRNA-sequencing in samples from patients treated with duloxetine or placebo to identify novel miRNA predictors of antidepressant response. The preliminary findings and strategies used to analyze the Lundbeck samples will be discussed. The

identification of miRNAs that can be used as biomarkers of antidepressant response has tremendous clinical potential due to the fact that MDD is highly prevalent in the population and the low rate of adequate response to antidepressant treatment.

Cell free circulating biomarkers in depression

Jian Chen,PhD, Indoc Research, Toronto Canada and Dept of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada Anthony Vaccarino,PhD, Indoc Research, Toronto, Canada and Dept of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada Moyez Dharsee, Indoc Research, Toronto, Ontario, Canada Bob Gooding, Depts of Physics and Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada Harriet Feilotter, Dept of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada and Indoc Research, Toronto, Canada Ken Evans. Indoc Research, Toronto, Canada and Dept of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada

Introduction The plasma is a rich source of circulating biomarkers that can take the form of DNA, RNA or protein. These circulating markers may be present in the plasma through processes that include cell death, or through active secretion from living cells. While miRNA and protein are being widely used to investigate the systemic state of an individual, their use in brain disease is still emerging in relation to assessment of disease status or response to therapy. Methods We have studied protein and miRNA biomarkers found circulating in plasma of a cohort of depression patients treated with Duloxetine or Placebo. Results We will present data on the utility of key dynamic biomarkers in predicting drug response, and showcase the approach for integration of different classes of biomarker from the same sample. Conclusion: The utility of using low level cell free circulating biomarkers for predicting responses to therapies is a key part of our investigation, and our results suggest that a mining multiple data types may provide interesting insights into complex disease. Refining methods for integrating analysis of different types of biomarkers will be critical.

Genetic variation of inflammatory markers (IL-1beta, IL-2, IL6, TSPO) and BDNF in response to treatment with duloxetine and placebo

Daniel Mueller

Background: Major depression is a frequent psychiatric disorder treated with antidepressant medication such as duloxetine. In addition, placebo is known to improve depressive symptoms in a subgroup of patients. This study examined the role of genetic variation of inflammatory markers (IL-1beta, IL-2, IL6, TSPO) including the brain-derived-neurotrophic factor (BDNF) in response to duloxetine and placebo. Methods: Twenty functional and tag single nucleotide polymorphisms (SNPs) across IL-1beta, IL-2, IL-6, TSPO and BDNF were genotyped in 215 patients receiving duloxetine and in 235 patients receiving placebo for 6 weeks. Samples were obtained through a partnership between the Canadian Biomarker Integration Network for Depression (CAN-BIND) and Lundbeck. Interleukin tag SNPs ($r2 \geq 0.8$, MAF>0.05) covered ~100% of the common genetic variation. MADRS score changes (%) from baseline to endpoint was used as dependent variable using ANCOVA. Results: Four SNPs of the IL-6 gene were associated with response to duloxetine after 6 weeks of treatment $P < 0.05$). One of the IL-6 SNPs was also significantly associated with response to placebo after 6 weeks. When dichotomizing response into response vs. non-response defined by at least 50% of reduction of MADRS scores, markers of IL-6 were also found to be associated with response to duloxetine and placebo. Some statistical trends were also observed for SNPs of the IL-2 gene.
Conclusions: SNPs across IL-2 and IL-6 may play a role in response to duloxetine and placebo. Notably, we have started GWAS analyses in these samples and first results will be presented at the CCNP meeting. Ackowledgments: We are greatly indebted to the patients who consented to

the study. Thanks to the Lundbeck Foundation and to the Canadian Biomarker Integration Network in Depression (CAN-BIND) for providing the study samples. Thanks to Natalie Freeman (CAMH, Toronto) for coordinating the laboratory work. Keywords: Pharmacogeneteics, Depression, inflammatory markers, antidepressants, placebo.

DNA mutations and redox modulations

Scola G. PhD, Andreazza, A.C. PhD, Young L.T. PhD, MD. University of Toronto, Departments of Pharmacology and Psychiatry, Toronto, ON, Canada.

Introduction: There is increasing evidence that energy dysfunction (i.e. altered bioenergetics) through mitochondrial dysfunction and consequent cellular redox modulation may play a role in the determination and expression of psychiatric illnesses. In recent years, sophisticated clinical measures are unveiling links between mitochondrial dysfunction, redox modulation to protein and DNA and disease domains. Moreover, preclinical work is convergent in identifying redox modulations as a key element in neuronal connectivity and overall brain function. Here we investigate the clinical evidence of altered DNA redox modulations in patients with depression treated with duloxetine.
Methods: Dotblot and ELISA techniques were used to evaluate the levels of DNA methylation (5mC), hydroxymethylation (5HmC) and oxidation (8-OHdG). Montgomery–Åsberg Depression Rating Scale (MADRS) scores were used as clinical outcome to define which patients with depression responded (RES) or not (NR) to 6 weeks of duloxetine treatment.
Results: Levels of 5mC, 5HmC and 8-OHdG did not differ between RES or NR patients treated with duloxetine. Conclusion: Redox modulation are common findings in patients with psychiatric disorders; although, the findings of this study does not support the role of DNA redox modulation in response of duloxetine treatment. Further studies are, indeed, warranted to investigate levels of DNA redox modulations before and after treatment with duloxetine in patients with depression.

Symposium 4 –Behavioural and neurobiological substrates of compulsive drug use: insights from rats to humans

How fast and how often: the pharmacokinetics of cocaine use determine the later motivation to self-administer the drug

Anne-Noël Samaha, PhD, Florence Allain, MSc and Ellie-Anna Minogianis, MSc. Department of Pharmacology and CNS Research Group, Université de Montréal, Montréal, PQ, Canada

How often and how fast a drug reaches the brain determine the behavioural and neuroplastic changes associated with the addiction process. Despite the critical nature of these variables, the drug addiction field often ignores pharmacokinetic issues, and this can lead to false conclusions. I will present data demonstrating that pharmacokinetic variables play a decisive role in determining outcome in animal models of addiction. A first study compared rats allowed to self-administer rapid infusions of cocaine (delivered intravenously over 5 seconds) to rats self-administering more sustained infusions of the drug (90 seconds). In spite of equivalent drug intake, the rats consuming rapid cocaine injections subsequently showed greater motivation to obtain the drug. Using a new model proposed by Zimmer et al., (2012), a second study compared rats allowed to maintain continuously high brain cocaine levels during each self-administration session, to rats given access to the drug in an intermittent pattern that would produce repeated, fast-rising spikes in brain cocaine levels. Remarkably, in spite of being exposed to significantly less cocaine, the rats given intermittent access were more motivated to self-administer the drug in the future. Together, these findings challenge the belief that simply maintaining high levels of drug intake is sufficient to develop an addicted phenotype. Instead, rapid drug onset and intermittent drug

exposure both appear to push the addiction process forward most effectively. This has clear implications for refining animal models of addiction and for better understanding the neuroadaptations that are critical for the disorder.

Neurophysiological dysregulation underlying compulsivity in rats
Eric C. Dumont PhD[1], Emily R. Hawken, Catherine P. Normandeau, James Gardner Gregory, Cynthia Di Prospero, Michael N. Naughton, Julian deBacker, Staci Angelis, Amanda Maracle, Mary C. Olmstead, Michal Krawczyk
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There is an inherent conflict between engaging in appetitive behaviors resulting in essential outcomes for individual and species survival whilst remaining vigilant to potentially harmful situations. Animals or humans engaging in compulsive behaviors may result from an incorrect resolution of this conflict whereby, for instance, appetitive behaviors may become exaggerated, repetitive, vain or may occur despite potential negative consequences. The Bed nucleus of the Stria Terminalis (BNST) is critical when time comes to translate the final 'decision' into the right adaptive physiological and behavioral outcome. Here, we will show neurophysiological dysregulation in the BNST contributing in the expression of compulsive behaviors in rats including compulsive food and drug intake and obsessive-compulsive disorder-like behavioral manifestations.

Factors that impact measures of tobacco reinforcement in human laboratory models
Sean P. Barrett, PhD Department of Psychology & Neuroscience, Dalhousie University Halifax, Nova Scotia, Canada

Introduction: In humans, drug-related responses might be influenced by a variety of pharmacological (e.g. drug dose, pharmacokinetics) and non-pharmacological factors (e.g. perceived drug availability, drug content instructions). The impacts of such factors on on subjective (e.g. craving, withdrawal) and behavioural (e.g. self-administration) measures of tobacco reinforcement were examined.
Methods: In a series of experiments smokers completed experimental sessions in which pharmacological and non-pharmacological factors were manipulated. Cigarette craving was assessed before and after the manipulations and in some experiments participants were then allotted one hour to self-administer as many cigarette puffs as they wished using a progressive ratio task.
Results: Across studies, non-pharmacological factors exerted a substantial impact on subjective responses and self-administration ($ps<0.05$) and in many cases these effects were more robust than those associated with pharmacological manipulations.
Conclusions: Non-pharmacological factors exert a substantial influence on experimental drug responses in humans. It is recommended that such factors are given consideration when designing and interpreting studies of human drug reinforcement.

Investigating the d3 dopamine receptor and its relationship to addiction-relevant behavioral endophenotypes: positron emission tomography imaging with [11c]-(+)-phno
Isabelle Boileau, Doris Payer, Research Imaging Centre and Campbell Family Mental Health Research Institute Centre for Addiction and Mental Health, University of Toronto, Dept of Psychiatry

Background: In contrast to consistent findings of low D2-type dopamine receptor levels in addiction, levels of the D3 receptor, a member of the D2 family expressed primarily in limbic regions and associated with drug-seeking in animals, may be elevated. The study aimed to

assess D3 levels in humans, and to determine whether high levels are characteristic across methamphetamine-dependent (MA), cocaine-dependent (COC), and pathological gamblers (PG). Methods: Subjects included 16 MA and 16 healthy controls (HC); 12 COC and 16 HC; 13 PG and 12 HC. MA/COC/PG met DSM-IV dependence criteria, and were medication-free and otherwise healthy. Subjects completed a PET scan with the D3 preferring agonist [11C](+)PHNO and measures of impulsivity, subjective states, disease severity and risk-taking were recorded. Results: [11C]-(+)-PHNO binding in the substantia nigra (SN), where 100% of the signal is attributable to D3, was higher in both MA (46%, p=.02) and COC (25%, p=.1) than their HC counterparts. D3-to-D2 ratio was also higher in both MA (55%, p=.004) and COC (27%, p=.04) than HC. SN binding correlated with self-reported drug-wanting in MA (r=.8, p= .001), and risk-taking in COC (r=.6; p=.03). In PG, binding did not differ from HC (p=.74), but correlated positively with risk-taking (r=.48, p=.096), impulsivity (r=.65, p=.031), gambling (r=.57, p=.042), and alcoholic drinks/wk (r=.49, p=.087).
Conclusions: The study suggests that D3 may be implicated across addictions, and is the first to show elevated D3 receptor binding in human stimulant (but not behavioural) addiction, supporting therapeutic strategies targeting D3-antagonism.

Symposium 5 - Major depression: a GABA-ergic disorder? A multilevel translational perspective

Gaba and glutamate in default-mode network in depression
Northoff, G.

Background. Metabolic and neural studies in major depressive disorder (MDD) demonstrated abnormally high resting state activity in especially peri- and subgenual anterior cingulate cortex (PACC). The biochemical underpinnings of such increased resting state activity and abnormally shifted excitation-inhibition balance (EIB) remain unclear though. The aim of my talk therefore is to show various results from different studies combining fMRI, PET and/or MRS in both healthy and MDD subjects that focus on measuring the levels of Glutamate and GABA in PACC. Studies in healthy subjects demonstrate that regional activity levels as well as functional connectivity within the default-mode network in PACC is positively mediated by Glutamate and negatively related to GABA. This seems to be altered in MDD where GABA concentration is no longer properly coupled and linked to resting state activity levels and functional connectivity while the latter are abnormally related to Glutamate. Most interestingly, recent studies in healthy subjects show GABA-A receptors in PACC to be specifically related to neural activity during extero- rather than interoceptive awareness. This has major implications for MDD which will be pointed out at the end of my talk.

What can ect and rtms tell us about gaba in depression?
Daskalakis ZJ, Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, University of Toronto

Repetitive transcranial magnetic stimulation (rTMS) is effective in treatment resistant depression (TRD). Dysfunctional cortical inhibition has been postulated as a mechanism underlying TRD. Cortical inhibition refers to the neurophysiological process in which ?-aminobutyric acid (GABA) inhibitory interneurons attenuate cortical pyramidal activity. TMS combined with EMG or EEG represents a unique experimental modality used to directly index CI in the motor and prefrontal cortex, respectively. It has been demonstrated that treatment with electroconvulsive therapy (ECT) is associated with enhanced CI. In this presentation, data will be presented evaluating the parameters through which rTMS can potentiate CI to better optimize its therapeutic effects. Data will also be presented demonstrating that ECT and DBS are also associated with a potentiation of

CI in the prefrontal cortex. Collectively our data will provide compelling evidence for deficient CI in the prefrontal cortex in patients with TRD and also suggest that ECT, DBS and rTMS are associated with an increase in CI. Such findings will be expanded and discussed in relation to their potential as new biomarkers in predicting TRD response to novel brain stimulation therapies.

Chronic stress alters rates of gaba synthesis, and reduces expression of gad67 and other gaba-related genes in the pfc of the rat

Mouira Banasr, Golam Chowdhury, Carly Kiselycznyk, Kevin Behar, Gerard Sanacora

Background: Evidence from brain imaging studies showing reduced levels of GABAergic neurotransmission and GABA content, to postmortem findings of changes in GABAergic cell number and protein expression in the prefrontal cortex (PFC) of depressed patients, indicates that GABAergic neuronal deficits are involved in the pathophysiology of major depressive disorder (MDD).
Methods: The effects of chronic unpredictable stress (CUS), a well-documented rodent model of MDD, on the expression of an array of GABA markers and GABA cycling in the PFC and hippocampus were examined using western blot, RT-PCR, and 13C-MRS analyses. To partially explore the mechanisms associated with changes, the direct action of corticosterone and dexamethasone on GABA marker expression in cortical and hippocampal primary cultures was also investigated.
Results: CUS induced several changes in GABAergic neurons including reduced expression of calbindin, parvalbumin, somatostatin, NPY and GAD 67 in the rat PFC. In the hippocampus, CUS induced a reduction in GAD 67 protein levels however there were no changes in the other GABAergic markers. 13C-MRS studies suggest rates of PFC GABA synthesis are decreased following CUS. Similar to the rodent model, direct administration of corticosterone and dexamethasone to primary cultures reduced protein levels of GAD 67.
Conclusions: CUS produced expression changes in variety of GABAergic biomarkers in the PFC of rats similar that seen in postmortem tissue from patients with MDD. The data further suggest the effects of glucocorticoids may contribute to the pathological changes in the GABAergic neurotransmitter system observed in MDD and possibly other stress-related disorders.

