CCNP PROGRAM
The Banff Centre, Banff, Alberta
June 18 – 21, 2014

The Kinnear Centre for Creativity & Innovation at The Banff Centre. Photo: Donald Lee, The Banff Centre.

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Dear Participants:

It is with great pleasure that I welcome you to the 37th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) at the Banff Centre in the spectacular vista of the Rocky Mountains. This is the third visit of the Meeting to Banff, and it has always been a favorite because of the beauty of the surroundings, and the excellent science being done in the West. We are excited about the great response and participation from research across Canada and beyond.

Today, we continue the tradition of the College to promote the exchange of ideas, discussion of new findings, and to seek better ways of treating mental illness. This year's theme of "**Discovery and Translational Research in Major Psychiatric Disorders**" reflects the goal of the meeting to present novel findings that have the potential to be applied to the development of improved clinical approaches. We welcome our invited plenary speakers, Drs. Joel Kleinman (Lieber Institute), Francesc Artigas (CCNP Presidential Plenary), Caroline Tait (Aboriginal Mental Health speaker from University of Saskatchewan), Alan Hudson (University of Alberta) and a special welcome to our Chinese guests participating in a symposium sponsored by the National Natural Science Research Foundation of China and CIHR. We are particularly pleased to welcome trainees with several activities for them including the poster sessions and Next Generation Symposium and the Mentor-Mentee mixer, a new tradition that was well received at the last meeting in Toronto.

This meeting would not be possible without the support of our sponsors and the dedicated work of the Local Organizing Committee. In particular, I wish to thank Drs. Thomas Raedler (Chair) and the Scientific Program committee for their tireless efforts in organizing what promises to be an exceptional program. In addition, I am pleased to congratulate the outstanding recipients of our 2013 CCNP Awards who will be presenting their research at this meeting. On behalf of the CCNP Executive and Council, I wish you all a stimulating and fruitful meeting, and hope that you will take away an enduring sense of community in our struggle to combat mental illness.

Sincerely,

Paul R. Albert, Ph.D.
President, CCNP

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Wednesday June 18, 2014

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19:30 – 21:30 Reception (Three Ravens Restaurant & Wine Bar)

Thursday June 19, 2014

07:30 – 08:30 Breakfast (Vistas Dining Room)

08:15 – 08:30 Introductory remarks (KC 203)

08:00 – 17:00 Registration (KC 200 Financial Galleria)

08:30 – 10:30 **Symposium 1: NO (Nitric Oxide) and Schizophrenia: Off the Bench and Into the Clinic** (KC 205)

Co-Chairs: Drs. Harold Robertson (Dalhousie University) and Serdar Dursun (University of Alberta)

Dr. Harold Robertson (Dalhousie University) – *PCP, glutamate and schizophrenia: just say NO*

Dr. Jim Fawcett (Dalhousie University) – *Defining a role for the nitric oxide synthase 1 adaptor protein (NOS1AAP) in the synapse*

Dr. George Robertson (Dalhousie University) – *NO mediates improved cognitive performance produced by erythropoietin in a genetic mouse model of schizophrenia*

Dr. Serdar Dursun (University of Alberta) – *Rapid improvement of schizophrenia symptoms after intravenous administration of the NO donor sodium nitroprusside*

08:30 – 10:30 **Symposium 2**: **Neurogenesis, Stress and Depression** (KC 203)

Chair: Dr. Paul Albert (University of Ottawa)

Dr. Divya Mehta (Max Planck Institute of Psychiatry, Munich, Germany)

The environment matters – environment modulation of genomic risk factors and their role in stress-related disorders

Dr. Tak Pan Wong (McGill University) – *Stress susceptibility and hippocampal function*

Dr. Shawn Hayley (Carleton University) – *Genetic and neurotrophic interactions in depression and its treatment*

Dr. Francis Bambico (University of Toronto) – *Roles for serotonin and neurogenesis in the antidepressant action of deep brain stimulation*

10:30 – 11:00 Coffee Break (KC 200 Financial Galleria)

11:00 – 12:00 **Young Investigator Award Lecture: Dr. Alasdair Barr** (University of British Columbia) – *Translational animal models of antipsychotic drug side-effects* (KC 203)

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Dr. Fabricio Moreira (Federal University of Minas Gerais, Brazil) – *Role of CB1 receptors and TRPV1 channels in brain regions related to anxiety and depression*

Dr. Xia Zhang (University of Ottawa) – *Molecular dissection of cannabis modulation of acute depressive behavior*

Dr. Gabriella Gobbi (McGill University) – *Cannabis consumption among adolescents increases risk for mood disorders: preclinical and clinical studies*

13:30 – 15:30 **Symposium 4**: **Neuropsychopharmacology Research in China: A Window Into Opportunities for Collaboration** (KC 203)

National Natural Science Foundation of China (NSFC) /Canadian Institutes of Health Research (CIHR)

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Dr. Tao Li (Sichuan University, China) – *A longitudinal study of alterations of gray matter volumes in previously treatment-naïve patients with first-episode schizophrenia after 1 year of treatment*

Dr. Qingjun Huang (Shantou University, China) - *Elevated proinflammatory cytokines and white matter abnormalities in brains of chronically stressed rats with depression-like behavior*

Dr. Zhijun Zhang (Southeast University, China) – *SID1900, targeting the TREK1 channel, plays a role in antidepressive treatment*

Dr. Xingshun Xu (Soochow University, China) – *Ahi1, a potential target for neuropsychiatric diseases, regulates early brain development and depression-like behaviors in mice*

Dr. Handi Zhang (Shantou University, China) – *Behavioural and neurochemical alterations in mice exposed to chronic defeat stress during the adolescent period: an in vivo ^{1}H-MRS study at 7T*

15:30 – 16:00 Coffee (KC 200 Financial Galleria)

16:00 – 17:30 **Next Generation Speakers** (KC 203)

Co-Chairs: Drs. Jane Foster (Hamilton) and Darrell Mousseau (Saskatoon)

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Weam Fageera (McGill University) – *Association of catechol-O-methyltransferase (COMT) gene with the reverse placebo effect in children with ADHD*

Jennifer Nyarko (University of Saskatchewan) – *Phosphorylation of the insulin receptor substrate-1 regulates monoamine oxidase-A in primary and immortalized neuronal, but not glial, cultures*

Kevin Hamdullahpur (McGill University) – *Illicit and prescription opiate abuse: understanding treatment failure and improving outcomes*

17:30 – 19:00 Poster Session I (KC 201)

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(Sponsored by CIHR, CCNP and NSFC)

Friday June 20, 2014

07:30 – 08:30 Breakfast (Vistas Dining Room)

08:00 – 17:00 Registration (KC 200 Financial Galleria)

08:30 – 09:30 **Plenary Lecture: Dr. Alan Hudson** (University of Alberta)

Emerging new psychoactive substances: from bath salts to zombie drug, take your pick (KC 203)

09:30 – 10:00 Coffee Break (KC 200 Financial Galleria)

10:00 – 11:00 **Innovations Award Lecture: Dr. Andres Lozano** (University of Toronto) – *Deep brain stimulation for treatment-resistant depression and Alzheimer's disease* (KC 203)

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13:00 – 15.00 **Symposium 5**: **Translating the Healthy Active Lives (HeAL) Declaration for Young People with Psychosis into a Reality**

(KC 205)

Co-Chairs: Drs. Scot Purdon (University of Alberta) and Katherine Aitchison (University of Alberta)

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Dr. Scot Purdon (University of Alberta) – *Metabolic dysfunction in young people with psychosis: a prospective longitudinal follow-up study*

Dr. Katherine Aitchison (University of Alberta) – *A biomarker of weight gain in young people treated with risperidone: a potential route for developing clinical recommendations*

Dr. Adrian Heald (University of Manchester) – *Lifestyle factors contributing to metabolic dysfunction in schizophrenia: there is hope for intervention*

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Chair: Dr. Zelma Kiss (University of Calgary)

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Dr. Rajamannar Ramasubbu (University of Calgary) – *DBS for depression: optimizing stimulus parameters*

Dr. Clinton McCracken (University of Calgary) – *DBS for psychiatry: insights from mechanistic preclinical studies*

Dr. Clement Hamani (University of Toronto) – *Animal models of depression and DBS*

15:00 – 15:30 Coffee (KC 200 Financial Galleria)

15:30 – 16:30 **Heinz Lehmann Award Lecture: Dr. Glenda MacQueen** (University of Calgary) - *Cognitive dysfunction in patients with mood disorders: psychiatry needs help* (KC 203)

17:00 – 19:00 Mentee/Mentor Mixer (MB 252)

18:00 – 19:00 Cocktails (KC 101)

19:00 – 22:00 Banquet (KC 101)

Special Guest Speaker: Dr. Caroline Tait – *The Mental Health of First Nations and Metis Peoples of Canada: What role does intergenerational trauma play?*

(University of Saskatchewan) (approx. 20:00-20:30)

Saturday June 21

07:30 – 08:30 Breakfast (Vistas Dining Room)

08:30 – 11:00 Registration (KC 200 Financial Galleria)

08:30 – 10:00 **Presidential Plenary Lecture: Francesc Artigas, PhD** (Dept. of Neurochemistry & Neuropharmacology, Institut d'Investigacions Biomèdiques de Barcelona, CSIC-IDIBAPS, CIBERSAM, Barcelona, Spain) (KC 203)

Antidepressant effects of RNAi strategies: focus on 5-HT genes"

10:00 – 10:30 Coffee (KC 200 Financial Galleria)

10:30 – 12:30 **Symposium 7**: **Mental Health & Comorbidity Research – "Eureka Discovery" Through Stakeholder Internetwork Collaboration**