Somatostatin neurons as new targets for gaba-related deficits in depression

Etienne Sibille, Ph.D., Campbell Family Mental Health Research Institute at CAMH; Departments of Psychiatry, and of Pharmacology and Toxicology, University of Toronto

Somatostatin (SST) deficits are common features in neurological disorders with mood disturbances, but little is known about the contribution or cause of these deficits to mood symptoms. I will present evidence from human postmortem brains for molecular changes affecting SST-positive GABA neurons in depression. I will then discuss mouse genetic studies suggesting that low SST and reduced SST-positive GABA neurons have causal roles in generating illness symptoms and are targets for novel antidepressant modalities. Specifically, we show that mice lacking Sst exhibit elevated behavioral emotionality, high basal plasma corticosterone and reduced gene expression that together recapitulate behavioral, neuroendocrine and molecular features of human depression. Using laser-capture microdissection, we show that cortical SST-positive interneurons display greater transcriptome deregulations after chronic stress compared to pyramidal neurons. Protein translation through eukaryotic initiation factor 2 (EIF2) signaling, a pathway implicated in neurodegenerative diseases, was most affected and suppressed in stress-exposed SST neurons. We then show that activating EIF2 signaling through EIF2 kinase inhibition mitigated stress-induced behavioral emotionality in mice. Finally, as the function of SST-positive GABA neurons is mediated by post-synaptic GABA-A receptors containing the alpha5 subunit, we show that boosting Alpha5-mediated GABA function (through positive allosteric modulation) has antidepressant activity in chronically stress mice. Together, the data presented suggest that (1)

low SST plays a causal role in mood-related phenotypes, (2) deregulated EIF2-mediated protein translation may represent a mechanism for vulnerability of SST neurons, (3) global EIF2 signaling has antidepressant/anxiolytic potential, and (4) boosting postsynaptic SST-positive GABA neuron signaling has antidepressant/anxiolytic potential.

Symposium 6 - Harnessing neuroinflammatory processes to treat neurodegeneration

The role of hematogenous transport of pathological proteins in neurodegenerative diseases

Cicchetti Francesca, PhD, Centre de recherche du CHU de Québec (CHUQ), Québec, QC, Canada G1V 4G2; Département de psychiatrie et neurosciences, Université Laval, Québec, QC, Canada

Huntington's disease (HD) is caused by a genetically encoded pathological protein (mutant huntingtin (mHtt)), which is thought to exert its effects in a cell-autonomous manner where degeneration occurs within individual cells that carry the aberrant gene. Here, we investigated the hypothesis that mHtt (like pathogenic protein species involved in other neurodegenerative conditions) is capable of spreading between tissue compartments.
The brains of four patients with HD who received genetically unrelated fetal neural allografts at least a decade earlier were examined post-mortem. The presence of mHtt aggregates within the grafted tissue was confirmed using an array of techniques including microscopy (brightfield, fluorescence and electron), western immunoblotting and infrared spectroscopy, as well as different antibodies targeting different epitopes of mHtt aggregates.
A number of mHtt protein aggregates were located within intracerebral allografts of striatal tissue in these HD patients. The mHtt+ aggregates were observed in the extracellular matrix of the genetically unrelated transplanted tissue while in the host brain they were localized in neurons, neuropil, extracellular matrix and blood vessels. In addition, peripheral immune cells in separate HD patients contained mHtt. There are thus a number of non cell-autonomous mechanisms which could explain these observations, including trans-synaptic propagation as well as hematogenous transport of mHtt.
In summary, we have shown, for the first time, the presence of mHtt in genetically normal and unrelated allografted neural tissue transplanted into the brains of HD patients. These observations raise questions on the importance of non-cell autonomous mechanisms of protein spread, and in particular immune-derived processes, in genetic disorders of the CNS, and further provide new targets for the development of therapeutic strategies.

Tumor necrosis factor as a modulator of synaptic plasticity and its relevance for neuronal recovery

GM Lewitus, S Konefal, D Stellwagen, Centre for Research in Neuroscience, McGill University

Neuroinflammation is a hallmark of almost all neuronal pathologies, and is prominent during early stages of disease progression. However, it is unclear if the inflammation is part of the disease process or a response to the neuronal dysfunction. We have previously determined that the pro-inflammatory cytokine Tumor Necrosis Factor-alpha (TNF), a major component of the inflammatory response, is a regulator of synaptic function and a critical mediator of homeostatic synaptic plasticity, an important form of plasticity that provides stability to neuronal circuits. In the striatum, a critical structure for motor and reward processing, TNF acts on glutamatergic synapses on medium spiny neurons to reduce synaptic strength. We have tested the idea that TNF acts to stabilize circuit function in the face of disruption in several mouse models of striatal dysfunctions, including dyskinesia, behavioural sensitization to drugs of abuse, and in neurodegenerative

disease. In general, the inflammatory response appears adaptive, and decreases the synaptic and behavioural changes induced in these models. In models of Huntington's disease, however, this reactive system appears to become maladaptive and contributes to the early development of motor symptoms. Defining the role of inflammation in specific situations will be critical to determining if up or down-regulating this system is advisable.

The role of inflammation processes on mitochondrial mechanisms in neurodegeneration
Matthew Nichols[1], Jin Zhang[1] and George S. Robertson[2] Departments of Pharmacology[1] and Psychiatry[2], Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada $B^3H^4R^2$

Introduction: Habitual consumption of a flavonoid-enriched diet known to improve mitochondrial bioenergetics and inhibit pro-inflammatory mediator generation reduces the risk for Parkinson's disease, stroke and dementia. Despite these encouraging findings, individual anti-oxidants or flavonoids have repeatedly failed to demonstrate neuroprotective efficacy in the clinic. To account for these discrepant results, neuroprotection by a flavonoid-enriched diet is proposed to be mediated by multiple compounds that activate convergent signaling pathways which synergistically increase mitochondrial performance.
Methods: This hypothesis was tested by comparing the individual and combined effects of two common dietary flavonoids, epicatechin (E) and quercetin (Q), on key aspects of mitochondrial function in central neurons subjected to an experimental stroke.
Results: Relative to E or Q alone, E+Q synergistically increased the survival of cortical neurons exposed to a lethal period of oxygen glucose deprivation (OGD). Moreover, neuroprotection with E+Q occurred at the same sub-micromolar concentrations (0.1-0.3 μM) achieved in brain following oral administration of these compounds in amounts that are neuroprotective. Confocal imaging revealed that Q, but not E, enhanced cytosolic calcium concentrations and the mitochondrial membrane potential indicative of elevated mitochondrial bioenergetics. Unlike E or Q (0.1 μM), E+Q (0.1 μM) enhanced mitochondrial gene expression, ATP production and prevented the loss of spare respiratory capacity after OGD. Oral administration of E+Q reduced pro-inflammatory cytokine gene expression and brain damage in mice subjected to an experimental stroke.
Conclusions: E and Q markedly increased the resistance of neurons to ischemic damage by activating distinct signaling mechanisms that synergistically improved mitochondrial performance.

The lrrk2-interferon pathway as a target for neuroprotection and neurorecovery
Shawn Hayley, Carleton University

Abstract: LRRK2 is a multi-domain complex protein linked to Parkinson's disease (PD). Yet, gene penetrance is highly variable and a role for environmental and/or immune factors as disease "triggers" has been suggested. Importantly, LRRK2 is also a target gene for the inflammatory cytokine, interferon-□ (IFN-□), which we previously found to be critically involved in the neurodegeneration observed in toxin based PD models. Hence, we assessed LRRK2 knockout and transgenic mice behavioural and neuronal profiles in response to toxicant and inflammatory challenges known to promote pro-inflammatory (including IFN-□□ signalling in microglia and peripheral immune cells. More recently, we have also assessed whether cytokines with known trophic properties (e.g. GM-CSF) can promote neuronal recovery (as opposed to protection) after some degree of neuronal death has already occurred and whether LRRK2-IFN play a role in such processes. In short, our preliminary data support the contention that: (1) LRRK2 is involved in systemic inflammatory and toxic responses, (2) LRRK2 mediates behavioural deficits induced by toxicant challenge, and that (3) GM-CSF might be a good candidate "neuro-recovery" factor.

Friday, June 12, 2015

07:30 – 08:30 Breakfast (Ontario Room Foyer)

08:30 – 11:00 Registration (Ontario Room Foyer)

08:30 – 9:30 **Young Investigator Award Lecture** (Ontario Room)
Dr. Sherif Karama (McGill University)

Cigarette smoking and thinning of the brain's cortex

09:30 – 10:00 Coffee Break (Ontario Room Foyer)

10:00 – 12:00 Symposium 7 (Ontario Room)

Involvement of astroglial cells in the antidepressant response and in mood disorders

Co-Chairs: Drs. Bruno Guiard (University of Toulouse) and Nasser Haddjeri (University of Lyon)

10:00 – 10:30 Dr. Naguib Mechawar (McGill University)
Astrocytic abnormalities in depression and suicide

10:30 – 11:00 Dr. David Stellwagen (from McGill University)
The role of astrocytic TNFalpha in the antidepressant response

11:00 – 11:30 Dr. Bruno Guiard (University of Toulouse)
The role of hippocampal astrocytic BDNF in the antidepressant/anxiolytic-like responses

11:30 – 12:00 Dr. Nasser Haddjeri (University of Lyon)
Glial loss impairs antidepressant-like effects of medial prefrontal cortex deep brain stimulation

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10:00 – 12:00 India-Canada Joint Symposium (Quebec Room)

Refining the role of genes in increasing risk for neurodevelopmental disorders

Chair: Dr. Ridha Joober (McGill University)

10:00 – 10:30 Dr. Sarojini Sengupta (McGill University)
GWAS derived molecular networks and brain morphology in patients with first episode schizophrenia

10:30 – 11:00 Dr. John P. John (Bangalore University, India)
Imaging-genetics in schizophrenia: association between genetic risk variants and brain morphology

11:00 – 11:30 Dr. Venkatasubramanian Ganesan (Bangalore University, India)
Translational implications of neuroimmune - neuroplastic interactions in schizophrenia: insights from imaging genetics

11:30 – 12:00 Dr. Sherif Karama (McGill University)
Interactive effects of dehydroepiandrosterone and testosterone on cortical thickness during early brain development

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12:00 Closing Remarks (Ontario Room)

15:00 – 16:00 **uOttawa-BMRI Plenary Lecture: Dr. Eric Nestler** (New York, USA) (University of Ottawa)

Friday, June 12, 2015
Abstracts for Oral Presentations

Young Investigator Award Lecture

Cigarette smoking and thinning of the brain's cortex

Sherif Karama, MD PhD FRCP(C), Department of Psychiatry, McGill University, Montreal, Quebec, Canada Simon Ducharme, MD MSc FRCP(C), Department of Psychiatry, McGill University, Montreal, Quebec, Canada Janie Corley, MA, Department of Psychology, University of Edinburgh, Edinburgh, UK François Chouinard-Decorte, MSc, Department of Neuroscience and Neurosurgery, McGill University, Montreal, Quebec, Canada John M. Starr, PhD, Department of Psychology, University of Edinburgh, Edinburgh, UK Joanna M. Wardlaw, Division of Neuroimaging Sciences, University of Edinburgh, Edinburgh, UK Mark E. Bastin, DPhil, Division of Neuroimaging Sciences, University of Edinburgh, Edinburgh, UK Ian J Deary, PhD, Department of Psychology, University of Edinburgh, Edinburgh, UK

Introduction: Cigarette smoking is associated with cognitive decline and dementia, but the extent of the association between smoking and changes in brain structure remains unclear. Further, it is not known if smoking-related brain changes are reversible after cessation.
Methods: We examined 504 participants for which recall of lifetime smoking data and a structural brain MRI scan at 73 years were available. Using general linear models, we examined associations between pack-years, length of time since quitting, and cortical thickness across the cortex.
Results: A diffuse dose-dependent negative association between smoking and cortical thickness was shown. For each pack-year smoked, the mean thickness of affected areas of the cortex was 3.21 µm thinner, a value roughly twice the yearly rate of cortical thinning reported for adult populations. In subjects who stopped smoking, the cortex was 3.69 µm (95% CI, 2.03 to 5.35 µm; $p<0.001$) thicker for each year since quitting, after adjusting for total amount of lifetime smoking. For those at the mean pack-years value of the sample (29.7), it took approximately 25 years without smoking for differences in cortical thickness to no longer be observed between ex-smokers and those that never smoked. The heaviest ex-smokers remained with a thinner cortex even after more than 25 years without smoking. Conclusion: Smoking is associated with diffuse and accelerated cortical thinning. Partial recovery of cortical thickness appears possible after smoking cessation but is a slow process that can take decades.

Symposium 7 - Involvement of astroglial cells in the antidepressant response and in mood disorders

Astrocytic abnormalities in depression and suicide

Susana G. Torres-Platas, Corina Nagy, Marina Wakid, GustavoTurecki, Naguib Mechawar, Associate Professor, Dept of Psychiatry, McGill University, Researcher, Douglas Mental Health University Institute

There is mounting evidence suggesting aberrant astrocytic function in depression and suicide. Independent studies have reported astrocytic abnormalities in certain brain regions, but it remains unclear whether or not this is a brain-wide phenomenon. We examined this question by measuring glial fibrillary acidic protein (GFAP) expression in postmortem brain samples from suicides completers and matched non-psychiatric controls. Suicide completers were selected based on their recent characterization as low GFAP expressers in prefrontal cortex (Brodmann

areas 8/9 [BA8/9] & BA10). Real-time PCR and immunoblotting were used to measure GFAP gene expression and protein levels in BA4 (primary motor cortex), BA17 (primary visual cortex), cerebellar cortex, mediodorsal thalamus, and caudate nucleus. We found downregulation of GFAP mRNA and protein in the mediodorsal thalamus and caudate nucleus of suicides compared to controls, whereas GFAP expression in other brain regions was similar between groups. Furthermore, a regional comparison including all samples revealed that GFAP expression in both subcortical regions was, on average, between 11- and 15-fold greater than in cerebellum and neocortex. Examining astrocytic morphology by immunohistochemistry showed that although less numerous, astrocytes in both thalamus and caudate displayed larger cell bodies and extended more ramified processes across larger domains than the previously described cortical astrocytes. This study reveals that astrocytic abnormalities in depression and suicide are not brain-wide, but rather restricted to cortical and subcortical networks known to be affected in mood disorders. Additionally, our results reveal a greater diversity of human astrocytic phenotypes than previously thought.

The role of astrocytic tnfalpha in the antidepressant response

R Duseja, R Heir, H Altimimi, G Lewitus, D Stellwagen, Centre for Research in Neuroscience McGill University

Recent studies have suggested that cytokines, and in particular tumor necrosis factor alpha (TNF), have a role in modulating antidepressant efficacy. To directly test this idea, we compared the response of TNF-/- mice and astrocyte-specific TNF-/- mice to the antidepressants fluoxetine and desipramine. Using standard behavior models for measuring antidepressant efficacy, the forced swim test (FST) and tail suspension test (TST), we determined that TNF-/- mice were essentially normal in basal behavior in the FST and TST. However, TNF-/- mice showed no behavioral response to a standard dose of chronic antidepressant treatment, in sharp contrast to wildtype mice. Similar results were seen with acute antidepressant treatment, but TNF-/- mice did respond to a very high-dose acute antidepressant treatment. We also assessed in vitro and in vivo effects of fluoxetine on TNF expression. Glia responded to serotonin in vitro and fluoxetine in vivo by upregulating TNF mRNA. Consistent with this source of TNF, mice with an astrocyte-specific deletion of TNF also did not respond to standard chronic antidepressant treatment. These data suggest that astrocytic TNF is important to the sensitivity of the behavioral response to administration of antidepressants.