(KC 205)

Chair: Dr. Zul Merali (Institute of Mental Health Research, Ottawa)

Dr. Zul Merali (Institute of Mental Health Research) – *Depression and co-occurring illnesses: collaborative research as a pathway to personalized medicine*

Dr. Marco Leyton (McGill University) – *Substance abuse – a concurrent disorder to treat with mental health disorders*

Dr. Darrell Mousseau (University of Saskatchewan) – *Depression and the road to Alzheimer pathology: will it eventually direct us to an effective treatment?*
Dr. Alice Aiken (Canadian Institute for Military & Veteran Health Research) - *The workplace and mental health – a focus on the military milieu*

10:30 – 12:30 **Symposium 8**: **Are Clinical Trials Still Feasible in Psychiatry?**

(KC 203)

Chair: Dr. Thomas Raedler (University of Calgary)

Dr. Stacey Page (University of Calgary) – *Are clinical trials in psychiatry ethical?*

Dr. Thomas Raedler (University of Calgary) – *Clinical trials from the perspective of a Principal Investigator*

Ms. Nita Arora (Hoffman-LaRoche Canada) – *Clinical trials from the perspective of the Pharmaceutical Industry*

Dr. Sandra Harris-Diotte (Stiris Research) – *Clinical trials from the perspective of a Contract Research Organisation (CRO)*

12:30 Closing Remarks (KC 203)

WEDNESDAY JUNE 18th

18:30 – 19:30

Keynote Lecture

Kinnear Centre Room 203

Keynote Lecture

Genetic neuropathology in human brain development and schizophrenia

Dr. Joel Kleinman

Lieber Institute for Brain Development, Johns Hopkins University, Baltimore, MD, USA

Introduction. A number of genetic variations are thought to increase risk for schizophrenia. These genetic variants play a critical role in human brain development. Elucidating the underlying mechanisms involves genetic neuropathology, the study of how genetic variations increase risk for brain disease.

Methods. Postmortem brains of approximately 800 subjects with schizophrenia, bipolar disorder, major depression and controls were donated with informed consent by the next-of-kin (NIMH protocol # 90-M-0142 and NICHD contracts NO1-HD-4 3368 and 3383 approved by the UMD, Baltimore, MD IRB) . Cerebellum from each brain has been genotyped for 650,000 to 1 million SNPs. Expression in prefrontal cortex (PFC), hippocampus and striatum was done with qRT-PCR, microarrays or RNA sequencing. Methylation on PFC was done with arrays.

Results. Genetic variation is associated with specific transcripts in a number of genes implicated in schizophrenia (KCNH2, NRG1-IV, DISC1, GAD1, CACNA1C, DRD2, GRM3 and ZNF804A)($p<0.05$)(for a review see Kleinman JE et al., Biol. Psych.69: 140-145, 2011). An application, Brain Cloud, examines how genetic variation is associated with expression of over 20,000 genes in PFC across the lifespan from week 14 in the fetus to 80 years of age (n=269). There are over 10,000 genetic variation-expression associations ($p<10\text{-}8$ to 10-79) (Colantuoni C et al., Nature 478: 519-523, 2011). PFC epigenetic methylation data relevant to human brain development is also in Brain Cloud (Numata S et al., Am J Human Genet 90: 260-272, 2012.)

Conclusion. Genetic variation that increases risk for schizophrenia involves transcripts that are critical in human brain development.

THURSDAY JUNE 19th

08:15 – 08:30 Opening Remarks
Kinnear Centre Room 203

08:30 – 10:30
Symposium 1
Kinnear Centre Room 205

Symposium 1:
NO (nitric oxide) and schizophrenia: off the bench and into the clinic
Co-Chairs: Dr. Harold Robertson and Dr. Serdar Dursun

08:30 PCP, Glutamate and schizophrenia: Just say NO
Harold Robertson

09:00 Defining a role for the nitric oxide synthase 1 adaptor protein (NOS1AAP) in the synapse
Jim Fawcett

09:30 NO mediates improved cognitive performance produced by erythropoietin in a genetic mouse model of schizophrenia
George Robertson

10:00 Rapid improvement of schizophrenia symptoms after intravenous administration of the NO donor sodium nitroprusside
Serdar Dursun

Thursday, June 19th

Symposium 1: NO (nitric oxide) and schizophrenia: off the bench and into the clinic

PCP, Glutamate and schizophrenia: Just say NO

Harold A. Robertson and Serdar M. Dursun, Departments of Psychiatry and Pharmacology, Dalhousie University, Halifax, NS, Canada

Introduction: Phencyclidine (PCP) is a psychomimetic drug that induces schizophrenia-like symptoms in healthy individuals and exacerbates pre-existing symptoms in patients with schizophrenia. PCP also induces behavioral and cognitive abnormalities in non-human animals, making PCP-treated animals a reliable pharmacological model for schizophrenia. Although PCP interacts with various neuronal systems that are strongly implicated in the pathophysiology of schizophrenia, its most potent effects are on the glutamatergic system. PCP blocks the actions of glutamate, and glutamate, acting through NMDA receptors, appears to be the principal activation signal for neuronal nitric oxide (NO) production. PCP therefore might be expected to decrease neuronal NO levels and restoring NO levels might reverse this effect. Consistent with this idea, PCP has been shown to directly inhibit NO synthase (NOS) activity. It therefore seemed of interest to test the idea that PCP might be acting via NO.

Methods: We studied the effects of the NO donor sodium nitroprusside (SNP) on PCP-induced behavioural changes and neuronal expression of the immediate-early gene c-fos. We also investigated the effects of PCP in animals that had an antisense knockdown of nNOS or a genetic ablation of the nNOS gene.

Results: The NO donor SNP had no effect on normal rat behavior but blocked PCP induced behaviours and changes in c-fos expression. SNP blocked PCP-induced c-fos expression at doses similar to those that suppress PCP-induced behavioural effects.

Conclusion: The glutamate-NO system may represent a novel approach to the treatment of PCP-induced psychosis and schizophrenia. Recent successes in treating schizophrenia with SNP validate the usefulness of the PCP model.

Defining a Role for the Nitric Oxide Synthase 1 Adaptor protein (NOS1AP) in the Synapse

James P. Fawcett, Department of Pharmacology, Dalhousie University, Halifax, NS, Canada.

The formation and function of the neuronal synapse is dependent on the asymmetric distribution of proteins both pre- and post- synaptically. Recently, proteins important in establishing cellular polarity have been implicated in the synapse. We therefore performed a proteomic screen with known polarity proteins and identified novel complexes involved in synaptic function. Specifically, we show that the tumour suppressor protein, Scribble, associates with a Nitric Oxide Synthase binding protein NOS1AP (also known as CAPON). Interestingly, the NOS1AP locus has been

implicated in families with Schizophrenia and is thought to regulate the function of excitatory synapses. I will discuss the role NOS1AP has in the development of the mammalian synapse, and the potential role this protein has in the development of schizophrenia.

NO mediates improved cognitive performance produced by erythropoietin in a genetic mouse model of schizophrenia

George S. Robertson, PhD, Departments of Psychiatry and Pharmacology, Faculty of Medicine, Dalhousie University, Halifax, N.S. B3H 4R2 CANADA

Nitric oxide (NO) is a gaseous chemical messenger produced by nitric oxide synthase (NOS). Genetic association and functional studies have implicated reduced NO signaling in schizophrenia. Erythropoietin is a hematopoietic growth factor that stimulates NOS activity in cultured cells and improves the cognitive performance of schizophrenics. These findings suggest erythropoietin may alleviate cognitive deficits in schizophrenia by increasing central NO production. STOP (stable tubule only polypeptide) null mice display neurochemical and behavioral abnormalities resembling schizophrenia including deficits in the novel objective recognition test (NORT). My laboratory has therefore determined whether the erythropoietin analog darbepoetin alpha (D. alpha) improves NORT deficits in STOP null mice by stimulating neuronal NOS activity. The NORT performance of STOP null mice, but not wild-type littermates, was enhanced 3 h after a single injection of D. alpha (25 µg/kg, i.p.). Improved NORT performance was accompanied by elevated NADPH diaphorase staining in the ventral hippocampus as well as medial and cortical aspects of the amygdala, indicative of increased NOS activity. D. alpha significantly increased NO metabolite levels (nitrate and nitrite, NOx) in the hippocampus of both wild-type and STOP null mice. The NOS inhibitor, N (G)-nitro-L- arginine methyl ester (L-NAME; 25 mg/kg, i.p.), completely reversed the increase in hippocampal NOx levels produced by D. alpha. Moreover, L-NAME also inhibited the ability of D. alpha to improve the NORT performance of STOP null mice. Taken together, these results suggest D. alpha enhanced the NORT performance of STOP null mice by increasing production of NO.

Rapid improvement of schizophrenia symptoms after intravenous administration of the NO donor sodium nitroprusside

Serdar Dursun[1,2], MD, PhD, FRCPC and Jaime Hallak [1,2], MD, PhD
[1]Neurochemical Research Unit, Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada and [2]National Institute of Science and Technology in Translational Medicine, Ribeiro Preto, Brazil

Introduction: Pharmacotherapy of schizophrenia continues to be a challenge, and current antipsychotic drugs are far from ideal. In the search for additional antipsychotics, there has been increased interest in the glutamate-nitric oxide (NO)-cyclic GMP network as a possible target. Preclinical findings showing that the NO donor sodium nitroprusside (SNP) abolished the behavioural effects and c-fos expression induced by

the NMDA receptor blocker phencyclidine led us to believe that clinical studies should be conducted with this drug.
Methods: Studies were conducted in a university teaching hospital in Ribeiro Preto, Brazil. The participants were inpatients aged 19 to 40 years who were diagnosed with schizophrenia, were in the first five years of the disease and were taking antipsychotics other than clozapine. SNP (0.5 ug/kg/min) or placebo were administered for 4 hours and the effects on positive, negative, anxiety and depression symptoms were observed. The main outcome measures were the 18-item Brief Psychiatric Rating Scale (BPRs) and the negative subscale of the Positive and Negative Syndrome Scale.
Results: Improvement of symptoms was observed within 4 hours after SNP infusion ended. There were significant differences between the SNP and placebo groups in the 18-item BPRs total score and subscale scores, and these persisted for 4 weeks after infusion.
Conclusion: The remarkable findings with SNP in this small clinical trial indicate that additional studies on SNP in schizophrenia are warranted.