The role of hippocampal astrocytic bdnf in the antidepressant/anxiolytic-like responses

Quesseveur G ([1]), PhD; Déglon N([2]), PhD; Rampon C([3]), PhD; Guiard BP ([1],[3]), PhD. ([1]) Laboratory of Neuropharmacology, University Paris-Sud, EA[3544], F-9[22]96 Châtenay-Malabry Cedex, France ([2]) Laboratory of Cellular and Molecular Neurotherapies, University of Lausanne (UNIL), [1]0[11] Lausanne, Switzerland ([3]) Research Center on Animal Cognition, CNRS UMR[51]69, University Paul Sabatier, [31]06[2] Toulouse, France

Introduction: Growing clinical and preclinical evidence suggests the implication of glia in the therapeutic action of serotonergic antidepressant drugs. Astrocytes, as an active part of the tripartite synapse, may respond to 5-HT by promoting the synthesis of neurotrophic substances. We hypothesized that fluoxetine targets astrocytes in the adult hippocampus to stimulate the local synthesis/release of BDNF, which in turn, would favor neurogenesis and antidepressant-like responses.
Methods: To test this hypothesis, we applied a lentiviral approach aimed at overexpressing BDNF into mice hippocampal astrocytes (BDNF-vectorized) and tested whether this procedure influenced antidepressant activity.
Results: behavioral analysis revealed that BDNF-vectorized mice displayed an antidepressant-like behavior in the novelty suppressed feeding paradigm as observed after prolonged administration

of fluoxetine in control animals. Immunohistochemistry data paralleled these findings since an increase in neurogenesis was detected in the hippocampus of BDNF-vectorized mice or controls administered with fluoxetine. To further examine the role of glial BDNF, we then determined whether this factor also affected astrocytic activity itself. In particular, given the recent observation that astroglial connexins (Cxs) participate in antidepressant drugs response, we measured the hippocampal expression of Cxs 43 in BDNF-vectorized mice. Interestingly, these mice displayed increased ratio of non-phosphoryated Cx43/total Cx43 suggesting that BDNF-mediated antidepressant response might result from an action on astrocytic network. Conclusion: Collectively our results make astrocyte an important target in antidepressant response. Additional experiments are required to examine the effects of the inactivation of Cx43 on emotionality and the modalities linking these proteins with BDNF signaling.

Glial loss impairs antidepressant-like effects of medial prefrontal cortex deep brain stimulation

N. Haddjeri[1], C. Oosterhof[2], C. Bétry[1], E. Abrial[1], M. Novo-Perez[1], R. Rovera[1], H. Scarna[1], C. Devader[3], J. Mazella[3], G. Wegener[5], C. Sánchez6, V. Coizet7, J.M. Beaulieu[4], P. Blier[2], G. Lucas[1], A. Etiévant[1] [1]SBRI, INSERM U8[4]6, Bron, Univ. de Lyon, France, [2]IMHR, University of Ottawa, Ottawa, Ontario, Canada,[3]IPMC, CNRS, UMR6097, Univ. de Nice, Valbonne, France, [4]DPN, University-IUSMQ, Québec, Canada, [5]TNU, Aarhus University, Risskov, Denmark. 6Lundbeck Research USA, Paramus, USA, 7INSERM U8[3]6, GIN, Univ. Grenoble Alpes, France.

Introduction: Deep brain stimulation (DBS) of the cingulate gyrus 25 is currently evaluated as a new therapy in patients with treatment-resistant major depressive disorder. The effects of infralimbic prefrontal cortex DBS (IL-DBS) on several pre-clinical markers of the antidepressant-like response were assessed in rats to investigate the mechanisms underlying DBS antidepressant action, and particularly, the putative involvement of the glial system. Methods and Results: The present study shows that acute IL-DBS (130Hz, 150 µA) induced an antidepressive-like behaviour (evaluated in the forced swim-test) that was associated with an increase of dorsal raphe 5-HT neuronal firing activity and of dentate gyrus mitogenesis. Moreover, acute IL-DBS was able to reverse the effects of stress on hippocampal synaptic metaplasticity. Importantly, these neurobiological effects of IL-DBS were prevented by local pharmacological glial lesions with the L-alpha-aminoadipic acid gliotoxin. Congruently, gap junction blockade at the site of stimulation also prevented the antidepressant effect of IL-DBS. Further in vivo electrophysiological results revealed that this astrocytic modulation of DBS involved adenosine A1 receptors and K+ buffering system. Conclusion: acute IL-DBS influences, more rapidly than classical antidepressants, several neurobiological markers used to discriminate potential antidepressants (neurogenesis, dorsal raphe 5-HT neuronal firing and hippocampal synaptic metaplasticity) and highlights for the first time the crucial role of glial system in the mechanism of action of DBS. The present study, therefore, proposes that an unaltered glial system within stimulation areas may constitute a major prerequisite to optimize antidepressant DBS efficacy.

India-Canada Joint Symposium - Refining the role of genes in increasing risk for neurodevelopmental disorders

Gwas derived molecular networks and brain morphology in patients with first episode schizophrenia

Sarojini M. Sengupta PhD[1,2], Martin Lepage PhD[1,2], Ashok Malla MD[1,2], Ridha Joober MD, PhD[1,2,3,4]

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Introduction: Single nucleotide polymorphisms in TCF4 gene have been consistently associated with schizophrenia in genome wide association studies, including the C allele of rs9960767. However, its exact role in modulating the schizophrenia phenotype is not known. The objective of the study was to comprehensively investigate the relationship between rs9960767 risk allele (C) of *TCF4* and cognitive performance in patients with first episode psychosis (FEP).
Methods: 173 patients with FEP received a comprehensive neurocognitive evaluation and were genotyped for rs9960767. Carriers of the risk allele (CA/CC) were compared to non-carriers (AA) using Multivariate Analysis of Covariance MANCOVA. Ethnicity, negative symptoms and substance abuse were included as covariates.
Results: Carriers of the risk allele had a statistically significant lower performance in the cognitive domain of Reasoning/Problem-Solving compared to non-carriers ($F_{1,172}=4.4$, $p=.038$). There were no significant genotype effects on the other cognitive domains or general cognition. This effect on the Reasoning/Problem-Solving domain remained significant even when controlling for IQ ($F_{1,172}=4.3$, $p=.039$).
Conclusion: rs9960767 (C) of *TCF4* appears to be associated with neurocognitive deficits in the Reasoning/Problem-Solving cognitive domain, in patients with FEP. A confirmation of this finding in a larger sample and including other *TCF4* polymorphisms will be needed to gain further validity of this result.

Imaging-genetics in schizophrenia: association between genetic risk variants and brain morphology

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Structural brain abnormalities have been extensively investigated as potential endophenotypes of schizophrenia. However, apart from enlarged ventricles and whole brain volume reductions, no other brain morphometric abnormality has emerged from these studies to be consistently associated with the disorder. The differential effect of genetic variants on brain morphometry could be a major source of variability underlying such inconsistent findings. Schizophrenia is a polygenic disorder, wherein the complex interplay between common risk variants of small effect, rare risk alleles of large effect as well as epigenetic interactions confer vulnerability and mediate the final expression of the clinical phenotype. A comprehensive understanding of the effect of the schizophrenia risk genes on brain morphometry is essential for conceptualization of the structural endophenotype/s that can be linked with the genetic diathesis for development of schizophrenia. In a recent paper (John et al., Neurology, Psychiatry and Brain Research, 2015, 21:1-26), we have reviewed the effect of genes mediating neurodevelopment and brain signaling on brain morphometry in healthy subjects and in patients with schizophrenia. A majority of polymorphisms of neurodevelopmental and signaling genes was shown to be associated with whole brain and regional volumetric reductions; but importantly, many genes showed mixed effects, i.e., both volume reductions and increases. In two recent papers from our laboratory (Thirunavukkarasu, Vijayakumari, John et al., Asian Journal of Psychiatry, 2014, 10: 62-68; & Vijayakumari, John, Halahalli et al., Clinical Psychopharmacology and Neuroscience, 2015, 13(1): 68-82), we have demonstrated the individual and additive differential effects of genetic risk variants of schizophrenia risk genes mediating glutamatergic (neuregulin and dysbindin) and monoaminergic (COMT, 5HT2a and 5HTT) signalling respectively on brain morphometry. The risk alleles of polymorphisms of neuregulin (rs35753505) and dysbindin (rs1011313) (Thirunavukkarasu et al.,

2014) showed differences in their extent and direction of effects on brain morphometry, with the AA genotype of NRG1 associated with comparatively widespread volumetric increases and circumscribed volumetric reductions, while the CC genotype of DTNBP1 was associated only with a circumscribed volumetric reduction in the right parahippocampal gyrus. The additive effect of the above risk alleles on brain morphometry was an increase in regional gray matter volume in the left precuneus, left parahippocampal gyrus, right precentral gyrus and right caudate, perhaps as a result of the more extensive increase in regional gray matter volume associated with the AA genotype of NRG1 as mentioned above. Similarly, the risk alleles of polymorphisms of COMT (rs4680), 5HT2a (rs6314) and 5HTT (5HTTLPR) showed differences in the extent and direction of effects on brain morphometry, with the T allele of the rs6314 polymorphism of the 5HT2a gene showing greater regional brain volumes and the risk alleles of the other two gene polymorphisms showing decreased regional brain volumes (Vijayakumari et al., in press). The additive effect of the above risk alleles depended on the proportion of T allele-carriers of the rs6314 polymorphism of 5HT2a gene in the sample. The above studies strongly implicate the role of individual and additive effects of genetic variants in mediating regional brain morphometry in health and disease. These findings also provide a framework to explain the inconsistency of the reported brain morphometric findings in schizophrenia across various studies.

Translational implications of neuroimmune - neuroplastic interactions in schizophrenia: insights from imaging genetics

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Recent genetic studies have uncovered observations that reinvigorate the long speculated link between immune system and schizophrenia[1, 2]. Concurrent recent developments implicate persistent after effects of maternal immune activation to underlie the pathogenetic processes in schizophrenia[3]. Inflammation related genes contribute to neuroprogressive changes in this disorder through adverse impact on neuroplasticity[4, 5]. Interestingly, neuroimmunological as well as neuroplasticity differentially influence hippocampus – the nodal brain region in the network that is critically affected in schizophrenia[6]. Imaging genetics research methods have offered novel insights into the neurogenetic mechanisms in schizophrenia[7] including neuroimmunological as well as neuroplasticity bases. For instance, Brain Derived Neurotrophic Factor (BDNF) gene polymorphism influences hippocampal function in schizophrenia[8]. Another novel finding is the support for “differential susceptibility” in terms of the interaction between functional polymorphism interleukin-6 (rs1800795) and hippocampus volume in antipsychotic-naïve schizophrenia[9]. These findings extend and reiterate the significance of BDNF deficit[10] as well as aberrant cytokine profile in schizophrenia[9, 11]. Interestingly, neuroinflammation might underlie the antipsychotic induced metabolic syndrome in schizophrenia[12]. These multilevel interactions in schizophrenia involving neuroimmunological as well as neuroplasticity factors have potential translational implications in schizophrenia therapeutics[13]. Also, recent evidence offer promising support for certain neuroplasticity modulatory techniques like transcranial Direct Current Stimulation (tDCS) to ameliorate schizophrenia symptoms[14, 15]. Together, these emerging research observations strongly implicate compelling role for neuroimmune-neuroplasticity interactions in schizophrenia pathogenesis with potential translational implications.

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Interactive effects of dehydroepiandrosterone and testosterone on cortical thickness during early brain development

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Introduction: Humans and the great apes are the only species shown to exhibit adrenarche, an endocrine event associated with prepubertal increases in the adrenal production of androgens, most significantly dehydroepiandrosterone (DHEA) and to a certain degree, testosterone. Adrenarche also coincides with the emergence of prosocial and neurobehavioral skills of middle childhood and may therefore represent a human-specific stage of development. Both DHEA and testosterone have been reported in animal and in vitro studies to enhance neuronal survival and programmed cell death depending on the timing, dose and hormonal context involved, and to

potentially compete for the same signaling pathways. Yet, no brain-hormone studies have examined the interaction between DHEA- and testosterone-related cortical maturation in humans.

Methods: Linear mixed models to examine changes in cortical thickness associated with salivary DHEA and testosterone levels in a longitudinal sample of developmentally healthy children and adolescents 4-22 years old.

Results: DHEA levels were associated with increases in cortical thickness of the left dorsolateral prefrontal cortex and the right temporoparietal junction, premotor cortex, and entorhinal cortex between the ages of 4-13 years, a period marked by the androgenic changes of adrenarche. There was also an interaction between DHEA and testosterone on cortical thickness of the right orbitofrontal, cingulate and occipital cortices that was most significant in prepubertal subjects.

Conclusion: DHEA and testosterone appear to interact and modulate the complex process of cortical maturation during middle childhood, consistent with evidence at the molecular level of fast/non-genomic and slow/genomic or conversion-based mechanisms underlying androgen-related brain development.

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uOttawa-BMRI Plenary Lecture: Dr. Eric Nestler (New York, USA) (University of Ottawa)

Poster Session I – Wednesday, June 10, 2015
16:30 – 18:30 – Laurier Room

#1. The separate and combined effects of monoamine oxidase a inhibition and nicotine on resting state eeg

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Introduction: While nicotine is often associated with the neuropsychological effects of tobacco smoke, the robust monoamine oxidase (MAO) inhibition observed in chronic smokers is also likely to play a role. Electroencephalographically (EEG) indexed alterations in baseline neural oscillations by nicotine have previously been reported in both smokers and nonsmokers, however, little is known about the effects of MAO inhibition on resting state EEG.
Methods: In a sample of 24 healthy nonsmoking males, the effects of 6 mg nicotine gum, as well as MAO-A inhibition via 75 mg moclobemide, were investigated in separate and combined conditions over four separate test sessions.
Results: Drug effects were observed in the alpha2, beta2, and theta band frequencies. Nicotine increased alpha2 power, and moclobemide decreased beta2 power. Theta power was decreased most robustly by the combination of both drugs. Conclusion: Therefore, this study demonstrated that the nicotinic and MAO inhibiting properties of tobacco may differentially influence fast-wave oscillations (alpha2 and beta2), while acting in synergy to influence theta oscillations.

#2. Chronic psychosocial stress: consequences for the microbiota-gut-brain-axis and immunity

Aadil Bharwani, B.Sc. (Hon.), M.Sc. (candidate) ([1], [3]), John Bienenstock, CM, MD ([1], [3]), Jane Foster, PhD ([3], [4]), Mike Surette, PhD ([2], [5]), & Paul Forsythe, PhD ([2], [3]) [1]. Department of Pathology & Molecular Medicine, McMaster University, Hamilton, Ontario, Canada, [2]. Department of Medicine, McMaster University, Hamilton, Ontario, Canada, [3]. McMaster Brain- Body Institute, St. Joseph's Healthcare, Hamilton, Canada, [4]. Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada, [5]. Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada.

Introduction: The gut microbiota and brain are engaged in consistent bidirectional interplay—a phenomenon that influences host neural function and behaviour. However, the functional relationship between the microbiota and stress-induced changes in brain and behaviour, and corresponding pathways of communication, remain unknown. To elucidate this relationship, we profiled the intestinal microbiome, behaviour, and immune function of mice exposed to psychosocial stress. We also investigated the potential of microbe-based strategies to modulate such changes, through chronic administration of Lactobacillus rhamnosus (JB-1).
Methods: Male C57BL/6 mice subjected to chronic social defeat for ten days were assessed for changes in social, anxiety-like, and exploratory behaviours. Genomic DNA was isolated from fecal samples to characterize the microbiome profile. To investigate gut-brain signalling, splenocytes were analyzed for changes in the immune cell population using flow cytometry. Serum and supernatant from anti-CD3/CD28- and LPS-stimulated splenocytes were assessed for functional changes in the release of soluble signals. In a preliminary study, mice were orally administered 1.67x10^9 CFU of L. rhamnosus (JB-1) for 28 days, leading into the defeat procedure.
Results: Stress-exposure induced changes in the microbiome diversity and profile. Defeated mice exhibited reduced social and exploratory behaviours, and lasting changes in the immune profile, including dendritic cell activation, reduction in a Treg population, and altered IL-6 and IL-10 release. Preliminary results suggest that L. rhamnosus administration attenuated stress-induced

behavioural deficits.
Conclusions: These findings demonstrate an association between the microbiota and stress-induced behavioural deficits. The study also identifies immune changes as a potential cause or consequence of microbiota-gut-brain communication.

#3. Contribution of mu opioid receptor expressed in gabaergic forebrain neurons to opioid responses: a conditional knockout approach

Pauline Charbogne, MSc[1,2]; Olivier Gardon, PhD[2]; Elena Martín-García, PhD[5]; Helen Keyworth, PhD[4], Audrey Matifas[2], Katia Befort, PhD[2,3]; Ian Kitchen, Pr[4]; Alexis Bailey, PhD[4]; Rafael Maldonado, PhD[5]; Brigitte L. Kieffer, Pr[1,2] [1] GPCR and mental disorders, McGill University, Montreal, Canada [2] Opioid system and brain functions, IGBMC, University of Strasbourg, Illkirch, France [3] Neuroadaptations to psychostimulants, LNCA, University of Strasbourg, Strasbourg, France [4] Receptors and Cellular Regulation Research Group, University of Surrey, Guildford, UK [5] Neuropharmacology Laboratory Research Group, University Pompeu fabra, Barcelona, Spain

Introduction. The mu opioid receptor (MOR) is a G protein-coupled receptor widely expressed throughout the nervous system; our team previously showed that this receptor is responsible for analgesic and addictive morphine effects. In this study, we investigated the role of a subset of MORs expressed in the forebrain, potentially involved in addiction-related behaviors. Methods. We developed a conditional knockout line (Dlx-mu) by crossing floxed mice for the MOR gene with transgenic mice expressing Cre recombinase in GABAergic forebrain neurons (Dlx5/6-Cre). We determined MORs distribution in these animals using qRT-PCR and autoradiographic binding, and examined opiate effects on behavior. Results. Receptor mRNA expression was strongly reduced in the striatum (95%) amygdala (84%) and hippocampus (70%) of Dlx-mu mice, and remained intact in midbrain and brainstem areas. Morphine analgesia was maintained in mutant mice. Heroin failed to increase locomotor activity, but produced stronger catalepsy in mutant mice. Striatal MORs, therefore, contribute to heroin-induced motor responses. However, despite a lack of MORs in the striatum, a region involved in drug reward, heroin conditioned place preference was preserved. We further studied motivation for heroin, as well as palatable food, using self-administration. Surprisingly, progressive ratio paradigm revealed higher motivation for drug and chocolate in Dlx-mu mice (breaking points +415±150% and +77±24% respectively). Conclusion. Our results indicate that MORs expressed in GABAergic forebrain neurons modulate motor responses to opiates, and suggest that this particular receptor population acts as a brake on reward seeking. Together, this study reveals unanticipated MOR functions at the level of reward circuitry.

#4. Effect of bupropion and naltrexone on hedonic responses in laboratory rats

AnneMarie Levy, Stephen Daniels, Amanda Flynn, Thomas Horman, Roger Hudson, Alex Chisholm and Francesco Leri

Introduction: One defining feature of anhedonia is impaired reactivity to rewarding stimuli. We have been investigating two sub-processes of reward reactivity: set-point and primed-seeking. In this study, we attempted a pharmacological validation of these constructs by administering a bupropion (BUP; monoamine reuptake inhibitor) and naltrexone (NTX; opioid antagonist) alone, or in combination as employed to alleviate symptoms of depression in obese individuals. Methods and results: In animals trained to self-administer intraoral infusions of sugar in operant chambers on fixed ratio 1 schedules of reinforcement (measure of set-point seeking), acute or chronic administration of BUP+NTX reduced responding. Both acute and chronic NTX alone reduced sugar self-administration while BUP alone had no effect compared to vehicle. On a progressive ratio schedule (measure of primed-seeking), acute BUP+NTX and BUP alone enhanced sugar self-administration compared to vehicle and NTX alone. Similar effects were observed following

chronic administration. In animals self-administering sugar from a sipper tube in home cages, chronic administration of combination BUP+NTX reduced both sugar and food intake. Alone, NTX also reduced sugar consumption without altering food intake; however, BUP did not affect either food or sugar consumption.
Conclusions: These findings suggest that set-point and primed seeking can be pharmacologically dissociated. The former is primarily dependent on reward "satiety" and is enhanced by anorexic drugs like BUP and NTX. The latter is primarily dependent on reward "anticipation", and is enhanced by monoamine activation, but only after acute administration. In combination, BUP and NTX act synergistically to increase reward satiety and primed-seeking.

#5. Comparing adme-related genes with various technologies

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Introduction: ADME-related genes are involved in drug Absorption, Distribution, Metabolism and Excretion.The CYP450 family of enzymesincluding CYP2D6 and CYP2C19plays a key role in the metabolism of most drugs. A highly important for the distribution of many drugs is the multidrug resistance transporter (ABCB1).
Methods: We have data available forCYP2D6 and CYP2C19 using the Roche AmpliChip CYP450 Test®, with which we can cross-validate output from the AffymetrixDMETPlusarray,TMwith prior data on ABCB1 via candidate marker genotyping.In addition, we have other data previously runusing the DMETPlusarrayTMon anonymized controls.
Results: Preliminary analysisshows some discrepancies in the data between the AmpliChip and DMETPlus arrays. For example, sample GDP0101 was calledCYP2D6*1/*1by DMETPlus, whilethe AmpliChipCYP450 Test® datawasCYP2D6*1/*5. In addition, GDP0106 was called *2XN/*2XNby DMETPlus, while theAmpliChipCYP450 Test®was *2XN/*41. For the SNP rs2235015 in ABCB1, the apparent discrepancy in fact simply results from forward vs. complementary strand usage by different technologies(TaqMan, HapMap, A>C; Affymetrix, G>T).Finally, it appears that the latest version of the DMETPlussoftware is able to call rs28381915in ABCB1with a higher call rate than previously.
Conclusions: There are some contrasts betweenthe two platforms; we will be further investigating these anomalies (e.g., conducting copy number analysis using CYP2D6-specific probes).

#6. Moderating effects of anxiety on sensory gating and its response to gabaergic agonists in healthy humans

Ashley Beaudoin, MSc, Clinical Neuroelectrophysiology and Cognitive Research Laboratory, University of Ottawa Institute of Mental Health Research; Sara de la Salle, PhD (Cand.), Psychology, University of Ottawa; Robert Aidelbaum, MSc (Cand.), Psychology, Carleton University; Brittany Duncan, BSc, Psychology, Carleton University; Justin Piché, BSc, Psychology, University of Ottawa; Joelle Choueiry, PhD (Cand.), Cellular & Molecular Medicine, University of Ottawa; Danielle Impey, PhD (Cand.), Psychology, University of Ottawa; Renee Nelson, MSc (Cand.), Cellular & Molecular Medicine, University of Ottawa; Molly Hyde, BSc, Psychology, University of Ottawa; Noreen Rahmani, BSc, Psychology, University of Ottawa; Vadim Ilivitsky, MD, Royal Ottawa Mental Health Centre; Verner Knott, PhD, C. Psych, Clinical Neuroelectrophysiology and Cognitive Research Laboratory, University of Ottawa Institute of Mental Health Research

Introduction. Anxiety and shifting states of emotion have been shown to impact basic mechanisms of information processing including inhibitory gating, as indexed by P50 event-related potential (ERP) suppression. As GABA neurotransmission mediates P50 sensory gating in animal models,

the objective of this human study was to investigate the moderating effects of trait and state anxiety on gating and its response to acute GABAA and GABAB receptor agonist treatment. Method. Auditory sensory gating was assessed with a paired-stimulus (S1-S2) paradigm in 30 healthy volunteers. Single dose GABAA (lorazepam: 1 mg) and GABAB (baclofen: 10 mg) agonist administration with ERP recordings and state anxiety ratings were conducted within a randomized, placebo control trial. ERPs and trait and state anxiety (STAI) were also assessed in an independent baseline session. Results. Treatment comparisons showed gating reductions with lorazepam but not baclofen. Neither trait nor state anxiety affected gating at baseline, but response to baclofen was significantly correlated with trait anxiety, with higher scores being associated with lower gating ability as indicated by higher P50 ratio ($p = .002$) and S2 amplitude ($p = .017$). Conclusion. These results suggest that although not directly moderating gating itself, trait anxiety does appear to moderate gating response to GABAergic enhancement and this is specific to manipulation of the GABAB receptor
system.

#7. Investigating the motivational component of high fructose corn syrup withdrawal

Stephen E. Daniels,MSc; Francesco. Leri, PhD, Psychology, University of Guelph, Guelph, Ontario, Canada

Introduction It has been suggested that withdrawal from sugars produces somatic symptoms resembling those observed following withdrawal from opiate drugs. Whether this also applies to the “psychological” aspect of withdrawal remains unknown. The current study determined whether naltrexone precipitates a negative affective state in laboratory rats (male Sprague-Dawley) that received acute or chronic pre-exposure to a sugar solution. Methods To interpret the findings, the same experiments were repeated in rats pre-exposed to acute or chronic heroin. In different experiments, animals received: intragastric acute administration of high fructose corn syrup (HFCS; 0.5, 1 or 2 g/kg); drank 0% or 50% solutions of HFCS in their home cages for 22 days (food restricted and non-food restricted); received acute subcutaneous (SC) injections 2 mg/kg heroin; or were implanted (SC) with osmotic mini-pumps releasing 3.5 mg/kg/day heroin. Following pre-treatments, animals were tested on conditioned place aversion (CPA) induced by naltrexone (1 or 3 mg/kg, SC). Results HFCS pre-exposure did not significantly amplify CPA induced by naltrexone. Food restricted rats with increased HFCS consumption demonstrated naltrexone induced CPA not seen in animals given 0% HFCS, yet no significant interaction was observed. NTX-induced CPA with acute infusions of HFCS at higher but not lower doses, yet effects were not significantly different from 0% HFCS. NTX-induced CPA was observed after acute and chronic heroin pre-exposure, which was greater than control animals. Conclusion These results fail to support the hypothesis that an opioid antagonist can precipitate similar affective withdrawal states following pre-exposure to sugars and opiates.

#8. Burden of copy number variants (cnvs) implicated in psychiatric and non-psychiatric phenotypes in a toronto schizophrenia population

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Increasing evidence supports the significance of copy number variants (CNVs) – regions of =1kb to =1Mb of duplications/deletions – in the genetic contribution to psychiatric illnesses, particularly schizophrenia (SCZ). This study utilizes a robust approach to uncover genetic variants in SCZ by delineating correlations and associations between CNV data and extensive phenotypic data in SCZ patients. Phenotypic and genotypic data of 348 SCZ patients were collected from patient

medical history records, and Affymetrix 6.0 SNP array, respectively. Statistical tests were performed among the various categories (e.g. CNV count, age of onset, presence of substance abuse, etc.) to identify any significant associations. Significant associations were found between: substance abuse in probands and number of other psychiatric illnesses in probands ($p<0.0001$*); suicide attempt in probands and number of autosomal CNVs ($p = 0.0274$); and head injury in probands and number of autosomal CNV duplications ($p = 0.0449$) and deletions ($p = 0.049$). Moreover, head injury was found to have a significant association with cognitive impairments ($p = 0.005$*) and seizures/EEG abnormalities in probands ($p = 0.011$*). Our results suggest a strong association between CNVs and specific phenotypic presentations in the SCZ patients. This is compatible with the increasing evidence of CNV burden implicated in SCZ and our findings may contribute to expanding the neuropsychiatric phenotypes associated with these genetic variants. Further analyses will be undertaken to define specific CNVs and genes contained within the affected regions to better characterize potential effects on the phenotypic presentation of SCZ patients.

#9. Separate and combined effects of nicotine and nabilone on involuntary and voluntary attention in healthy volunteers: a brain event-related potential study

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Introduction: Schizophrenia (SZ) is a mental health disorder with cognitive deficits, which unfortunately do not respond well to current anti-psychotic medications, resulting in self-medication with tobacco and cannabis by SZ patients. The objective of the present study in healthy volunteers is to examine the effects of nicotine and a CB1 agonist nabilone on attentional processing as assessed with two components of the auditory P300 event-related potential (P300), which measures involuntary (P3a) and voluntary (P3b) attention.
Methods: In a randomized, double blind, placebo-controlled design, 20 healthy males who were non-users of both tobacco and cannabis, were assessed in four test sessions where they received (1) nicotine gum (6 mg), (2) nabilone capsule (0.5 mg), (3) nicotine plus nabilone and (4) placebo.
Results: Evidenced by amplitude increases, nicotine (vs. placebo) improved involuntary attention (P3a) to novel sounds and voluntary attention (P3b) to target stimuli in individuals with low baseline amplitudes. Nicotine alone and combined with nabilone shorted (vs. placebo) P3b latency (speeded target processing). Nabilone alone did not affect amplitudes or prevented nicotine from increasing P3a/P3b amplitudes in low baseline individuals. Performance changes were limited to nabilone (vs. placebo), which slowed reaction time and increased incorrect responses in individuals with low and high baseline P3b amplitudes, respectively. Conclusion: These results highlight the cognitive enhancements that occur under acute nicotine administration and their relationship to endocannabinoid activity. The current findings may inform future studies examining nicotinic agonists as a potential therapeutic direction for treating cognitive deficits in schizophrenia.

#10. Analysis of genome-wide significant schizophrenia risk variant in relation to antipsychotic-induced side effects - tardive dyskinesia and weight gain

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Introduction: The recent Psychiatric Genomics Consortium genome-wide association study identified a genetic variant, rs2514218, located 47kb upstream of the dopamine D2 receptor gene (DRD2) associated with schizophrenia risk (p=2.75e-11). Since all antipsychotics bind to D2 receptors, we previously examined rs2514218 in relation to antipsychotic treatment response, observing an association. Here, we investigated this variant in relation to antipsychotic-induced side-effects: tardive dyskinesia (TD) and weight-gain (AIWG).
Methods: We analyzed rs2514218 in three samples of Caucasian and African-American ancestry in relation to TD (total N=114) and AIWG (total N=218). TD was assessed using the Abnormal Involuntary Movement Scale (AIMS) or modified Hillside Simpson Dyskinesia Scale (HSDS) and was determined according to Schooler and Kane criteria. Weight-gain was measured as percentage change from baseline over the duration of treatment, with baseline weight as a covariate. Caucasians and African-Americans were analyzed separately, as ethnicity was significantly correlated with both TD and AIWG. Genotyping was conducted using Taqman assays.
Results: rs2514218 did not deviate from HWE (p>0.05). We did not observe an association between genotype and AIMS scores for either Caucasians or African-Americans (p=0.953; p=0.857) or TD (p=0.948; p=0.671). Additionally, we did not find an association with percentage weight-gain for either ethnicity (p=0.409; p=0.478) or number of weight-gainers/non-gainers (defined using 7% weight-gain threshold) (p=0.188; p=0.565). Conclusion: Our results suggest rs2514218 is not associated with either side-effect. However, in light of our positive findings for this variant in antipsychotic response, this variant remains an interesting target for future pharmacogenetic studies in psychiatric illnesses.