THURSDAY JUNE 19th

08:30 – 10:30

Symposium 2

Kinnear Centre Room 203

Symposium 2:
Neurogenesis, Stress and Depression
Chair: Dr. Paul Albert

08:30	The environment matters – environment modulation of genomic risk factors and their role in stress-related disorders *Divya Mehta*
09:00	Stress susceptibility and hippocampal function *Tak Pan Wong*
09:30	Genetic and neurotrophic interactions in depression and its treatment *Shawn Hayley*
10:00	Roles for serotonin and neurogenesis in the antidepressant action of deep brain stimulation *Francis Bambico*

Thursday, June 19th

Symposium 2: Neurogenesis, Stress and Depression

The environment matters - environmental modulation of genomic risk factors and their role in stress-related disorders

Divya Mehta [1, 2], Elisabeth B Binder [2, 3]
The University of Queensland, Queensland Brain Institute, Brisbane, Australia[1]
Max Planck Institute of Psychiatry, Munich, Germany[2]
Emory University, Atlanta, USA.[3]

There is an intricate mesh of genetic and environmental risk factors and these modulate risk for psychiatric diseases via gene expression and DNA methylation changes. Research findings from our group in identification of distinct biological subtypes of PTSD based on genetic (Mehta et al, Archives of General Psychiatry, 2011) or environmental risk factors (Mehta et al, PNAS, 2013) will be discussed. These studies have revealed that early life stress can trigger global changes in DNA methylation and gene expression profiles that persist into adulthood, conferring risk for PTSD, depression and other psychiatric disorders. Moreover, depending on the presence or absence of childhood maltreatment, distinct and almost non-overlapping biological pathways are altered among patients with PTSD. The gene expression changes observed only in PTSD patients with childhood maltreatment are driven by up to 12 fold higher by changes in DNA methylation, highlighting distinct biology of PTSD depending on early environment. These results indicate that even among individuals with the same diagnosis (i.e. PTSD), distinct biological underpinnings are observed, raising the critical question whether these individuals would benefit from separate treatments. These findings have implications for psychiatric disease prognosis and treatment.

Stress susceptibility and hippocampal function

T.P. Wong
McGill University, Department of Psychiatry, Douglas Mental Health University Institute, Montreal, Canada

Although stressful life events are risk factors for several stress-related psychiatric disorders such as depression and post-traumatic stress disorder, not everyone experiencing stressful life events develops those disorders. Understanding biological factors that underlie individual differences in stress susceptibility could explain why some individuals are vulnerable to stress-related psychiatric disorders. Recent findings suggest that individual differences in stress susceptibility are related to alterations of the brain reward system, in particularly the mesolimbic dopaminergic pathway. Another brain region that has been highly implicated in stress-related psychiatric disorders is the hippocampus. The hippocampus plays important roles in the negative feedback of the hypothalamic-pituitary-adrenal axis. Importantly, hippocampal shrinkage has been frequently observed in patients with stress-related psychiatric disorders. Nonetheless, little is known about whether changes in hippocampal structure and function contribute to individual differences in stress susceptibility. In this talk, I will present findings we

obtained from the chronic social defeat model, which allowed us to separate mice that are susceptible or resilient to chronic stress, to reveal potential contributions of the hippocampus to stress susceptibility. Using a longitudinal magnetic resonance imaging (MRI) approach, we examined changes in hippocampal volume in mice before and after they experienced chronic social defeat stress. We found that a bigger hippocampus before stress correlated with higher stress susceptibility. In addition, normal hippocampal growth that was found between pre- and post-stress MRI scans in control and resilient mice was arrested in susceptible mice. Since stress-related hippocampal volume changes may involve activation of NMDA subtype of glutamate receptors, we hypothesized that changes in hippocampal NMDA receptor function affect stress susceptibility. Indeed, we found that not only synaptic NMDA receptor function in susceptible mice was higher than resilient and control mice, susceptible mice also exhibited lower extrasynaptic NMDA receptor function than other mouse groups. Taken together, these findings strongly suggest that alterations of hippocampal structure and function are related to individual differences in stress susceptibility.

Genetic and neurotrophic interactions in depression and its treatment

Shawn Hayley, Darcy Litteljohn, Warren Caldwell, Megan Osborn, Sara Ramzjou, Melanie Clarke, Chris Rudyk, Hymie Anisman. Department of Neuroscience, Carleton University, Ottawa, ON, Canada

Introduction: Depression is often a lifelong condition associated with multiple relapses and, in many cases, treatment resistance. It is hypothesized that changes in neuroplasticity [e.g. brain derived neurotrophic factor (BDNF), neurogenesis] and neuroinflammatory (e.g. cytokines, microglia) processes might underlie the protracted nature of depressive pathology.
Methods: Three lines of interrelated research are presented: 1.) Human studies that assessed BDNF levels, as well as the Val66Met polymorphism in relation to depression or coping, 2.) Parallel stressor-based animal models that evaluated novel antidepressant strategies involving ketamine and the hematopoietic cytokine, erythropoietin (EPO) and finally, 3.) Animal work that assessed stressful and pro-inflammatory challenges together and in mice lacking the protein, leucine-rich repeat kinase 2 (LRRK2), which has been linked to the inflammatory immune system.
Results: 1.) Individuals diagnosed with depression and died by suicide had gender and brain region-specific reductions of BDNF. Coping style was influenced by Vall66Met genotype. 2.) Ketamine and EPO treatments had antidepressant-like consequences and promoted hippocampal neurogenesis 3.) Immune and stressor challenges additively induced neurohormonal outcomes and these were modulated by LRRK2 knockout.
Conclusion: Alterations of neurotrophic and neuroimmune systems appear to contribute to depressive pathology. In particular, deficits in neurogenesis and BDNF, along with heightened inflammatory activation might be particularly important for cases of treatment resistance. Hence, novel treatments, such as ketamine and EPO, or possibly, combinations of neurotrophic and anti-inflammatory factors might be a useful future clinical approach.

Thursday, June 19th

Roles for serotonin and neurogenesis in the antidepressant action of deep brain stimulation

Francis R. Bambico, PhD Research Imaging Centre, Centre for Addiction and Mental Health (CAMH) and University of Toronto, Toronto, ON, Canada

Introduction: Deep brain stimulation (DBS) is a surgical intervention for motor and psychiatric disorders. It involves the use of a pacemaker that systematically delivers electrical current into a target brain structure. High frequency and low power DBS directed at the medial prefrontal cortex (mPFC) has been shown to elicit antidepressant-like effects in animal models, but its therapeutic-like mechanism has not yet been fully elucidated.
Methods: To understand the neurobehavioural changes associated with mPFC DBS, we employed the chronic unpredictable stress (CUS) model of depression, exposing rats to at least 4 weeks of stressors. We then tested the effect of 3 weeks of mPFC DBS on depressive-like reactivity (reduced sucrose preference/SP) and other affect-related behaviours. We also examined effects on serotonergic neurotransmission (electrophysiology), BDNF expression (ELISA) and hippocampal neurogenesis (immunohistochemistry).
Results: CUS resulted in an anhedonia-like progressive decrease in sucrose preference (SP), which was reversed by 3 weeks of mPFC DBS. In parallel, DBS increased prefrontocortical BDNF and enhanced serotonergic neurotransmission and the tonic activity of 5-HT1A receptors in the hippocampus. These were associated with an increase in the number of BrdU-positive cells in the hippocampus indicating an increase in neurogenesis. These effects of DBS will be discussed in comparison to the known action of conventional and other experimental antidepressant treatments.
Conclusion: mPFC DBS appears to elicit antidepressant-like activity by recruiting a serotonin-modulating mechanism. This results in pro-neurogenic effects in the hippocampus, which may be linked to the enhanced tonic input on hippocampal 5-HT1A receptors.

THURSDAY JUNE 19th

11:00 – 12:00

Young Investigator Award Lecture

Kinnear Centre Room 203

Young Investigator Award Lecture

Translational Animal Models of Antipsychotic Drug Side-Effects

Dr. Alasdair Barr

Alasdair M. Barr[1], Ph.D.; Heidi N. Boyda[1], Ph.D.; Catherine C.Y. Pang[1], Ph.D., William G. Honer[2], M.D., Ric M. Procyshyn[2], Pharm.D., Ph.D. [1] Departments of Pharmacology and [2]Psychiatry, University of British Columbia, Vancouver, BC, Canada

Introduction: Over the past two decades, there has been a notable increase in the use of antipsychotic drugs, as they are prescribed to treat an expanding number of neuropsychiatric indications. This rise has been led predominantly by greater use of the second generation antipsychotic (SGA) drugs, which have a low incidence of neurological side-effects. However, many SGAs cause metabolic and cardiac dysregulation, increasing the risk of cardiometabolic disorders. Presently, we describe some of our experience working with translational animal models of SGA drug side-effects.

Methods: To measure the effects of SGAs on loss of glycemic control and insulin resistance, which represent the core symptoms of Type 2 diabetes mellitus, adult female rats were treated acutely or chronically with the SGA drugs olanzapine, iloperidone, lurasidone and asenapine. Glycemic control was measured with the glucose tolerance test, while insulin resistance was measured with the hyperinsulinemic euglycemic clamp. The effects of different antidiabetic drugs and exercise on SGA-induced glucose intolerance were also measured.

Results: SGAs displayed a range of different metabolic liability, consistent with the human literature. Greatest metabolic effects were observed with olanzapine and iloperidone. Glucose intolerance with chronic treatment with olanzapine did not change over time. Both exercise and specific combinations of the antidiabetic drugs metformin, rosiglitazone and glyburide improved glycemic control.

Conclusion: Animal models can accurately model the human side-effects of antipsychotic drugs, and will be essential for understanding the physiological mechanisms involved.

THURSDAY JUNE 19th

13:30 – 15:30

Symposium 3

Kinnear Centre Room 205

Symposium 3:

Cannabis and Mood Disorders: From Animal Developmental Research to Clinical Studies

Co-Chairs: Dr. Xia Zhang and Dr. Gabriella Gobbi

13:30	Molecular dissection of cannabis sensitivity in the developing brain *Tibor Harkany*
14:00	Role of CB1 receptors and TRPV1 channels in brain regions related to anxiety and depression *Fabricio Moreira*
14:30	Molecular dissection of cannabis modulation of acute depressive behavior *Xia Zhang*
15:00	Cannabis consumption among adolescents increases risk for mood disorders: preclinical and clinical studies *Gabrielle Gobbi*

Thursday, June 19th

Symposium 3: Cannabis and Mood Disorders: From Animal Developmental Research to Clinical Studies

Molecular dissection of cannabis sensitivity in the developing brain

Tibor Harkany, PhD, Division of Molecular Neurobiology, Department of Biochemistry and Biophysics, Scheeles vag 1:A1, Karolinskja Institute , SE-17177 Stockholm, Sweden and School of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom

Introduction: Besides acting as retrograde messengers in the adult nervous system, endocannabinoids have recently emerged as modulators of neuronal development. Available data furnish the hypothesis that a continuum of endocannabinoid actions overarches the differentiation and postnatal modulation of particular synapses. My laboratory has dissected the molecular and cell biology of endocannabinoid signalling in developmental contexts by describing its anatomical blueprint, characterizing roles in neurogenesis, cell migration, and axonal growth and guidance, and highlighting molecular hubs for endocannabinoid signal diversification and upstream control. However, it is unknown whether Δ^9-tetrahydrocannabinol (THC) can trigger a cannabinoid receptor-driven molecular cascade to disrupt neuronal specification, imparting permanent structural deficits.
Methods: Neuroanatomy, iTRAQ protein profiling and biochemistry, mRNA quantification and neurophysiology in mouse models and in human fetal specimens were deployed to link THC action to cytoskeletal reorganization in cortical neurons provoking long-lasting alterations of synaptic wiring of the cerebral cortex.
Results: We established that repeated THC exposure erroneously times CB_1 cannabinoid receptor activation to rewire the fetal cortical circuitry. By interrogating the THC-sensitive neuronal proteome we identified Superior Cervical Ganglion 10 (SCG10)/stathmin-2, a microtubule-binding protein in axons, as a substrate of altered neuronal connectivity. We found SCG10 reduced in the hippocampus of midgestational (week 18-22) human fetuses exposed *in utero* to cannabis, defining SCG10 as the first cannabis-driven molecular effector of the developing cortical circuitry. CB_1 cannabinoid receptor activation recruits c-Jun N-terminal kinases to phosphorylate SCG10, promoting its rapid degradation *in situ* within motile axons and microtubule stabilization. In doing so, THC enables ectopic formation of filopodia and neurite branching.
Conclusions: Our data highlight key sites of neuronal vulnerability to phytocannabinoids in the developing cerebral cortex, and define the maintenance of cytoskeletal dynamics as a first-order molecular target for cannabis whose imbalance can greatly limit the computational power of neuronal circuitries in affected offspring.

Thursday, June 19th

Role of CB1 receptors and TRPV1 channels in brain regions related to anxiety and depression

Fabricio A. Moreira, PhD, Department of Pharmacology, Institute of Biological Sciences, Federal University of Minas Gerias, 31270-901, Belo Horizonte, Brazil.

Introduction: Anandamide exerts its functions in the brain largely though the activation of cannabinoid CB1 receptors. Nonetheless, evidence has emerged that it may also bind TRPV1 channels. These targets seem to mediate opposite functions of anandamide on neural activity and neurotransmitter release. Therefore, we have been investigating how they work in concert in certain brain regions controlling responses to stressful stimuli. Our working hypothesis is that CB1 inhibits, whereas TRPV1 facilitates, anxiety- and depression-related behaviours.
Methods: Behavioural paradigms in mice and rats, molecular biology, immunohistochemistry.
Results: The anxiolytic- and antidepressant-like effects of cannabinoids were mimicked by local injection into the dorsal periaqueductal gray (DPAG) and the medial prefrontal cortex (mPFC). The responses to non-selective cannabinoids were reproduced with selective CB1 agonists and prevented by selective antagonists. Similarly to CB1 agonists, TRPV1 antagonists also induced both anxiolytic- and antidepressant-like effects when injected into the DPAG and the mPFC. We also found that these receptors are co-localized in these brain regions, further suggesting that a reciprocal interaction can exist among them.
Conclusions: We have demonstrated that CB1 receptors and TRPV1 channels have opposite functions in modulating behavioural responses to aversive stimuli. The overt effect of anandamide may depend on which of these targets is preferentially activated in certain brain regions. Further understanding these mechanisms may help to explain the complex role of this endocannabinoid/endovanilloid in responses related to anxiety and depression.

Molecular dissection of cannabis modulation of acute depressive behavior

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Introduction: Synthetic cannabinoid (sCB) can produce acute antidepressant effects, but its underlying mechanism is unclear. We have recently showed that an acute sCB exposure produces in vivo long-term depression (LTD) at hippocampal CA3-CA1 synapses through sequential activation of astroglial CB1R and postsynaptic glutamate receptors [Han et al, Cell 2012, 148: 1039-1050]. This study aimed to explore the role of sCB-elicited astroglial LTD in the modulation of acute depressive behaviour.
Methods: We employed behavioural paradigms and in vivo electrophysiological recordings.
Results: We treated naïve mice with increasing doses of HU210 before the forced swimming test. The 50 and 100 microgram/kg doses of HU210 significantly suppressed and enhanced immobility, respectively. The suppression and enhancement effects of

HU210 were completely blocked by pretreatment of mice with the LTD-blocking peptide Tat-GluR2 and the GABA-A receptor agonist muscimol, respectively. We will soon conduct behavioral and electrophysiological experiments on mutant mice with a selective deletion of CB1R gene from astroglial cells, gutamatergic and GABAergic neurons. Conclusion: We propose that low dose sCB suppresses despair behavior through astroglial-LTD at CA3-CA1 synapse overpasses, whereas high dose sCB enhances despair behavior through activation of presynaptic CB1R in GABAergic synapses.

Cannabis consumption among adolescents increased risk for mood disorders: preclinical and clinical studies

Gabriella Gobbi, MD, PhD, Francis R Bambico, Department of Psychiatry, McGill University, Montreal, QC H3H 1A1, Canada.

Introduction: Cannabis is the most abused illicit substance in the world by adolescents, with reports of unabated escalation in the last decades. This is particularly alarming, since clinical retrospective correlational and longitudinal prospective studies have suggested that its long-term use early in life increases the risk for anxiety, depression, and amotivational syndrome, as well as other mental diseases, including schizophrenia.
Methods: Clinical and epidemiological studies on the impact of cannabis on mood disorders are reviewed, along with fundamental research carried out in laboratory animals, using behavioral paradigms and in vivo electrophysiology.
Results: The risk of developing depression increases if cannabis is smoked in younger age (preadolescence) and in heavy consumers. In preclinical research, my laboratory has targeted the neurobiological mechanisms at the root of the influence of cannabis on depression and anxiety in adolescents. Teenager rats who are exposed to cannabis or synthetic CB1 agonists have decreased levels of serotonin firing activity, which leads to mood disorders and anhedonia or lack of pleasure, as well as increased norepinephrine activity, which leads to greater long-term susceptibility to stress and anxiety. Even if cannabis use was stopped at the end of adolescence, changes are still detectable in adulthood. On the other hand, the consumption of cannabis in adulthood in rats does not produce long-term consequences in monoamine systems and anxiety/depression-related behaviours.
Conclusion: Translational studies suggest that adolescence is a vulnerable period for cannabis exposure and society should be warned about the use of cannabis in young people.