#11. Brexpiprazole alters monoaminergic systems following its sustained administration: an in vivo electrophysiological study

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Background: Brexpiprazole (OPC-34721) is currently under investigation for treatment of schizophrenia and as add-on treatment of depression. To complement results from a previous study in which its acute effects were characterized, the present study assessed the effect of sustained brexpiprazole administration on monoaminergic systems.
Methods: Brexpiprazole (1 mg/kg, subcutaneous) or vehicle was administered once daily for two or 14 days. Single-unit electrophysiological recordings from noradrenergic neurons in locus coeruleus (LC), serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN), dopaminergic neurons in the ventral tegmental area (VTA), and pyramidal neurons in the hippocampus CA3 region were obtained in adult male Sprague-Dawley rats under chloral hydrate anesthesia.
Results: Brexpiprazole blunted D2 autoreceptor responsiveness, while firing activity of VTA DA neurons remained unaltered. Brexpiprazole increased the firing rate of LC noradrenergic neurons, and increased NE tone on a2-adrenergic receptors in the hippocampus. Administration of brexpiprazole for two but not 14 days increased the firing rate of serotonin neurons in the DRN. Despite this result, 5-HT1A receptor blockade had similar disinhibiting effects on pyramidal neurons in the hippocampus after two and 14 day brexpiprazole administration, suggesting that the full agonistic action of brexpiprazole on 5-HT1A receptors enhanced their tonic activation.
Conclusions: Compared to other atypical antipsychotics, sustained brexpiprazole administration had distinguishable effects on the dopamine system, presumably due to its partial agonistic action on D2 autoreceptors. Brexpiprazole enhanced serotonergic tone and noradrenergic tone in the hippocampus, effects common to antidepressant agents. Together, these results provide novel mechanisms to explain therapeutic effects of brexpiprazole.

#12. The effect of individual sensitivity to punishment and reward on sensory gating and its modulation with gabaergic agonists in healthy volunteers

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Introduction: Sensory gating, a fundamental neural process, indexed by P50 event related potential (ERP) suppression is useful in understanding neural systems underlying defective inhibitory control common in psychiatric disorders. As the process of sensory gating, which is mediated by GABA neurotransmission, is affected by emotion this study examined modulating effects of individual sensitivity to punishment/reward on gating and its modulation with GABAA and GABAB agonists.
Methods: Using a randomized double blind placebo controlled design, single doses of GABAA (Lorazopam: 1mg) and GABAB (Baclofen: 10mg) agonists were administered and P50 ERP recordings were conducted in 30 healthy volunteers. Sensitivity to punishment and reward ratings were measured using the Behavioral Inhibition System/Behavioral Approach System (BIS/BAS) questionnaire. BAS subscale scores measured drive, fun seeking, and reward responsiveness.
Results: Comparisons between treatments showed diminished gating in response to Lorazopam administration but not Baclofen. BAS fun seeking subscale scores were significantly correlated with participant's baseline gating ability with higher fun seeking scores being associated with decreased S1 amplitude, poorer gating ability as measured by both P50 ratio and P50 difference scores, and decreased S1 latency. BAS fun seeking subscale scores were also significantly correlated with participant's response to Lorazopam, with higher fun seeking scores being associated with reduced gating as indicated by lower P50 difference scores. Conclusion: These results suggest a moderating relationship between fun seeking/impulsivity and participant's baseline gating ability. Furthermore, base fun seeking scores seem to moderate sensory gating response to GABAA receptor system agonistic manipulation.

#13. Effects of gabaergic drugs on mmn-indexed sensory discrimination processes linked with schizophrenia: an erp pilot study

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Introduction: Schizophrenia (SZ) is a psychiatric disorder that is often defined by positive/psychotic symptoms (e.g., hallucinations) and negative symptoms (e.g., social

withdrawal). Additionally, various impairments in memory, attention, learning, and other cognitive processes are observed in SZ patients; dopamine antagonist drugs that are traditionally used to treat schizophrenic symptomatology do not alleviate these cognitive deficits. Gamma-aminobutyric acid (GABA) has been shown to play an important role in modulating the brain's inhibitory circuitry and maintaining cognitive function. Specifically, GABA neurons may play a significant role in the generation of mismatch negativity (MMN), an event-related potential (ERP) that measures pre-attentive stimulus deviance and is linked to higher-order cognitive functioning; SZ patients consistently display reduced MMN amplitudes. The current pilot study investigates the acute effects of GABAergic drug treatments on MMN in healthy volunteers with relatively low (SZ-like), medium, and high MMN-indexed sensory discrimination.
Methods: In a randomized, double-blind, placebo controlled design, participants (N=30) were assessed using electroencephalography (EEG) over three testing sessions where they received (1) lorazepam (Ativan®; 1.0 mg) (2) baclofen (Lioresal®; 10 mg) or (3) a placebo.
Results: The results exhibited a significant difference between baseline groups (low, medium, and high) for all MMN deviants; however, no main drug effects were determined for any MMN deviant.
Conclusion: These findings highlight the roles of GABAergic receptors in cognitive processing and may translate from a healthy population to SZ patients. Our subsequent investigations will examine the moderating influence of GABA-related genes (e.g., GAD1) on individual differences in GABAergic drug response.

#14. Dcc confers susceptibility to depression-like behaviors in humans and mice and is regulated by mir-218

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We recently identified dcc (deleted in colorectal cancer) as the first gene shown to control the adolescent maturation of the medial prefrontal cortex (mPFC). Furthermore, we have found that DCC mRNA expression is significantly increased in the PFC of antidepressant-free subjects who committed suicide. Here we examined whether (1) epigenetic mechanisms control the expression of DCC in humans and mice and (2) variations in DCC expression in the mPFC confer susceptibility to depressive-like behaviors. We performed in silico analysis and identified the microRNA, miR-218, as a strong candidate regulator of DCC expression. We then confirmed that DCC and miR-218 are co-expressed by human PFC neurons. Using qPCR we found that while DCC expression is increased in the PFC of suicide completers, in comparison to sudden death controls, miR-218 expression is downregulated. In parallel, we measured dcc expression in the mPFC of mice exposed to chronic social defeat stress (CSDS). We found that susceptible, but not resilient, mice exhibit increased expression of both dcc mRNA and protein. Susceptible mice also show reduced miR-218 expression. Pyramidal neurons in the mPFC co-expressed DCC and miR-218. Remarkably, knocking out dcc in mPFC pyramidal neurons prior to CSDS prevents the development of the susceptible phenotype. We are now investigating functional interactions between miR-218 and DCC. This is the first demonstration of miRNA control of DCC expression. Our results support the idea that increased DCC expression confers susceptibility to depression-like behaviors and point at miR-218 as a target of risk factors that induce stress-related psychopathologies.

#15. Does immune and endocrine signaling influence the neuroanatomy of the bed nucleus of the stria terminalis?

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Introduction: The crosstalk between the brain, immune, and endocrine system plays a central role in developmental programming of brain circuitry and behaviour. The bed nucleus of the stria terminalis (BST) is a well-established sexually dimorphic brain region that is larger in males than in females. Using structural MRI, our lab has shown that adult T cell deficient mice lack a sex difference in brain volume in the BST. Here we investigate microglial colonization and gonadal hormones in T cell deficient mice to address the role of immune and endocrine signaling in the sexual dimorphic development of the BST.
Methods: Immunohistochemistry using anti-Iba1 was used to examine microglia in adult BST from wild type (WT-C57Bl/6) and mice lacking the ß and d chains of the T cell receptor (TCRß-/-d-/-), which are functionally deficient of T cells. Similar processing of brain tissue from postnatal day 7 mice is ongoing. The trajectory of postnatal changes in serum levels of anti-Müllerian hormone (AMH), a gonadal hormone implicated in development of the BST, will also be assessed.
Results: Preliminary results from adult mice demonstrated a significant difference in microglial size between WT and TCRß-/-d-/- male mice in the dorsal and ventral BST as well as between WT male and female mice.
Conclusions: These preliminary results demonstrate a significant effect of immunodeficiency in the BST, a brain region implicated in anxiety. Further work will explore whether these changes are observed in early development and whether endocrine differences are present in TCRß-/-d-/- mice.

#16. The role of microglia-t cell communication in brain regions implicated in anxiety-like behaviour

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Introduction: The influence of immune-brain communication to risk of psychiatric illness is an important topic for today's neuroscientists. Our group has focused on the role of the adaptive immune system using T cell deficient mice and demonstrated that loss of T cells leads to reduced anxiety-like behaviour. Using ex vivo structural MRI we also showed regional brain volume differences including amygdala, dorsal raphe, hypothalamus, hippocampus, and periaqueductal grey in immunocompromised mice. Over the last few decades the importance of microglia, the resident immune cell of the brain, in the brain function has become evident. Here we examine the relationship between microglia, T cells, and neuroanatomy.
Methods: Microglia number and activation state was examined using immunohistochemistry in wild type (WT-C57Bl/6) and mice lacking the ß and d chains of the T cell receptor (TCRß-/-d-/-), which are functionally deficient of T cells.
Results: Sex and genotype differences were observed in the number of small microglia in the hippocampus and dorsal raphe. A significant difference between WT and TCRß-/-d-/- female mice was observed in medium size microglia in the prefrontal cortex. In male mice, a significant difference was observed between WT and TCRß-/-d-/in medium sized microglia in the hippocampus. No differences were observed in the periaqueductal grey. Conclusion: Many brain regions with genotype and sex-by-genotype volume differences in TCRß-/-d-/- are implicated in anxiety-like behaviour. Microglia number also varies in several of these brain regions, suggesting that T cell- microglia communication may affect the neuroanatomy of brain regions implicated in anxiety-like behaviour.

#17. The creb-regulated transcription coactivator 1 (crtc1) gene and antipsychotic-induced weight gain

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OBJECTIVES: Our previous studies have revealed that gene variants involved in the hypothalamic control of food intake are particularly involved in antipsychotic-induced weight gain (AIWG). Interestingly, a marker of the hypothalamic CREB-regulated transcription coactivator 1 (CRTC1) gene (rs3746266; causing a missense polymorphism from threonine to alanine) was recently reported to be associated with obesity in psychiatric patients and in the general population (Choong et al., 2013). METHODS: We tested whether rs3746266 was associated with AIWG in our patient samples using Taqman(®) assay. We included 211 schizophrenia patients on antipsychotic treatment prospectively assessed for AIWG for up to 14 weeks. Mean weight change (%) from baseline was compared across genotypic groups using analysis of covariance (ANCOVA). RESULTS: The CRTC1 rs3746266 variant did not show significant association with antipsychotic-induced weight gain in our combined sample or in refined subsamples of patients of European or African ancestry or patients treated exclusively with clozapine or olanzapine (p=0.891 and 0.874 respectively). CONCLUSIONS: Our analyses did not indicate a major role of this CRTC1 gene variant in AWIG. We are currently evaluating this marker in other samples as more research is warranted to elucidate its role on antipsychotic induced weight gain.

#18. A cellular mechanism for chronic stress-induced anxiety

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The oval bed nucleus stria terminalis (ovBNST) is an important area in pathological anxiety, where the neuropeptide neurotensin (NT) is highly concentrated. It is currently unknown if NT is involved in the underlying cellular mechanisms of the ovBNST in pathological anxiety but our preliminary study suggest it plays an important role. We combined brain slice neurophysiology and behavioral pharmacology in adult male Wistar rats. Rats underwent the chronic unpredictable stress (CUS) paradigm for 4 weeks. Animals were then tested for locomotion in the open-field test, anxiety in the elevated plus maze and behavioural despair in the force-swim test while receiving intra-ovBNST microinjections of saline or the NT non-selective antagonist. Inhibitory synaptic transmission (GABAA-IPSCs) from the ovBNST in naïve and CUS animals were electrically evoked at 0.1 Hz. NT was endogenously released using repetitive depolarization and its effect was blocked using non-selective NT receptor blocker SR-142948 (10uM). Endogenous NT in naïve rats reversibly increased (+30%-40%) ovBNST GABAA-IPSC amplitude however this increase was sustained in CUS animals. The NT receptor antagonist SR-142948 significantly reduced time spent in open-arm (-25%) in the elevated plus maze in rats previously exposed to CUS. SR had no effect on open field. Preliminary data shows no differences in in force-swim test. Our data show sustained potentiation of GABAA synaptic transmission in the ovBNST in CUS animals compared to naïve. Blockade of ovBNST NT receptors reduced anxiety in stressed rats but not despair behaviour. Therefore, our study expands understanding of the neural underpinnings of anxiety.

#19. Target-specific modulation of descending prefrontal cortical inputs to the dorsal raphe nucleus by endocannabinoids

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Introduction: The serotonin (5-HT) system is implicated in mood regulation. The coding features of 5-HT neurons per se are however complex and multifaceted, and it has historically been difficult to capture them in a simple and unifying framework. This complexity in part arises from the nature of the synaptic network in the dorsal raphe nucleus (DRN) where the majority of 5-HT neurons are embedded: the DRN receives strong innervation from a vast array of subcortical and cortical regions. It has further been historically difficult to study these descending inputs in isolation in order to identify with precision how they modulate the excitability of DRN neurons. For instance, the medial prefrontal cortex (mPFC) send axons to the DRN but the basic processing features of this input remains elusive and controversial. The details of this top-down control from the mPFC to the DRN are of particular interest, partly because of its role in stress processing and in mediating antidepressant-like effects.
Methods: Using a combination of immunohistochemistry, optogenetics and electrophysiological whole-cell recordings, we dissect out the functional properties of mPFC-DRN projections.
Results: We show that mPFC inputs to the DRN are: 1) glutamatergic; 2) mono-synaptically activate 5-HT and GABA neurons in the DRN; 3) permissive to strong feedforward inhibition; 4) are powerfully gated, in a target-specific manner, by endocannabinoids. Conclusion: We identify a target-specific CB1R-mediated neuromodulation of mPFC inputs to the DRN. This results in powerful gating of PFC information flow through the DRN by favoring a direct excitatory drive to 5-HT neurons.

#20. Altered resting-state functional brain connectivity during early recovery from alcohol use disorder

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Introduction: Alcohol use disorder (AUD) is a persistent health problem affecting approximately 5.43% of males over the age of 15 in Canada (WHO, 2012). Dynamic brain changes associated with AUD and its treatment are only partially understood. We compared changes in the resting state networks in patients undergoing treatment for AUD during very early recovery.
Methods: 23 male patients (age 24-64) with AUD (DSM-IV TR) were recruited 5-10 days after detoxification and scanned (4.7 Tesla Varian system) before and after a 21-day residential treatment. 16 healthy volunteers matched for age, handedness, and education level were scanned for comparison. Both scanning sessions included an anatomical scan, a resting-state functional magnetic resonance scan, and a diffusion tensor scan. The functional data was analyzed using an independent component and region of interest analyses with FMRIB Software Library.
Results: Our analyses revealed changes in several resting state networks including the default mode network, the frontal network, the fronto-parietal network etc. In comparison to controls, patients had significant differences in functional connectivity between anterior cingulate cortex and an array of somatosensory, motor, visual, and association regions.
Conclusions: These findings suggest changes in functional connections of anterior cingulate cortex in AUD patients during early abstinence. Due to the role of anterior cingulate cortex in modulating execution of appropriate and suppression of inappropriate responses during reward

anticipation and impulse control, these results could help us better understand dynamic changes in functional connectivity which are closely associated with addiction.

#21. Acute effects of nicotine and nabilone on the mismatch negativity: a combined time-frequency and event-related potential study

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Introduction: While the high prevalence of concomitant cannabis and nicotine use in schizophrenia (SZ) has been viewed as a form of self-medication for cognitive and stress/emotional processing, the interaction of these substances has received limited study in terms of sensory/cognitive processes. The objective of this study was to assess the acute effects of nabilone (synthetic version of THC) and nicotine on the mismatch negativity (MMN) event-related potential, and to evaluate cannabinoid-nicotinic receptor interactions within a pilot study using healthy controls.
Methods: 20 male non-smokers and non-cannabis-users were assessed using a 5-stimulus 'optimal' multi-feature MMN paradigm within a randomized, double-blind design (placebo; nabilone [0.5 mg]; nicotine [6 mg]; and nicotine + nabilone). The MMN was quantified in the time domain and the time-frequency domain.
Results: The separate and combined effects of nicotine and nabilone were region- and deviant-dependent. Temporally, the MMN was impaired by nabilone and nicotine separately, whereas co-administration resulted in no impairment. Frontally, the MMN was enhanced by co-administration of nicotine and nabilone. Nabilone and the combination treatment decreased frontal evoked theta power.
Conclusions: It is possible that 1) cannabinoid and nicotinic receptor systems in the frontal and auditory cortex regulating sensory processes are differentially affected, and/or 2) the functional connectivity between the two MMN generators is differentially affected by the two interacting systems. Given the high prevalence rates of tobacco and cannabis use in SZ, understanding the effect of these substances and their interactions on early sensory processes underlying higher-order cognitive processes is of clinical and scientific relevance.

#22. Gaba-modulation effects on early attentional processing indexed by the n2, p3a, and p3b event related potentials

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Introduction: Sustained attention and executive functioning deficiencies in schizophrenia patients (SZ) have been consistently highlighted and related to inhibitory processing alterations mediated by the ?-aminobutyric acid (GABA) neurotransmitter system. Studies have shown working memory impairments following the administration of a GABA-A receptor agonist (lorazepam) in humans. While baclofen, a GABA-B receptor agonist has been shown to reverse cognitive impairments in monkeys. The effects of these agonists has not been examined on stimulus discrimination, voluntary, and involuntary attentional processing indexed by N2, P3b, and P3a event related potentials (ERPs) respectively, and for which substantial impairments have been reported in SZ. The objective of this study was to examine the effects of lorazepam and baclofen on N2, P3a, P3b, and behavioural performance in humans. Baclofen and Lorazepam were expected to decrease amplitudes for these ERP components, and to decrease correct responses while increasing incorrect responses and reaction time.
Methods: ERPs were assessed in thirty non-smoking male volunteers during an auditory oddball paradigm following administration of lorazepam (1.0 mg), baclofen (10 mg), or placebo during three separate double blinded, placebo-controlled, & crossover designed sessions.
Results: Lorazepam (vs. placebo) significantly ($p<.02$) decreased N2a amplitudes and ($p<.001$) correct responses while it increased reaction time ($p<.001$) and incorrect responses ($p=.021$).
Conclusions: Lorazepam impaired early stimulus discrimination and behavioural performance. Enhanced understanding of the GABAergic system will translate to better treatments for individuals imprisoned by cognitive deficiencies. Furthermore, it is essential to examine whether genetic components (e.g.GAD1 gene; catalyzes GABA production) moderate cognitive processing and drug response.

#23. Voxel-based morphometry in midlife men and women with major depressive disorder

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Introduction: Females are at increased risk of developing major depressive disorder (MDD) during perimenopause. Few studies have examined possible effects of perimenopause on female brain structure. There is a paucity of studies examining sex differences in brain structure in middle-age.
Methods: Thirty-four healthy control participants (CTRL; mean age = 50.7±5.0 years; 10 male, 24 female), and 31 untreated and unmedicated participants with MDD (mean age = 51.9±4.4 years; 11 male, 20 female) were examined for grey (GMV) and white matter volume (WMV) differences, using voxel-based morphometry analysis (VBM8; $p<0.05$, FWE) of high-resolution structural MRI. A 2 x 2 ANOVA of sex and diagnosis, with age and Montgomery–Åsberg Depression Rating Scale scores as covariates, was calculated.
Results: Compared to female CTRL, male CTRL participants had smaller GMV in parahippocampal gyrus, and cuneus. Within MDD, males had smaller GMV in parahippocampal gyrus, middle temporal gyrus, middle occipital gyrus, medial frontal gyrus, precuneus, and lentiform nucleus and greater WMV in cerebellar tonsil. There were no GMV/WMV differences between CTRL and MDD participants. Between sexes, males demonstrated smaller GMV in inferior frontal gyrus, parahippocampal and medial frontal gyrus, middle temporal gyrus, thalamus, superior occipital gyrus, precuneus and pyramis, and greater WMV in cerebellar tonsil and medial dorsal nucleus of the thalamus.
Conclusions: These preliminary findings indicate sex differences in brain structure in middle-age across groups, within an MDD group, and within a CTRL group, but not between CTRL and MDD groups. Further studies are required to elucidate the nature of these sex differences.

#24. The role of 5-ht1a autoreceptor in response to antidepressant treatment

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Introduction: Selective Serotonin Reuptake Inhibitor (SSRIs) are the first-line treatment for major depression, but require several weeks for clinical effect. A promising theory implicates gradual desensitization of 5-HT1A autoreceptors to permit enhanced firing and increased serotonin at the synapse following chronic SSRI. We hypothesized that in absence of 5-HT1A autoreceptors, Fluoxetine (SSRI) will improve behaviour faster and more effectively.
Results: To specifically knockout 5-HT1A autoreceptors, we crossed TPH2-CREERT2 and flx5HT1A-YFP mice (from Dr. Rene Hen, Columbia Univ.) to generate TPH2-flx5HT1A-/- mice, a Tamoxifen-inducible and conditional knockout. Following tamoxifen treatment in adult mice, co-staining of GFP (CRE-mediated recombination results in YFP expression) and tryptophan hydroxylase (TPH) in the TPH2-flx5HT1A -/- mouse brain confirmed that recombination occurred specifically in serotonin neurons of the dorsal raphe. Preliminary results of the novelty suppressed feeding test show that while there was no difference in untreated mice, female TPH2-flx5HT1A-/- treated mice showed a higher anxiety than wild-type mice treated for 8 days with fluoxetine. Preliminary results of the elevated plus maze suggest that the TPH2-flx5HT1A-/- female treated may mice spent less time in the open arm then the non-treated one. This could indicate that fluoxetine increases anxiety in the TPH2-flx5HT1A-/- mice. Conclusion: Specific knockout of 5-HT1A autoreceptors in the TPH2-flx5HT1A mouse model was confirmed by immunofluorescence. Preliminary behaviour results could suggest an anxiety-like phenotype in the knockout mice when treated with the SSRI. To confirm these results, more animals and more behaviour tests will be performed.

Poster Session II – Thursday, June 12, 2015
12:00 – 14:00 – Laurier Room

#1. Eye movement assessment in adult patients with bipolar disorder or attention-deficit hyperactivity disorder. a preliminary comparison

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Introduction: Bipolar Disorder (BD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two disorders with similar functional deficits and overlapping clinical presentations. Finding discrete biomarkers for each of these clinical entities is expected to improve diagnosis validity and treatment outcomes. This study used eye movement paradigms to distinguish adult patients with BD from patients with ADHD. Methods. Adults, aged 18-62, with ADHD (n=22) and BD (n=20) performed an interleaved pro- and anti-saccade task modified to include task irrelevant emotional faces. The test variables were compared on their ability to accurately differentiate by diagnosis using supervised analytic techniques: a decision tree analysis and logistic regression. Results. In our decision tree, two variables predicted diagnosis with an overall accuracy of 86%: multistep saccade trial percentage and direction error percentage. The logistic regression provided similar results; multistep saccade percentage (p=.015), error percentage (p=.025), and saccadic reaction time (p=.022) contributed significantly to the model. Only saccadic reaction time (SRT) was impacted by emotional stimuli, specifically neutral faces. The logistic regression had 81% accuracy using these variables. Conclusion. The integrity of the motor plan (multistep saccade trials) best discriminated ADHD from BD in these models, while measures of response disinhibition (direction errors) and processing speed also differentiated them. Importantly, emotional stimuli played a role in modulating processing speed. Limited by a small sample size and the rather heterogeneous patient groups, these results provide a promising first step in capturing relevant physiologic dimensions to better distinguish patients with BD and ADHD using a cost effective method.

#2. Akt/gsk-3ß kinase activities are associated with tardive dyskinesia induced by prolonged antipsychotic treatments in a non-human primate model

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Introduction: Tardive dyskinesia (TD) is a delayed and potentially irreversible motor complication arising in patients chronically exposed to dopamine receptor antagonists. Typical antipsychotic drugs, metoclopramide and several atypical drugs are associated with generation of TD. But, the pathophysiology of TD remains elusive and difficult to treat. Antipsychotic drugs modulate multiple kinase pathways, but their involvement in TD is unknown.
Methods: To investigate the neurochemical basis of TD, we exposed capuchin (Cebus apella) monkeys to prolonged haloperidol (N=11) or clozapine (N=6) treatments. Six untreated animals were used as controls. Five haloperidol-treated animals developed mild TD movements similar to those found in humans. No TD was observed in the clozapine group. We measured ERK1/2,

GSK-3ß and Akt activities with phospho[Thr202/Tyr204]-p44/42 (pERK1/2), phospho[Ser9]-GSK-3ß (pGSK-3ß) and phospho[Ser473]-Akt (pAkt) specific antibodies by Western blots. Relative pERK1/2, pGSK-3ß and pAkt levels were calculated from respective total kinase levels. Results: Haloperidol, but not clozapine, strongly enhanced pERK1/2 immunoreactivity in the putamen. Nonetheless, both dyskinetic and non dyskinetic animals showed similar pERK1/2 levels. On the other hand, haloperidol reduced putamen pAkt and pGSK-3ß immunoreactive signals. Interestingly, only haloperidol-treated monkeys that did not develop dyskinesia have reduced pAkt and pGSK-3ß levels, as compared to dyskinetic animals, and pAkt levels nicely correlated with dyskinetic scores (r2 = 0.916; p value = 0.011). Conclusion: These results suggest that a reduced Akt/GSK-3ß activity minimizes the risk of haloperidol-induced TD. This work was supported by the CIHR (MOP-300152). GH holds a HH Jasper post-doctoral fellowship from the GRSNC University of Montreal FRQS group.

#3/ Dopamine and light: effects on facial emotion recognition

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Introduction: Bright light can affect mood. The relevant neurobiology is poorly understood but might include changes in catecholamine transmission. Here, in the present study, we tested the effects of transiently decreasing dopamine synthesis, in combination with bright or dim light, on facial emotion recognition.
Methods: Healthy women with subsyndromal seasonal affective disorder were studied on two days. Sixteen were studied in bright light (3,000 lux) and 16 were studied in dim light (10 lux). Dopamine synthesis was reduced on one day using acute phenylalanine/tyrosine depletion (APTD). On the other day they ingested a nutritionally balanced mixture (BAL). Four hours post-ingestion, participants completed mood questionnaires and a facial emotion recognition task (sad, happy, fear, angry, surprised, disgusted).
Results: Following APTD, compared to BAL, participants in the dim light condition became more accurate at recognizing sad faces, less likely to misclassify them, and faster at responding to them, independent of changes in mood. There were no effects of APTD on responses to sad faces in the bright light group. There were no APTD effects on responses to other emotions with one exception: a significant light x amino acid mixture interaction was seen for reaction time to fear, but the pattern of effect was not predicted a priori or seen on other measures.
Conclusions: The recognition of sad emotional stimuli might be greater when dopamine transmission is low. The ability of bright light to prevent this effect might have implications for its clinical efficacy in the treatment of seasonal and non-seasonal mood disorders.

#4. Abnormal spontaneous neural activities within the cognitive control

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Objectives: Obsessive-compulsive disorder (OCD) is associated with deficits in response inhibition and planning. Both of these cognitive functions are governed by the cognitive control network. Although several neuroimaging studies have investigated the cognitive control network connectivity, intrinsic local neuronal activity within the cognitive control network in OCD remains poorly understood.

Methods: We performed regional homogeneity (ReHo) and region-of-interest functional connectivity analyses of intra and inter-regional resting-state brain activation synchrony within the cognitive control network in 30 OCD patients and 30 matched, healthy controls using resting-state functional magnetic resonance imaging.
Results: OCD patients exhibited increased ReHo activation in the prefrontal cortex (PFC) and the middle cingulate cortex but decreased homogeneity in the insula. The PFC also exhibited increased functional connectivity to the inferior temporal gyrus but decreased functional connectivity to the middle temporal gyrus. The ReHo value of the right inferior frontal gyrus was negatively correlated to the duration of OCD ($r = -0.368$, $P = 0.046$).
Conclusions: These findings provide evidence of altered intra- and inter-regional synchronized activities in the cognitive control network at resting-state in OCD patients. The altered PFC-temporal gyrus neural circuitry may be the primary disturbance associated with cognitive impairment in OCD. Keywords: Obsessive-compulsive disorder; Cognitive control network; Regional homogeneity; Functional connectivity; Resting-state.

#5. Physicians' opinions following pharmacogenetic testing for antidepressant and antipsychotic medication

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Background: Pharmacogenetics seeks to improve patient drug response and decrease side effects by personalizing prescriptions with genetic information. As a result, pharamcogenetic testing is becoming increasingly applied in clinical practice and providing training to health care practicioners and staff physicians will be important. Given the increasing evidence for genetic influences on treatment response, the Pharmacogenetics Research Clinic was created at CAMH in 2008 to deliver genetic testing of liver enzymes (e.g., CYP2D6 and CYP2C19) and to study physicians' opinions following testing of their patients.
Methods: Patents who were referred to our clinic were tested and an interpretation was sent to the physicians. Several weeks later, surveys were completed by 168 Canadian physicians who had ordered at least one pharmacogenetic test for the prescription of psychiatric medication. One important outcome measure has been to assess physicians' opinions on pharmacogenetic testing.
Results: Our results indicate that 80% of respondents believe genetic testing will become common standard in psychiatric drug treatment and 76% of respondents reported satisfactory or higher than satisfactory understanding of the pharmacogenetic report provided. Significantly more male physicians believed they had a higher understanding of the pharmacogenetic report compared to female physicians ($p=0.04$).
Conclusions: Our study demonstrate a positive opinion of physicians on pharmacogenetics and indicate great potential for future clinical application. However, our results also indicate that providing genetic test information to physicians can still be improved, and it remains crucial to provide pharmacogenetic training for healthcare professionals, medical students and residents.