THURSDAY JUNE 19th

13:30 – 15:30

Symposium 4

Kinnear Centre Room 203

Symposium 4:

Neuropsychopharmacology Research in China: A Window Into Opportunities for Collaboration

Co-Chairs: Dr. Tony Phillips (CIHR), Dr. Xin-Min Li (CCNP) and Dr. Zhijun Zhang (NSFC)

13:30	A longitudinal study of alterations of gray matter volumes in previously treatment-naïve patients with first-episode schizophrenia after 1 year of treatment *Tao Li*
13:50	Elevated proinflammatory cytokines and white matter abnormalities in brains of chronically stressed rats with depression-like behavior *Qingjun Huang*
14:10	Effects of atypical antipsychotics (APDs) on vascular mood and cognitive disorders and regulating the proliferation and differentiation of oligodendrocytes in global cerebral ischemia (GCI) mice *Xiaoying Bi*
14:30	SID1900, targeting the TREK1 channel, plays a role in antidepressive treatment *Zhijun Zhang*
14:50	Ahi1, a potential target for neuropsychiatric diseases, regulates early brain development and depression-like behaviors in mice *Xingshun Xu*
15:10	Behavioural and neurochemical alterations in mice exposed to chronic defeat stress during the adolescent period: an in vivo ^{1}H-MRS study at 7T *Handi Zhang*

Thursday, June 19th

Symposium 4: Neuropsychopharmacology Research in China: A Window Into Opportunities for Collaboration

A longitudinal study of alterations of gray matter volumes in previously treatment-naive patients with first-episode schizophrenia after 1 year of treatment

Mingli Li[1], Wei Deng[1], Qiang Wang[1], Lijun Jiang[1], Xiaohong Ma[2], Yingcheng Wang[2], Qiyong Gong[3], Tao Li[1, 2]*. [1] The Mental Health Center & Psychiatric laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [2] The State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China,[3] Huaxi MR Research Center, Department of Radiology, West China Hospital, Sichuan University, Chengdu, China

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Background: It has been suggested that structural and functional abnormalities of gray matter play an important role in the pathophysiology of schizophrenia. Patients with schizophrenia exhibit significant gray matter reduction. Progressive volume decrease in first-episode patients with schizophrenia has been shown in many studies. However, it is not clear whether treatment with antipsychotics is associated with alterations of gray matter volume, and whether higher doses of antipsychotics are associated with this reduction of gray matter volume. The purpose of the present study was to quantify brain structural change in first-episode, drug-naïve patients with schizophrenia after 6 weeks of antipsychotic treatment, and to explore the relationship between brain volume change and psychopathology improvement in order to identify potential biological indicators of treatment efficacy.
Methods: Thirty-four patients with first-episode schizophrenia were recruited from the Mental Health Center in West China Hospital in the present study. All patients were experiencing their first-episode of psychosis and were treatment-naïve when recruited to the study. They were assessed by a trained psychiatrist using the Structured Clinical Interview for the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) (SCID-P), and were found to fulfill diagnostic criteria for schizophrenia or schizophreniform psychosis as described in DSM-IV. All patients diagnosed with schizophreniform psychosis were followed up for at least 6 months and found to meet the DSM-IV diagnosis criteria of schizophrenia. Before the patients took any antipsychotic medication, all patients underwent assessment of psychopathology and social function by an experienced psychiatrist using the positive and negative syndrome scale (PANSS) and global assessment function scale (GAF), respectively. All patients also underwent MRI brain scans at baseline. At 6 months and 1 year follow-up, MRI scans and clinical assessments were scheduled for all patients. All patients were scanned on a Signa 3.0-T scanner (General Electric, Medical Systems, Milwaukee, WI,

USA) in the Department of Radiology at West China Hospital. High resolution T1 images were acquired by 3D spoiled gradient echo sequence (SPGR). All patients with schizophrenia received anti-psychotic medication, including risperidone, olanzapine, quetiapine, aripiprazole, sulpiride and haloperidol, according to the case-clinician's preference. The average daily dose of antipsychotic medication taken by each patient were recorded and converted to chlorpromazine equivalent dosages. There were 16 patients with the daily dose of antipsychotic <200mg (chlorpromazine equivalent) (low-dose group) and 18 patients with ≥ 200mg (high dose group) in the maintenance period after 6 months.
Results and conclusions: There was a significant decrease in frontal and temporal cortex in the 6 month and 12 month follow-up period in both low and high dose groups. This volume change was negatively correlated with drug doses during the initial 6 month follow-up period. However, decreased volume in frontal and temporal cortex, to some extent, could be reversed in the low dosage group but there was a progressive decrease in the high dose group in the following 6 month follow-up. Volume of parahippcampus and amygdala were increased at 12 months when compared to 6 months in both groups. The association of dose of antipsychotics with decreased gray matter volume in schizophrenia merits further investigation and replication in larger longitudinal studies.
Acknowledgments: This work was partly funded by National Nature Science Foundation of China (81130024, 30530300 and 30125014), National Key Technology R & D Program of the Ministry of Science and Technology of China during the 12th Five-Year Plan (2012BAI01B06), the Ph.D. Programs Foundation of Ministry of Education of China (20110181110014).

Elevated proinflammatory cytokines and white matter abnormalities in brains of chronically stressed rats with depression-like behavior

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Background: Depression is an incapacitating psychiatric ailment affecting about 21% of the world population. The pathogenesis of this psychiatric disorder remains largely unknown. Of the proposed hypotheses, the so-called 'cytokine hypothesis of depression' claims that proinflammatory cytokines are the key factors in mediating behavioral, neuroendocrine and neurochemical features of depressive disorders. Previous human and animal studies suggest that both proinflammatory cytokines and

pathological oligodendrocytes (OLs) are two important factors in the pathophysiology of depression. This study examined these two factors in the brains of rats following 4 weeks of unpredictable chronic mild stress. The hypothesis was that chronic stress may affect OLs and elevate proinflammatory cytokines in the brain.
Methods: Male Sprague-Dawley rats (8 weeks old, 220-270 g) were purchased from the Animal Center of Shantou University Medical College. The rats in the stressed group were housed individually in small cages and subjected to various stressors according to a 'random' schedule for 4 weeks. The control group was undisturbed except for necessary procedures such as routine cage cleaning. Behavioral tests, including open-field test, forced swimming test and sucrose preference test, were conducted after 4 weeks of exposure to stressors.
MBP expression, number of oligodendrocytes, and the expression of IL-6, IL-1β, and TNF-α were examined with immunohistochemical staining in prefrontal cortex, corpus callosum, internal capsule, external capsule, caudate putamen, hippocampus and hypothalamus.
Results and conclusions: 4 weeks of unpredictable chronic mild stress induced depression-like behavior in the forced swimming test, open-field test and sucrose preference test. Immunoreactivities of IL-6, IL-1β, and TNF-α were increased in different brain areas after chronic stress. White matter was assessed by LFB-PAS staining and immunohistochemical staining with antibodies to MBP and GST-π. LFB-PAS staining did not detect any demyelination in the examined brain regions of stressed rats. MBP immunoreactivity was significantly decreased in some brain areas of stressed rats compared to controls. As expected, the number of OLs in prefrontal cortex was also significantly decreased in stressed rats compared to controls.
Acknowledgments: This study was funded by National Nature Science Foundation of China (30770771 and 30370518).

Effects of APDs on vascular mood and cognitive disorders and regulating the proliferation and differentiation of oligodendrocytes in global cerebral ischemia (GCI) mice

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Objective: Ischemic injury of oligodendrocytes (OLs) resulting in impaired axonal conduction and reduction in transmission speed may be an important reason for vascular mood and cognitive disorders. Our previous research indicated that atypical antipsychotic drugs (APDs) prevented OL injury. In the present study, we investigated the effects of APDs on behavioral changes, OL survival and development in the brains of cerebral global ischemia (GCI) mice.

Thursday, June 19th

Methods: The mice were treated with APDs or vehicle for two weeks prior to GCI surgery. After behavioral tests, mice were sacrificed and the brains were collected for immunohistochemistry staining and western blotting. Mature OLs and OL progenitors were identified using anti-GST-pi and anti-NG2 antibodies respectively. Cell proliferation and differentiation were analyzed by co-localization of NeuN, GFAP, GST-pi, NG2 and Bromodeoxyuridine (BrdU). Myelination and demyelination were detected by Western Blotting of MBP.
Results: GCI mice showed significant behavior disorders and decreased mature OL numbers in hippocampus. APD pretreatment significantly attenuated the behavioral changes, prevented the OL loss and enhanced the OL progenitor cell genesis and maturation.
Conclusion: These results indicate that the mechanism of APDs in the therapy of vascular psychiatric disorders may be the effects in protecting OLs and myelin from ischemic injury and promoting OL restoration during recovery.
Key Words: global cerebral ischemia; oligodendrocyte; APDs; quetiapine; progenitor

SID1900, targeting the TREK1 channel, plays a role in antidepressive treatment
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The present study involved screening, identification and antidepressive behavioral evaluation of a TREK1 channel blocker, and further observed the effect of the screened blocker on the field potential and expression of PKA-CREB-BDNF signaling in the dorsal raphe nucleus (DRN), hippocampus CA1/CA3 and PFC of CUMS-modeling rats. This research involved screening of 487 compounds with selected affinity to potassium channels (IC_{50}: 40nM-120μM) from the National Chemical Library of Shanghai Institute of Materia Medica affiliated Chinese Academy of Sciences by using FluxOR™ high throughput screening (HTS). The data showed that compounds SID1900 and A1899 might inhibit TREK1 channel activity. The IC_{50} value for inhibition of the TREK1 channel activity by SID1900 was 28.72μM, and that of A1899 was 67.54μM. Consequently, SID1900 was applied in subsequent experiments related to the selection criteria (IC_{50}<50μM, Titus SA et al., 2009). SID1900 was further assessed for sensitivity to TREK1 channels by patch clamp, and the results indicated that SID1900 could block TREK1 channel currents in HEK293 cells in a dose-dependent manner (IC_{50}=29.72μM). SID1900 did not block Na^+, mixed K^+ or Ca^{2+} channel currents in hippocampal pyramidal neurons, which indicated this compound is a specific blocker of K_2P channels. Pharmacokinetic data revealed that SID1900 has satisfactory blood-brain barrier (BBB) permeation and biological availability (78.03±9.65%). A study, based on use of the chronic unpredictable mild stress model assessed the antidepressant effect of SID1900 (5.1mg/kg) by utilizing the force swimming test, the sucroce preference test and an open field test. The behavioral data showed that a 2 week treatment with SID1900 reversed behavioral deficits. A similar effect was observed in rats treated for 2 weeks with spadin (a blocker of TREK1, 0.1mg/kg; Jean Mazella et al. 2010). The onset of SID1900 was superior to that of citalopram (10mg/kg, 3 weeks treatment to onset). Electrophysiological experiments in vivo indicated that SID1900

enhanced the firing rate of serotonergic neurons in rat dorsal raphe nuclei (21.43±3.21spikes/10s, 1.43-fold higher compared with control), which indicated that SID1900 could enhance release of and transmission by serotonin in dorsal raphe nuclei and have similar antidepressant actions to spadin. Western blotting and real-time PCR data showed that 2 weeks treatment with SID1900 upregulated expression of PKA-CREB-BDNF signaling in dorsal raphe nuclei (DRN), hippocampus CA1/CA3 and PFC of CUMS-modeling rats compared with CUMS-depressive rats (p<0.001), and a similar effect was observed in rats treated for 2 weeks with spadin or 4 weeks with citalopram. In addition, a 1 day treatment with SID1900 and 8-OH-DPAT (5-HT_{1A} receptor agonist) upregulated expression of PKA-CREB-BDNF signaling in primary-cultured hippocampal neurons compared with single SID1900 treatment. Meanwhile a 1 day treatment with SID1900 and WAY100635 (5-HT_{1A} receptor antagonist) down-regulated significantly expression of PKA-CREB-BDNF (p<0.05), which demonstrated that SID1900 blocked TREK1 channnel to upregulate PKA-CREB-BDNF signaling mediated by the 5-HT_{1A} receptor.
Therefore, the screened compound SID1900 might block TREK1 channels efficiently and induce a rapid antidepressant response, which could be related to a satisfactory BBB permeation rate, improvement of 5-HT transmission and downstream signal transduction of 5-HT receptors.

Ahi1, a potential target for neuropsychiatric diseases, regulates early brain development and depression-like behaviors in mice

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Mutations of Abelson helper integration site-1 (AHI1) is a cause of Joubert syndrome, an autosomal recessive neurological development disorder associated with abnormal axonal decussation. Recent multiple fine mapping, association, and replication studies have identified that AHI1 is a susceptibility gene for schizophrenia and autism, two major neuropsychiatric disorders with comorbid depression. Given the association of AHI1 with these neuropsychiatric diseases, it is important to investigate how Ahi1 dysfunction in mouse brains can lead to the neurological phenotypes or psychiatric phenotypes. In Ahi1 KO neonatal mice, retarded growth was observed. Mass spectrometry analysis confirmed that Ahi1 binds cell cycle exit and neuronal differentiation protein 1 (Cend1), a neuronal protein that mediates neuronal differentiation. Ahi1 KO reduced Cend1 levels in brain regions; however,

overexpression of Cend1 rescued the neurite extension defects in hypothalamic neurons of Ahi1 KO mice. Over-expressed Ahi1 increased Cend1 level in cultured neurons. These suggested that Ahi1 deficiency reduced neuronal differentiation and delayed early brain development by affecting the stability of Cend1 protein. Adult Ahi1 KO mice showed depression-like behaviors: immobility time in the tail suspension test and forced swimming test markedly increased in Ahi1 KO mice. Total TrkB and phosphorylated TrkB were found to decrease in theseAhi1 KO mice. Over-expression of TrkB in the amygdale alleviated depression-like behaviors. Further findings indicated that Ahi1 deficiency promoted the degradation of endocytic TrkB and reduced TrkB recycling in neuronal cells. Impaired endocytic sorting of TrkB in Ahi1 deficiency mice suggested that Ahi1 may be involved in the cellular trafficking related to depression. Due to delayed brain development and depression-like behaviors caused by Ahi1 deficiency, therefore, Ahi1 is a potential therapeutic target for neuropsychiatric diseases.

Acknowledgments： This work was supported by the grants from National Natural Science Foundation of China (81071095 and 81120108011).

Behavioural and neurochemical alterations in mice exposed to chronic defeat stress during the adolescent period: an in vivo ^{1}H-MRS study at 7T

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Background: Chronic psychosocial stress during the adolescent period is a risk factor for emotion- related disorders such as depression, anxiety and post-traumatic stress disorder. The disturbance of adolescent brain development may be the underlying mechanism for the onset of these disorders. We aimed to dynamically examine both the behaviour and neurochemical alterations in mice exposed to chronic stress during the adolescent period.
Methods: Adolescent Balb/c mice were divided into control and stress groups. Mice in the stress group were exposed to intermittent chronic social defeat stress for 2 weeks. Behaviour, including locomotor activity, anxiety status and social interaction were

evaluated right after the stress and 3 weeks later. At both time points, neurochemical changes were assessed in the frontal cortex of mice by ^{1}H-MRS at 7T.
Results: Right after exposure to stress, mice showed hypoactivity and decreased social interaction when interacting with a novel CD1 mouse, which they had been beaten by during the previous stress process. Stressed mice displayed comparative locomotor activity 3 weeks later, but still demonstrated impaired social interaction. The anxiety status and social interaction with a novel Balb/c mouse was not changed at either time point examined. The concentrations of Cr+pCr and Glu+Gln were lower right after stress in these mice, but not 3 weeks later. However, the concentrations of NAA decreased and NAAG increased only 3 weeks after stress.
Conclusion: These results indicate that adolescent chronic stress leads to both short-term and long-term behavioural and neurochemical changes which may be relevant to the pathophysiology of emotion- related disorders.
Acknowledgments: This work was funded by National Natural Science Foundation of China (81301170).

THURSDAY JUNE 19th

16:00 – 17:30

Next Generation Symposium

Kinnear Centre Room 203

Next Generation Symposium

Co-Chairs: Dr. Jane Foster and Dr. Darrell Mousseau

16:00 Neuroprotection by improved mitochondrial performance

Matthew Nichols

16:20 Association of catechol-O-methyltransferase (COMT) gene with the reverse placebo effect in children with ADHD

Weam Fageera

16:40 Phosphorylation of the insulin receptor substrate-1 regulates monoamine oxidase-A in primary and immortalized neuronal, but not glial, cultures

Jennifer Nyarko

17:00 Illicit and prescription opiate abuse: understanding treatment failure and improving outcomes

Kevin Hamdullahpur

Thursday, June 19th

Next Generation Symposium

Neuroprotection by improved mitochondrial performance

Matthew J Nichols and George S Robertson, PhD. Departments of Psychiatry and Pharmacology, Faculty of Medicine, Dalhousie University, Halifax, N.S. B3H 4R2 CANADA

Habitual consumption of dietary flavonoids known to reduce the excessive production of reactive oxygen species by improving mitochondrial function decreases the risk of Parkinson's disease, stroke and dementia. In view of these findings, we have developed a flavonoid-enriched extract from apple peel termed AF4 that dramatically reduces neuronal cell loss, neuroinflammation and motor deficits in our mouse models for stroke and multiple sclerosis. We report here for the first time that quercetin and epicatechin, the two most abundant flavonoids in AF4, are primarily responsible for the neuroprotective effects of this flavonoid-enriched extract. Combining quercetin with epicatechin resulted in supra-additive reductions in the death of primary cultures of mouse cortical neurons exposed to a lethal period of oxygen glucose deprivation. This was accompanied by synergistic increases in the expression of mitochondrial genes encoding members of the electron transport chain. Furthermore, neuroprotection produced by quercetin and epicatechin was accompanied by increases and decreases in mRNA levels for bcl-2 (anti-apoptotic) and p53 (pro-apoptotic), respectively. Confocal microscopy revealed that combining epicatechin with quercetin markedly increased oscillations in intracellular and mitochondrial calcium concentrations indicative of increased neuronal activity. These findings suggest that the synergistic increases in neuronal cell survival produced by combining quercetin with epicatechin are mediated by activity-dependent increases in mitochondrial performance.

Association of catechol-O-methyltransferase (COMT) gene with the reverse placebo effect in children with ADHD

Weam Y. Fageera [1,2], Zia Choudhry [1,2], Sarojini M. Sengupta [1,3], Marie-Eve Fortier [1,2], Natalie Grizenko [1,3], and Ridha Joober [1,2,3]. [1] Douglas Mental Health University Institute, Montreal, Quebec, Canada, [2] Department of Human Genetics, McGill University, Montreal, Quebec, Canada, [3] Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Placebo response (PR) is the subjective improvement while taking a non-active agent. The literature suggests that PR is modulated by specific brain circuits, especially the brain dopamine (DA) system.Thus, genetic factors coding for proteins involved in DA neurotransmission may modulate PR. Variations within the Catechol-O-methyltransferase (COMT) gene, a major catabolizing enzyme for DA, may therefore be implicated in modulating PR.
Methods: Four SNPs (rs6269, rs4633, rs4818, and rs4680) in the COMT gene were genotyped in 371 Caucasian children with ADHD (6-12 years). COMT genotypes and

diplotypes were tested for association with Placebo and methylphenidate response (MR) using ANOVA. PR and MR were calculated as the difference in Restricted Academic Situation Scale score (RASS) before and after PBO and methylphenidate(MPH) respectively in a two-week double-blind, placebo-controlled MPH trial.
Results: Children's performance on the RASS deteriorated after PBO administration, suggesting a reverse placebo effect (RPE). This RPE was completely reversed by methylphenidate. Two SNPs, rs6269 [P = 0.011] and rs4818 [P = 0.008], and the haplotypes [P = 0.046], were significantly associated with the RPE in children with ADHD but response to methylphenidate was not. Both homozygous genotypes, putatively associated with suboptimal levels of DA in the PFC, were associated with higher RPE compare to heterozygous children.
Conclusion: These results suggest that the DA system and COMT gene variation are involved in RPE in ADHD.