#6. Fluoxetine and norfluoxetine induce apoptosis of microglia

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Introduction: Having previously found that the antidepressant fluoxetine promoted neuronal survival by attenuating the release of glutamate and D-serine from activated microglia, and that

fluoxetine reduced the number of cells in microglial cultures, we hypothesized that fluoxetine and its active metabolite norfluoxetine promote the apoptosis of microglia.
Methods: Primary microglia were treated with fluoxetine or norfluoxetine and compared with representatives of tricyclics (imipramine), MAO inhibitors (phenelzine) and SSRIs (citalopram). Various assays of cell viability and markers of apoptosis were assessed.
Results: Fluoxetine and norfluoxetine decreased the viability of microglia and showed greater numbers of dying microglia by live/dead nuclear staining. Both fluoxetine and norfluoxetine showed increased cleavage of caspase 3 and decreased levels of caspase 8, hallmarks of apoptosis. In contrast, neither imipramine, phenelzine, nor citalopram showed evidence of induction of apoptosis of microglia. Gas chromatography – mass spectrometry analysis showed negligible conversion of fluoxetine to norfluoxetine in vitro, so effects of fluoxetine on the microglia were due to the parent drug itself; however, in the clinical situation, considerable amounts of norfluoxetine are formed and could contribute to microglial apoptosis. Conclusion: Induction of microglial apoptosis by fluoxetine may contribute to the attenuation of glutamate and D-serine release from those cells, an effect specific to fluoxetine and its metabolite norfluoxetine since citalopram, another SSRI, did not show evidence of microglial apoptosis, nor did imipramine or phenelzine. Funds provided by CIHR (KGT and GBB), AHS (KGT) and the University of Alberta (GBB). KSD held a QEII scholarship and MAC AI-HS fellowships.

#7. Effects of deaf1 and mecp2 on htr1a promoter regulation

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Introduction: Recently, MeCP2 was shown to enhance the transcription of certain genes, a dual role that could be explained by its interaction with other transcription factors. Deaf1 represses 5-HT1A receptor (HTR1A) transcription at the rs6295 C(-1019) HTR1A polymorphism but not the G-allele. The G-1019 allele has been associated with increased 5-HT1A autoreceptor expression, reduced 5-HT, major depression and resistance to antidepressant treatment. Since MeCP2 is also implicated in serotonergic regulation and the C-allele can be methylated, it was hypothesized that MeCP2 alters Deaf1's regulation of HTR1A.
Results: Yeast one-hybrid methylation studies showed that MeCP2 interaction with the C(-1019) site was dependent on DNA methylation. In contrast, co-expression of MECP2 and Deaf1 increased the recruitment of Deaf1 to its site on the HTR1A promoter independently methylation. Significant effects of MeCP2, Deaf1 and MeCP2-Deaf1 combination on HTR1A promoter activity were demonstrated by reporter assay using co-transfection with a mouse and human HTR1A promoter-luciferase construct in HEK-293 cells and MEF cells. Mutants of these constructs (including the 1128G human allele) showed a loss of Deaf1-MeCP2 regulation and interaction effects. MeCP2 and Deaf1 were shown to interact by co-immunoprecipitation assay. Lastly chromatin immunoprecipitation of the HTR1A promoter showed that both Deaf1 and MeCP2 binding were significantly reduced in the absence of Deaf1, indicating Deaf1 dependent binding when the promoter is presumably unmethylated. Conclusion: These results suggest that MeCP2 can regulate 5-HT1A receptor expression both directly through methylation-dependent recruitment, and indirectly via its interaction with Deaf1.

#8. Increased neuroinflammation in major depressive disorder and relation to symptom severity

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Introduction: Peripheral markers of inflammation are frequently reported in MDD, however, to date, there is a paucity of evidence for brain inflammation during MDE. The objective of this study was to determine whether translocator protein (TSPO) is elevated in MDE compared to healthy controls. Increased TSPO, found in activated microglia, is a hallmark of neuroinflammation which may be quantified using positron emission tomography (PET).
Methods: [18F]FEPPA PET was applied to measure TSPO total distribution volume (TSPO VT) in 20 subjects with MDE secondary to MDD and 20 healthy controls. MDE subjects were medication-free for at least 6 weeks. All participants were otherwise healthy, and non-smoking.
Results: In MDE, TSPO VT was significantly elevated in the prefrontal cortex, ACC, and insula (on average 30%, MANOVA, $F_{3,35}=4.73$, $P<0.007$). In MDE, greater TSPO VT in the ACC and insula correlated with greater depression severity and lower body mass index (BMI), respectively (ACC: $r=0.628$, $P=0.005$; insula: $r=-0.605$, $P=0.006$). Conclusion: These results provide the most compelling evidence to date for neuroinflammation in MDE. The correlations between higher ACC TSPO VT with severity of MDE and higher insula TSPO VT with lower BMI are consistent with the concept that neuroinflammation in these regions may contribute to sickness behaviors which overlap with the symptoms of MDE. Therapeutics which reduce microglial activation may be promising in a subset of the clinical population with relevant symptoms.

#9. Negative childhood experiences alter a prefrontal-insular-motor cortical network in healthy adults: a preliminary multimodal rsfmri-fmri-mrs-dmri study

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Introduction: Negative childhood experiences (NCE) can have long-term effects on the structure and function of the brain. Alterations have been noted in the resting state/medial prefrontal cortex (mPFC), the glutamatergic system, white matter, and on neural responses to aversive stimuli. Taken together, the hypotheses were that more NCEs in healthy people would: 1) correlate with disruptions in mPFC resting-state activity and decreased glutamate levels; 2) result in reduced neural reactivity to aversive stimuli; 3) correlate with disruptions in white matter connectivity to the mPFC.
Methods: Twenty-five healthy, right-handed, participants underwent resting-state functional MRI (rsfMRI), aversion task fMRI, glutamate magnetic resonance spectroscopy (MRS), and diffusion magnetic resonance imaging (dMRI) scanning with a Siemens 3T Trio. Subjects also completed the Childhood Trauma Questionnaire (CTQ) as a measure of NCEs. Twelve subjects (6 female, 23 ± 3.5 years) with a complete set of data were included in the final analysis.
Results: High NCEs were related to lower resting-state mPFC glutamate levels ($r=-0.64$, $p=0.009$) and higher entropy ($r=0.8$, $p=0.002$). NCEs, mPFC glutamate, and entropy correlated with neural BOLD responses to aversive stimuli with a strong overlap in the motor cortex and left insula ($p<0.05$, FWE whole-brain corrected). MPFC-left insula structural connectivity strength, measured using mean fractional anisotropy, correlated to aversion-related signal changes in the motor cortex ($r=0.68$, $p=0.023$). Conclusion: NCEs impact inter-related brain systems in healthy humans and correlate to altered aversion-related processing. The role of a prefrontal-insular-motor cortical network was highlighted and underscores its potential adaptability by NCEs.

#10. Post-stroke depression in a new focal ischemic mouse model is reversed by chronic fluoxetine treatment and involves brain region-specific fosb induction

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Introduction: Post-stroke depression (PSD) is a prevalent and disabling disorder, yet the evidence regarding its etiology/effectiveness of treatment remains inconclusive. Suitable animal models are required to study the biological basis of PSD and the discovery of novel therapeutic targets.
Methods: We have established a new mouse model of PSD using microinjection of endothelin-1 targeting the left medial prefrontal cortex (mPFC) that results in a consistent small lesion and a robust anxiety/depression phenotype. We treated PSD mice for 4 weeks with exercise (free access to running wheel) or serotonin specific reuptake inhibitor (SSRI, fluoxetine 18 mg/kg, po) comparing common treatments given to PSD patients. In order to begin to identify changes in cellular activity associated with the SSRI treatment, we examined number of cells expressing Fos-B, which is a marker of chronic neuronal activation implicated in plasticity.
Results: The behavioral phenotype persists at least 6 weeks following the injury making this model ideal to study clinically relevant recovery interventions, their effects on behavior and corresponding neuronal activity. Chronic treatment with fluoxetine alone reversed the anxiety/depression phenotype. Chronic SSRI induced a significant Fos-B elevation expressing cells in the right (contralateral) side of the brain in regions including mPFC, nucleus accumbens, septum, basolateral amygdala and serotonin neurons of the dorsal raphe. Conclusion: Thus overall treatment with SSRI was sufficient to reverse the anxiety phenotype and activate discrete brain areas. Future work is now aiming to dissect how these regional changes may be involved in the effects of SSRI PSD treatment.

#11. Association of il-1b, il-2, il-6, tspo and bdnf gene variants with response to treatment with duloxetine and placebo in patients with major depression

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Introduction: Major depressive disorder (MDD) is a prevalent psychiatric disorder treated with antidepressant medication such as duloxetine. In addition, placebo treatments have been shown to improve depressive symptoms in a subgroup of patients. This study examined the role of genetic variation of inflammatory markers (IL-1B, IL-2, IL-6, TSPO) including brain-derived-neurotrophic factor (BDNF) in response to duloxetine and placebo.
Methods: Twenty single nucleotide polymorphisms (SNPs) across IL-1B, IL-2, IL-6, TSPO and BDNF were genotyped in 215 patients receiving duloxetine and 235 patients receiving placebo for 8 weeks. Samples were obtained through a partnership between the Canadian Biomarker Integration Network for Depression (CAN-BIND) and Lundbeck. Interleukin SNPs ($r2 = 0.8$, MAF > 0.05) covered ~100% of the common genetic variation. For ANCOVAs, we used quantitative and binary response variables. Quantitative response was defined as percentage change in MADRS score from baseline to endpoint. Binary response versus non-response was defined by at least 50% of reduction of MADRS scores from baseline.
Results: Two SNPs, rs2066992 ($p=0.047$) and rs10242595 ($p=0.028$), in the IL-6 gene were

associated with response to duloxetine after 6 weeks of treatment. IL-6 variant rs2066992 was also significantly associated with response to placebo after 6 weeks (p=0.026). When dichotomizing response into response vs. non-response, IL-6 variant rs10242595 was also found to be associated with response to duloxetine (p=0.003), but not placebo. Conclusion: SNPs across IL-6 may play a role in response to duloxetine and placebo. We have started GWAS analyses in these samples and results will be presented at the meeting.

#12. Genome-wide association study on antipsychotic-induced weight gain in the catie sample

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Introduction: Antipsychotic treatment is associated with a high risk for weight gain. Marked inter-individual variability and twin studies indicate a genetic contribution. We have re-analyzed the genome-wide association study (GWAS) data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for association with antipsychotic-induced weight gain (AIWG) in a refined subset of patients.
Methods: A subset of patients (n=358) most suitable for weight gain studies was selected and analysed for the influence of all potentially relevant covariates using mixed effect models. The final GWAS analysis was conducted in 189 individuals of European ancestry to avoid population stratification effects. The top SNPs from the GWAS were analysed in a second cohort of N=86 patients treated with clozapine or olanzapine.
Results: None of the SNPs reached the genome-wide significance threshold of 5*10-8. However, we observed interesting trends for several variants including rs9346455 (p=6.49*10-6) located upstream of OGFRL1, rs7336345 (p=1.31*10-5), rs1012650 (p=1.47 *10-5), both located in intragenic regions, and rs1059778 (p=1.49*10-5), located in IBA57. In the second cohort the top SNP rs9346455 showed significant association with weight gain (p=0.005).The combined meta-analysis p-value for rs9346455 was 1.94*10-7.
Conclusions: Our reanalysis of the CATIE GWAS data revealed interesting new variants that may be associated with antipsychotic induced weight gain. However, the functional relevance of the discovered polymorphisms is yet to be determined, and none of the SNPs reached genome-wide significance. Further studies are needed to determine their significance. Keywords CATIE, genome-wide association study, antipsychotic-induced weight gain, olanzapine, quetiapine, risperidone, BMI, rs9346455.

#13. Assessment of transcranial direct current stimulation (tdcs) on auditory sensory processing: a sham-controlled double-blind study

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Introduction: Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation which uses a very weak constant current to temporarily excite or inhibit activity in the brain area of interest via small electrodes placed on the scalp. Currently, tDCS is being used as a tool to investigate cognition and motor function in healthy controls and to improve symptoms in neurological (i.e. stroke) and psychiatric (i.e. depression and dementia) patients. tDCS has been found to improve cognitive performance on measures of attention, memory, and frontal-executive functions. Recently, a short session of anodal tDCS over the auditory cortex has been found to increase auditory sensory processing as indexed by the MMN event-related potential (ERP). The current study examined the effects of both anodal and cathodal tDCS on MMN-indexed sensory discrimination. Method: In a randomized, double blind design, the MMN was assessed before and after tDCS (2 mA, 20 minutes) in 3 separate sessions, one involving anodal stimulation (to temporarily excite cortical activity locally), one involving cathodal stimulation (to temporarily decrease cortical activity locally), and one involving 'sham' stimulation (device is turned off after 30 seconds).
Results: Anodal tDCS over temporal areas increased MMN-indexed sensory processing, $p < .01$, while cathodal tDCS decreased sensory processing in stratified groups, $p < .05$. Conclusion: These findings strengthen the position that tDCS is an efficacious method of limited cognitive modulation. Moreover, these results contribute to our understanding of sensory processing deficits and suggests future individualized treatments for clinical populations.

#14. A variant of presenilin-1 is a marker for monoamine oxidase-a function in human cortex

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Introduction: Mutations in the presenilin-1 (PS-1) gene are rare; however, a few have been associated with an increased incidence of clinical depression. We recently demonstrated, using mouse brain samples, that PS-1 can physically interact with a protein associated with depression, i.e. monoamine oxidase-A (MAO-A). We also observed that incubation of these brain samples with DAPT, a pharmacological inhibitor of PS-1, could alter MAO-A activity depending on whether the samples expressed normal or mutated forms of PS-1.
Methods: We chose to examine if this pharmacological test could detect mutated forms of PS-1 in human cortical brain samples. Using MAO-A activity as a read-out, we identified several samples that responded to DAPT treatment. The mRNA from these samples was extracted, reverse transcribed and sequenced to identify potential mutations in PS-1.
Results: Sequencing reactions identified a PS-1 mutation in one of the samples. However, sequencing also identified a transcript of PS-1 that we subsequently demonstrated was expressed in every human cortical sample tested. The levels of this transcript vary between samples, but appear to be positively correlated with MAO-A activity. We then developed an antibody against an epitope specific to the protein encoded by this transcript. This antibody is selective and of high-affinity (kinetics were modeled using surface plasmon resonance). Western blotting identifies the target PS-1 species, and expression levels of this species also are positively correlated with MAO-A activity in corresponding samples. Conclusion: We have identified a potential biomarker for depression. Our unique antibody requires testing in clinical samples.

#15. Disruption of the interaction between presenilin-1 and monoamine oxidase-a could predispose to a prodromal depressive phenotype in alzheimer disease progression

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Introduction: Mutations in presenilin-1 (PS-1) are associated with Alzheimer pathology and the aberrant cleavage of the Amyloid Protein Precursor (APP). Yet, some are also associated with risk of depression. We reported on a physical interaction between PS-1 and the depression-related enzyme, monoamine oxidase-A (MAO-A). MAO-B, which shares 75% sequence identity with MAO-A, does not interact with PS-1.
Methods: By aligning the sequences for MAO-A and MAO-B, with that of the PS-1 substrate, APP, we identified a motif in MAO-A as a putative target for PS-1. There is a single amino acid difference in the homologous region in MAO-B. An Alanine (Ala; A) occupies this position in MAO-A, while a serine (Ser; S) occupies this position in MAO-B.
Results: The substitution of the Ala in MAO-A for a Ser, i.e. MAO-A(A/S), disrupted the interaction between MAO-A and PS-1; this coincided with an increase in MAO-A activity in corresponding lysates. Interestingly, the overexpression of wildtype MAO-A inhibited PS-1-mediated cleavage of APP, whereas overexpression of MAO-A (A/S) did not. The complementary substitution in MAO-B (i.e. Ser-to-Ala) resulted in a decrease in MAO-B activity. We will determine if this promotes its interaction with PS-1. Conclusion: These data suggest that the interaction between PS-1 and MAO-A is mutually inhibitory. We propose that disruption of the interaction could activate MAO-A (perhaps leading to a depression-like phenotype) and concurrently disinhibit PS-1 and trigger the aberrant cleavage of APP that is associated with Alzheimer pathology.