Phosphorylation of the insulin receptor substrate-1 regulates monoamine oxidase-A in primary and immortalized neuronal, but not glial, cultures.

Zelan Wei[1], PhD; Jennifer N.K. Nyarko[1], PhD; Paul R. Pennington[1], Paul Fernyhough[2], PhD; Glen B. Baker[3], PhD; Darrell D. Mousseau[1], PhD. [1] Department of Psychiatry, University of Saskatchewan, Saskatoon; [2]Department of Pharmacology and Therapeutics and Physiology, University of Manitoba, Winnipeg; [3]Department of Psychiatry, University of Alberta

Introduction: The mechanism underlying the significant comorbidity between diabetes and depression remains unexplained.
Methods: We used tissues from db/db mice, a preclinical model of Type II diabetes, and primary and immortalized neuronal and glial cultures to determine the effect of insulin (INS) receptor signalling on the function of the depression-related enzyme, monoamine oxidase-A (MAO-A).
Results: In db/db mouse, circulating levels of INS are increased, whereas cortical levels of INS are similar to levels in the 'lean' control mice. In db/db mouse cortex, serotonin turnover is decreased and dopamine turnover remains unchanged. An increase in MAO-A activity and protein expression in these same tissues parallels an increase in immunodetection of the INS receptor as well as the phosphorylation of its major effector protein, the INS receptor substrate-1 (IRS-1). Treatment of primary neuronal cultures (C57BL/6 mouse brain) and mouse HT-22 neuronal cells with INS alters MAO-A activity and protein expression. This is positively correlated with the expression of the INS receptor and IRS-1 phosphorylation. In contrast, INS-induced changes in MAO-A activity and protein expression are independent of IRS-1 phosphorylationin in primary astrocytes and in C6 glioblastoma cells. These observations are corroborated by overexpression of IRS-1 variants containing targeted Serine-to-Alanine substitutions in HT-22 and in C6 cell lines.
Conclusion: INS influences cell type-dependent IRS-1 signalling that contributes to regulation of MAO-A function. Given the potential negative health consequences

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associated with comorbid diabetes and depression, knowledge of this molecular mechanism could benefit patients being treated for either pathology.

Illicit and Prescription Opiate Abuse: Understanding Treatment Failure And Improving Outcomes

Kathryn J. Gill[1,2], Ph.D; Kevin T.Hamdullahpur[1], MSc Candidate. [1]Addictions Unit and [2]Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Dependence on opiates is a major health issue in North America. The recent increases in both prescription and illicit opiate abuse have exacted enormous tolls in terms of health care, mental illness, quality of life, unemployment, and crime, while the difficulty in treating opioid dependent patients with standard abstinence-based therapies is not well understood. The objective of this study was to provide a novel approach to understanding the poor outcomes of opiate dependent patients by focusing on identifying predictors of treatment failure.
Methods: This study was conducted at the Addictions Unit of the McGill University Health Center in Montreal. Patients were prospectively monitored during inpatient detoxification for opiate dependence or sedative-hypnotic dependence in terms of craving, mood, withdrawal symptoms, vital signs, subjective experiences of pain, and objective measures of hyperalgesia and allodynia. Patient psychiatric comorbidity (Axis I and Axis II disorders), chronic medical conditions (pain syndromes), and severity of substance dependence were also considered.
Results: Results indicated that during treatment patients with cluster B personality disorders reported more negative mood symptoms (anger, anxiety, depression) and greater scores on objective measures of withdrawal. Opiate dependent patients were more likely to have chronic pain conditions, and demonstrate increased physical sensitivity and lower pain thresholds.
Conclusions: Together these findings suggest that hyperalgesic, highly sensitive opiate-dependent patients with cluster B personality disorders may have substantial difficulties tolerating both the physical and emotion symptoms of withdrawal, and may benefit from the development of targeted interventions.

FRIDAY JUNE 20th

08:30 – 09:30

Plenary Lecture

Kinnear Centre Room 203

Plenary Lecture

Emerging New Psychoactive Substances: From Bath Salts to Zombie drug, take your pick

Dr. Alan Hudson

Alan Hudson[1], Maggie Lalies[1], Katherine J Aitchison[2], Kristopher Wells[3] & Glen Baker[2]
Departments of Pharmacology[1]and Psychiatry[2] and Institute for Sexual Minority Studies[3], University of Alberta, Edmonton, AB, Canada.

The precise reasons for the rapid emergence of new psychoactive substances (NPS) are difficult to define, but users see the use of “herbal incense” and “legal highs” as safe alternatives to recreational drugs such as cannabis and ecstasy (3,4-methylenedioxymethamphetamine or MDMA) respectively. No doubt the internet has played a large role, not only in the supply of NPS, but also in the dissemination of user-friendly information in chat-rooms and online user forums. Harsh penalties for ecstasy use and frequent contamination of supply with para-methoxymethamphetamine (PMMA), a drug known on the street as “Dr Death”, have also helped the sales of NPS. It is not surprising that young people are taking to online shopping for NPS that are designed by chemists to be technically legal at a rate of around ten NPS per year. This has seen a concurrent rise in hospital admissions of NPS users with serious life threatening peripheral symptoms and also centrally mediated psychosis, confusion and hallucinations. Slang nomenclature for NPS makes it difficult to define the substance ingested in the acute medical situation. Names like “spice” and “K2” usually refer to synthetic cannabinoids, whereas “plant food”, “meow meow” and “bath salts” often refer to cathinone analogues and several new phenylethylamines. More recently, 3,4-methylendioxypyrovalerone (MDPV) has also been found in bath salts. MDPV is a potent monoamine reuptake inhibitor and users report psychomotor agitation, prolonged panic attack, hallucinations, delusions and psychosis. Coupled with media hysteria , this has led to the term “Zombie drug” because of these profound adverse effects following MDPV ingestion.

The precise pharmacological actions of NPS are unknown because many have not been studied even at the pre-clinical level. Spice and K2 contain a synthetic , but very potent cannabinoid, JWH-018 which has been partially studied, and we know acute ingestion can cause subjects to become extremely confused and disorientated. Benzylpiperazine and its analogues affect central monoamine release and turnover and

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Plenary Lecture cont.

have been widely used to substitute for MDMA. We now have evidence from our own studies that, like MDMA, benzylpiperazine elevates extracellular serotonin in rat prefrontal cortex. Mephedrone is widely snorted for its ability to mimic cocaine use and it is now thought that mephedrone affects dopamine pathways in the brain in a manner similar to cocaine. "Benzofury" (6-(2-aminopropyl)benzofuran or 6-APB) has to date been one of the most successful substitutes for MDMA. Our own brain microdialysis studies in rats have compared the effects of 6-APB with those of MDMA and find neurochemistry and behaviour to be very similar for both drugs, supporting the popularity of this NPS. Finally, a recent choice of NPS to emerge is a hallucinogen, (2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine) or 25C-NBOMe, which is so potent it is sold on small blotters. It is a serotonin 2A partial agonist and hence a drug that mimics LSD at microgram doses.
Although we do not fully understand the psychopharmacology of NPS, let alone their long-term toxicology, we are certainly spoiled for choice, bearing in mind the advice *caveat utilitor*.

FRIDAY JUNE 20th

10:00 – 11:00

Innovations in Neuropsychopharmacology Award Lecture

Kinnear Centre Room 203

Innovations in Neuropsychopharmacology Award Lecture

Deep brain stimulation for treatment-resistant depression and Alzheimer's disease

Dr. Andres Lozano

Dan Family Chair in Neurosurgery, University of Toronto
RR Tasker Chair in Functional Neurosurgery, University Health Network
Canada Research Chair in Neuroscience, Tier 1

There is increasing evidence that the clinical manifestations of psychiatric and cognitive disorders are at least in part a consequence of malfunction within brain networks. While this principle is well established in neurologic disorders including epilepsy and Parkinson's disease, there is nascent evidence that the same may be applicable to psychiatric disorders. In particular, disorders such as major depression, which is characterized by a variety of symptoms crossing cognitive, behavioral, affective and vegetative domains, may arise from disturbances in neural networks that interconnect multiple brain areas. We have used a biologically based and hypothesis-driven approach to unravel this circuitry to probe its function and to test specific brain areas for their potential usefulness as therapeutic targets. We have discovered that patients with treatment-resistant depression have a disturbance in brain function that is characterized by increased basal activity in the subgenual cingulate area coupled with decreased function in several frontal cortical areas.
We have led the first trial of Deep Brain Stimulation (DBS) in patients with treatment-resistant depression and have discovered that in many patients the metabolic abnormalities can be corrected and that, in some cases, this leads to clinical improvements. We have expanded this work to animal models, and have shown that infralimbic stimulation in rodents has antidepression-like effects. With the advances in DBS in the treatment of depression, we have also embarked on treating other neuropsychiatric disorders including bipolar disease and anorexia and have recently launched the world's first trial of DBS for Alzheimer's disease. Future work in this area promises to not only unravel the biological underpinnings of depression and the symptoms of psychiatric disease and cognitive disorders but may also offer new hope for therapies for these disabling conditions.