#16. Resting state connectivity is not affected by menstrual cycle phase in women with no history of pmdd

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Introduction: Most neuroimaging research in women does not account for menstrual cycle phase or control for the presence of premenstrual dysphoric disorder (PMDD). Studies that investigate menstrual cycle effects frequently do not utilize measures such as the SCID-IV or SCID-PMDD to control for psychiatric history. Therefore, we aimed to investigate the functional resting state connectivity (rs-FC) in a well-characterized sample of healthy women, with no history of psychiatric illness or PMDD.
Methods: 20 right-handed women between 18-45 years of age (mean age = 28.3±8.35), with regular menstrual cycles, not using any form of hormonal contraception were studied. The SCID-IV and SCID-PMDD were administered to ensure individuals did not present with a history of psychiatric illness. Participants were prospectively evaluated for two months using the Daily Record of Severity of Problems to confirm they did not meet criteria for PMDD. Rs-FC was measured in the same women at two points of the menstrual cycle (confirmed with hormonal assays): mid-follicular phase (day 5-10) and late luteal phase (within 5 days preceding menses).
Results: No significant differences in rs-FC were found between the mid-follicular and late luteal phases when controlling for multiple comparisons ($p>0.05$, FDR-corrected). Results remained consistent at a more relaxed threshold ($p<0.001$, uncorrected).
Conclusions: Our results indicate that in healthy women with no history of PMDD there may be no impact of endogenous hormonal fluctuations on rs-FC. This suggests that there is no need to

control for menstrual cycle phase when investigating rs-FC in healthy women with no history of PMDD.

#17. Brain-derived estradiol controls hunger state-dependent plasticity of gaba synapses

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The Bed Nucleus of the Stria Terminalis (BNST) is heavily involved in feeding and anxiety-related behaviors. Furthermore, the oval Bed Nucleus of the Stria Terminalis (ovBNST) is one of the most sexually dimorphic regions of the brain, containing both estrogen and androgen receptors. This study investigated how estrodial (E2) in the ovBNST modulates synaptic transmission and contributes to hunger states and risk-reward trade offs. We combined brain slice neurophysiology and behavioral pharmacology in Long Evans rats. ovBNST GABAA-IPSC were electrically-evoked at 0.1 Hz. E2 (1nM): GABA plasticity was induced by 5 mins of either low-frequency stimulation (LFS) or exogenous application of E2 and other E2 receptor agonists. Rats were either naïve (fully sated), subjected to food restriction (24hr) or food restriction (FR) followed by refeed (40 mins) and then underwent brain slice neurophysiology. Other groups were tested for exploratory activity in the open-field test and novelty-induced suppression of feeding while receiving intra-ovBNST microinjections of saline or estrogen receptor (ERa/ß) antagonist ICI 182780, 30 mins before paradigm. LFS produced long-term potentiation (LTP>150%) of ovBNST GABAA-IPSCs in naïve animals. FR unmasked long-term depression (LTD) but refeed reinstated LTP. Furthermore, ICI 182780 mimicked the effects of FR. Exogenous E2 produced a 60-80% increase of GABAA-IPSCs but only the ERa agonist PPT produced an increase in GABAA-IPSCs. Microinjections of the ERa/ß antagonist ICI 182780 modulated feeding behavior in high-risk situations. Conclusion: Our data show increased GABA transmission in the ovBNST may be a satiety signal that is modulated by E2 and influences risk-taking behavior.

#18. Applying polygenic scores to guide antipsychotic dosage

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Genetic variants have been identified to predict an ideal medication for patients with Schizophrenia to prevent potentially debilitating side effects, however, dosage also plays an important role in treatment response and may need to be adjusted accordingly. The purpose of this study is to quantify significant genetic risk variants prioritized from the Psychiatric GWAS Consortium as a polygenic score to test our hypothesis that the polygenic score can predict antipsychotic dosage. Antipsychotic medication and dosage were collected in our sample of 81 schizophrenia patients of a homogeneous European background. Antipsychotic dosage was standardized according to chlorpromazine equivalents (CPZe). In our sample, we calculated polygenic scores for the significant risk variants identified from the Psychiatric GWAS Consortium schizophrenia genome-wide association study. We used a regression model to predict CPZ dosage using polygenic risk scores. In our preliminary analysis, the polygenic scores showed no significant association with CPZe standardized dosage. Therefore, it is unclear whether the polygenic score is predictive of treatment response when considering antipsychotic dosage. While the polygenic scores of the top risk variants showed no significant predictive value for antipsychotic dosage, the polygenic scores from the PGC genome-wide study offers a novel approach to analyzing genomic data to predict other endophenotypic outcomes in schizophrenia.

#19. Frontal-limbic brain development in depressed adolescents with various levels of childhood abuse: a preliminary study

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Introduction: Our understanding of the pathophysiology of depression in adolescence is incomplete: little is known about how childhood abuse relate to alterations in early brain development, reflected in structural and functional differences in brain areas involved in emotion processing and cognitive control. The objective of this pilot study was to examine associations among childhood abuse and frontal-limbic brain development in depressed adolescents.
Methods: Seventeen depressed adolescents were carefully assessed using the Childhood Experience of Care and Abuse interview and for symptomatology. They underwent a 3T (f)MRI scan. Peripheral DNA methylation was also assessed, with an emphasis on SLC6A4 methylation, given its role in brain development and based on previous work in adult patients (Booij et al., 2015).
Results: Structurally, there was decreased anterior cingulate GM density in patients with a childhood history of abuse. Notably, there was also increased superior temporal gyrus GM density, increased WM density, and decreased corpus callosum WM density (pFWE all < .005), compared to those without a history of abuse. First analyses of the methylation data showed a positive association between SLC6A4 methylation and aspects of frontal-limbic functional brain development.
Conclusions: The stress associated with childhood abuse may alter early brain development in adolescence, shown by chronic superior temporal activation and density that impairs the anterior cingulate, developmental deficits in age-appropriate pruning, and/or delays in myelination. DNA methylation may underlie some of these alterations. We are currently following these adolescents to determine whether cognitive therapy can reverse some of these brain and epigenetic changes.

#20. Does acute tobacco smoking prevent cue-induced craving?

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Introduction: Smoking cessation aids appear to be limited in their ability to prevent craving triggered by exposure to smoking-associated stimuli; however, the extent to which cue-induced cravings persist following actual tobacco smoking is not known. This study aimed to assess the relative impact of nicotine administration and expectancy components of tobacco smoking on cue-induced craving.
Methods: Thirty two (18 male) =12 hour abstinent dependent smokers completed two sessions during which they smoked a nicotine-containing or denicotinized cigarette. Instructions regarding the nicotine content of the cigarette varied across sessions, and all participants were exposed to a neutral cue followed by a smoking cue after cigarette consumption. Craving was assessed before and after cigarette consumption and cue exposure.
Results: The acute administration of either nicotine-containing or denicotinized cigarettes were found to immediately reduce craving (p values<0.001) but smoking-associated stimuli increased craving regardless of nicotine expectancy or administration (p values<0.001). When analyses were limited to include only participants that believed nicotine content instructions, acute administration of nicotine-containing cigarettes lead to greater reductions in intention to smoke than acute administration of denicotinized cigarettes (p values<0.01); however, increased cue-induced craving was still observed regardless of nicotine content (p values=0.001).
Conclusions: While acute tobacco smoking reduces acute craving in the absence of smoking-related stimuli, neither smoking-related nicotine administration nor expectation prevents increases in craving following exposure to smoking-associated stimuli.

#21. The investicate project: identification of new variation, establishment of stem cells, and tissue collection aimed at treatment efforts

Liam Crapper, Raphael Pujol, Walla Al-Hirtani, Carl Ernst

Neurodevelopmental disorders (NDDs) are a large and complex group of disorders with varying etiologies. Recent advances in genomics and sequencing technologies have accelerated the pace of discovery of genes associated with NDDs, and suggested a large portion of non-syndromic NDDs are caused by rare, highly penetrant genetic variations. Exome sequencing studies and analysis of copy number variations in families are very effective in characterizing the genetic variability inherent in NDDs and suggesting that causal mutations cluster in several biological pathways, but so far they have not been successful in leading to the development of treatments for NDDs. The INVESTICATE project recruits patients for whom traditional genetic analysis has not identified the cause of their NDD, and uses exome or whole genome sequencing to provide state-of-the-art genetic information to families. After variant identification we generate patient derived induced pluripotent stem cells, which are used to determine functional information about the genetic variants we have identified. Stem cell data is complemented by the collection of whole brains from those cases that die during the course of the study. Finally we use high throughput screening to assess potential therapeutic molecules. INVESTICATE aims to provide genetic information to families not available through the public health system, to understand how genetic variants cause neurological disease, and to develop therapeutic strategies to provide treatment to affected individuals.

#22. In vivo optogenetics to examine the role of the serotonin system in depression

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Introduction Optogenetics is revolutionizing our understanding of neural function, network dynamics, and the neurophysiological underpinnings of behaviour. The objective of our research is to shine light on the role of the serotonin system in depression and anxiety. Methods Through in vivo optogenetics, a form of light-evoked brain stimulation, we are probing the roles of the serotonin (5-HT) system in anxiety- and depression-like behaviour using transgenic mice that selectively express light-activated opsins in 5-HT neurons of the dorsal raphe nucleus, DRN. Channelrhodopsin is activated with blue light and causes depolarization; Archaerhodopsin responds to green light and hyperpolarizes. We will use these opsins to increase and decrease 5-HT release, respectively. Results We are confirming selective opsin expression in 5HT neurons by co-staining for GFP (fused to opsins) and TPH (5-HT marker). We show that these opsins regulate firing of 5-HT neurons using ex vivo cellular electrophysiology in brain slices from the DRN. These data will be used to calibrate light delivery parameters to manipulate 5-HT neuron firing within a physiologically-relevant range during in vivo experiments. To reveal the contribution of different 5-HT projection pathways in depressive and anxiety-like behaviours, we will implant mice with optic fibers at different terminal locations including the mPFC, hippocampus and amygdala. The behavioural response to optogenetic stimulation will be characterized for anxiety- and depression-like behaviours. Conclusions Results from these optogenetic experiments will provide a better understanding of how serotonin modulates neural circuits to alter behavioural phenotype which will assist in the development of targeted clinical therapies.

#23. Stress system gene ska2 may be associated with antidepressant response

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Introduction: Major Depressive Disorder (MDD) has a strong genetic component and is characterized by a number of physiological impairments, including diminished ability of the HPA axis to mediate stress response. The current process used to determine pharmacological treatments is markedly inefficient, with more than 50% of antidepressant treated patients failing to reach remission. Genetic and epigenetic variation in SKA2 (Spindle and Kinetochore Associated Complex Subunit 2) appears to mediate HPA axis function, and has recently been associated with suicidal behaviour. We aimed to investigate whether genetic variation in SKA2 is associated with response to antidepressant medication.
Methods: 492 Caucasian MDD patients were selected from the STAR*D sample. Change in HAMD-17 score was used to measure response to citalopram. Linear regression analysis was used to model the relationship between seven single-nucleotide polymorphisms (SNPs) in SKA2 and antidepressant response.
Results: Marker rs7208505 was not significantly associated with antidepressant response (p=0.573) or baseline score on the HAMD-17 suicidality item (p=0.409). rs9892425, located in the 5' region of SKA2, was nominally associated with antidepressant response (p=0.017, pcorr=0.051). When examined separately, this marker was significant for males (p=0.003, pcorr=0.009), but not for females (p=0.396, pcorr=1.000). A trend was observed using a three marker haplotype window encompassing rs9892425 (p=0.068).
Conclusions: The results provide some evidence that SKA2 genetic variation may be a predictor of therapeutic response to antidepressant medication, particularly in male patients with MDD. Further work, and incorporation of epigenetic modification of SKA2 is warranted in larger samples.

#24. The effects of chronic sugar exposure on oxycodone reward in rats

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Introduction. The "food addiction" hypothesis is supported by evidence that some foods high in fats and sugars can activate brain reward centers in ways that closely resemble the action of drugs of abuse. On the basis of this interaction, it can be predicted that foods and drugs should interact at multiple neural and behavioural levels. The present study examined whether rats given chronic access to high fructose corn syrup (HFCS) display a sensitized response to oxycodone reward. Methods. Male Sprague-Dawley animals had ad libitum access to a 50% HFCS solution (n = 23), or water (n = 24), for 26 days. Followed a 9-day period during which access to the sugar was removed, animals were tested on place conditioning (biased design) involving: pre-test, place conditioning (0, 0.16, or 2.5 mg/kg oxycodone SC; 3 pairings each over 6 days), and a test of preference. Results. It was found that 0.16 and 2.5 mg/kg oxycodone produced a significant place preference, however there were no differences between animals previously given chronic access to HFCS or water. The same doses of oxycodone produced no differences in locomotor activity during conditioning. Conclusion. Under current experimental condition, chronic sugar consumption did not produce sensitization the rewarding property of oxycodone.

SURNAME	FIRST NAME	POSTER SESSION	POSTER #
AIDELBAUM	Robert	1	12
ALDERS	Gésine	1	23
BAKER	Glen	2	6
BEAUDOIN	Ashley	1	6
BHARWANI	Aadil	1	2
CARDIN	Valerie	1	24
CHARBOGNE	Pauline	1	3
CHIARELLA	Julian	2	19
CHOUEIRY	Joelle	1	22
CRAPPER	Liam	2	21
DANIELS	Stephen	1	7
DE LA SALLE	Sara	1	21
GEDDES	Sean	1	19
HAWKEN	Emily	2	17
HAYES	Dave	2	9
HETTIGE	Nuwan	2	18
HUANG	Eric	1	10
HUPÉ	Ginette	2	22
HYDE	Molly	1	13
IMPEY	Danielle	2	13
JUHAS	Michal	1	20
KHALID	Roksana	1	15
KISH	Maxine	1	17
LERI	Francesco	1	4
LÉVESQUE	Daniel	2	2
LI	Ping	2	4
LISOWAY	Amanda	2	23
MACIUKIEWICZ	Malgorzata	2	12
MARIN	Alina	2	1
MARSHE	Victoria	2	11
MINHAS	Meenu	2	24
MUELLER	Daniel	2	5
NELSON	Renee	1	9
NORMANDEAU	Catherine	1	18
NYARKO	Jennifer	2	14
OOSTERHOF	Chris	1	11
PHILIPPE	Tristan	2	7
QUARTEY	Maa	2	15
SCHLAGINTWEIT	Hera	2	20
SETIAWAN	Elaine	2	8
SMITH	Dylan	1	1
SRIRETNAKUMAR	Venuja	1	8
SYAN	Sabrina	2	16
THOMPSON	Shawna	1	16
TIPPLER	Maria	2	3
TORRES-BERRÍO	Angélica	1	14
VAHID-ANSARI	Faranak	2	10
WANG	Yabing	1	5