FRIDAY JUNE 20th

13:00 – 15:00

Symposium 5

Kinnear Centre Room 205

Symposium 5:

Translating the Healthy Active Lives (HeAL) Declaration for Young People with Psychosis into a Reality

Co-Chairs: Dr. Scot Purdon and Katherine Aitchison

13:00	Cardiovascular risk factors in schizophrenia *Thomas Raedler*
13:30	Metabolic dysfunction in young people with psychosis: a prospective longitudinal follow-up study *Scot Purdon*
14:00	A biomarker of weight gain in young people treated with risperidone: a potential route for developing clinical recommendations *Katherine Aitchison*
14:30	Lifestyle factors contributing to metabolic dysfunction in schizophrenia: there is hope for intervention *Adrian Heald*

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Symposium 5: Translating the Healthy Active Lives (HeAL) Declaration for Young People with Psychosis into a Reality

Cardiovascular risk factors in schizophrenia

Thomas J Raedler, MD, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

Serious mental illness (SMI) in general, and schizophrenia in particular, are characterized by significant increases in mortality rates as well as significant decreases in life expectancy. While schizophrenia is associated with higher rates of suicide and accidental death, most of the excess mortality in schizophrenia and SMI is due to death from cardiovascular disease. Subjects with schizophrenia frequently have a variety of different risk factors for cardiovascular disease (e.g. obesity, dyslipidemia, diabetes mellitus, hypertension, smoking, sedentary life-style). These risk factors may be further complicated by pharmacological treatment.

Metabolic dysfunction in young people with psychosis: a prospective longitudinal follow-up study

Scot E Purdon,[1,2] Leslie Roper,[2] Brett Granger,[2] Carol Bolt [2], Adrian Heald, [3,4] Kate Hibbard,[1,2] Katherine J Aitchison [2,5]

[1]Department of Psychiatry, University of Alberta; [2]Edmonton Early Psychosis Intervention Clinic; [3]Leighton Hospital, Crewe, Cheshire; [4]School of Medicine and Manchester Academic Health Sciences Centre, University of Manchester; [5]Departments of Psychiatry and Medical Genetics, University of Alberta, Canada

Introduction: Cardiovascular disease (CVD) is disproportionately represented in severe mental illness (SMI), as is Metabolic Syndrome (MetSyn), related to risk of CVD.[1,2] Suspected contributors to MetSyn include illness progression, medication, poor diet, and lack of exercise.[3] Effective intervention will require delineation of the relative contributors to risk, and timelines for potential interactions.
Methods: Patients (years' age ~20 and duration of illness ~1) enrolled in the Edmonton Early Psychosis Intervention Clinic (EEPIC) received prospective monitoring for metabolic dysfunction as part of good clinical practice, including measurement of fasting glucose, HDL, triglycerides, blood pressure, and waist circumference) at intake and 9, 27, 53, and 104 weeks post enrolment.
Results: Less than 5% of patients met criteria for MetSyn at intake, but over 20% met criteria after two years of treatment.
Discussion: A relatively young sample of patients suffering a first psychotic episode exhibited relatively low rates of Metabolic Syndrome at intake, and over two years this increased to a percentage similar to prior reports from more chronic patient samples.[4] Further investigation will identify associated biomarkers and their moderation by lifestyle factors, medication, and clinical interventions aimed at reducing the risk of metabolic dysfunction.

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References:
Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch Gen Psych, 2011, 68(6): 609-616.
Isomaa B et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diab Care. 2001;24:683-689.
Basu et al. (2007). The pharmacological management of schizophrenia. In: Stein G, and Wilkinson G (eds): College Seminar Series in General Adult Psychiatry, London, Gaskell (Royal College of Psychiatrists), 2nd edition: 238-294.
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A biomarker of weight gain in young people treated with risperidone: a potential route for developing clinical recommendations

Noor B Almandil ([1]), David Rossolatos ([2]), Caitlin Slomp ([2]), Ruth I Ohlsen ([3]), Macey L Murray ([1]), Abdulsalam A Al-Sulaiman ([4]), Paul Gringras ([5]), Frank MC Besag ([6]), Katherine J Aitchison ([2],[7]),* Ian CK Wong ([8]) * *joint senior authors ([1])The Department of Practice and Policy, UCL School of Pharmacy, UK; ([2]) Department of Psychiatry, University of Alberta, Canada; ([3]) Department of Post Graduate Research (affiliated with Mental Health), Florence Nightingale School of Nursing And Midwifery, King's College London, UK; ([4]) Vice President, University of Damman, Kingdom of Saudi Arabia; ([5]) Evelina Children's Hospital, Guy's and St Thomas' NHS Trust, UK ([6]) Twinwoods Health Resource Centre, Child and Adolescent Mental Health Service, Learning Disability Team (CAMHS LD), South Essex Partnership NHS Trust, UK; ([7]) Department of Medical Genetics, University of Alberta, Canada; ([8]) Department of Pharmacology and Pharmacy, The University of Hong Kong.

Introduction: Children and adolescents with various psychiatric diagnoses are treated with antipsychotics. This may result in weight gain, which is associated with metabolic dysfunction and cardiovascular risk.
Methods: Data on weight gain and other relevant variables were collected from 200 children and adolescents treated with risperidone. Body Mass Index (BMI) was measured at baseline when medication-free (T0), and at an average of 3 months follow-up (T1). BMIZ was calculated using the LMS growth method.[1] DNA was available from 198/200 patients, in whom the following SNPs were genotyped by TaqMan: rs8179183 (in the leptin receptor gene, *LEPR*), rs1414334 (in the serotonin-2C receptor gene, *HTR2C*), rs1137100 (*LEPR*), rs1137101 (*LEPR,* Gln223Arg, A>G), and rs7799039 (in the leptin gene, *LEP*); the call rate was 99%. As the primary outcome variable, change in BMIZ (between T0 and T1), was significantly skewed, this was log transformed.
Results: Increased weight gain was seen in *LEPR* Arg223Arg individuals, in male patients of Middle Eastern Origin (p=0.021 by linear regression analysis). Other variables (including baseline age and weight) correlated with the outcome variable and were therefore excluded.
Discussion: Interestingly, in recent a study of adult attendees of an outpatient Endocrinology Department, Becer et al. (2013)[2] reported that obese patients with the *LEPR* Arg223Arg had significantly higher triglyeride levels and waist and hip

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circumferences. Should our finding in children and adolescents be replicated, it could become the basis of a biomarker test for prediction of weight gain on risperidone treatment, and the development of appropriate guidelines.
Acknowledgement: Aitchison holds a Government of Alberta funded Alberta Centennial Addiction and Mental Health Research Chair. Almandil was funded by a scholarship from the Ministry of Higher Education, Kingdom of Saudi Arabia.

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[2]Becer E, Mehmetçik G, Bareke H, Serakınc N. *Gene* 529: 16-20.

Lifestyle factors contributing to metabolic dysfunction in schizophrenia: there is hope for intervention

Dr Adrian H Heald [1,2],*Kyaw Sein[3], Simon G Anderson[4], John Pendlebury[3], Mark Guy[5], Vinesh Narayan[3],*
Katherine J Aitchison[6], Peter Haddad[3]

[1]Leighton Hospital, Crewe, Cheshire; [2]School of Medicine and Manchester Academic Health Sciences Centre, University of Manchester; [3]Greater Manchester West Mental Health NHS Foundation Trust, Greater Manchester; [4]Department of Cardiovascular and Endocrine Sciences, University of Manchester; [5]Salford Royal Hospitals Foundation Trust, Salford, UK; [6]Departments of Psychiatry and Medical Genetics, University of Alberta, Canada

Background: Cardiometabolic disease is more common in patients with schizophrenia than the general population with associated higher cardiovascular morbidity and mortality.
Aim: To assess lifestyle factors including diet and exercise in patients with schizophrenia and calculate the prevalence of metabolic syndrome.
Method: Cross-sectional study of a representative group of outpatients with schizophrenia in Salford, England. An interview supplemented by questionnaires was used to assess diet, physical activity and cigarettes and alcohol use. Likert scales assessed subjects' views of diet and activity. A physical examination and relevant blood tests were conducted.
Results: Thirty-seven patients took part. 92% of men had central adiposity as did 91.7% of women (International Diabetes Federation Definition). The mean age was 46.2 years and the mean illness duration was 11.6 years. 67.6% fulfilled criteria for the metabolic syndrome. The mean number of fruit and vegetable portions per day was 2.8 ± 1.8. Over a third did not eat any fruit in a typical week. 42% reported doing no vigorous activity at all in a typical week. The Likert scale showed that a high proportion of patients had insight into their unhealthy lifestyles. 64.9% smoked and in many cigarette use was heavy.
Conclusion: Within this sample there was a high prevalence of poor diet, smoking and inadequate exercise. Many did not follow national recommendations for dietary intake of fruit and vegetables and daily exercise. These factors probably contribute to the high prevalence of metabolic syndrome.

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Many had insight into their unhealthy lifestyles. Thus there is potential for interventions to improve lifestyle factors and reduce the risk of cardiometabolic disease.

Acknowledgements: This work was supported by Salford Royal Hospitals Foundation Trust.

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FRIDAY JUNE 20th

13:00 – 15:00

Symposium 6

Kinnear Centre Room 203

Symposium 6:

Outcomes and Rationale for Deep Brain Stimulation (DBS) Targets Used for Psychiatric Conditions

Chair: Dr. Zelma Kiss

13:00	DBS for intractable OCD: population, outcomes, and "RDoC-ian" mechanisms *Darin Dougherty*
13:30	SGC-DBS for refractory depression: optimizing stimulus parameters *Rajamannar Ramasubbu*
14:00	DBS for psychiatry: insights from mechanistic preclinical studies *Clinton McCracken*
14:30	Animal models of depression and DBS *Clement Hamani*

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Symposium 6: Outcomes and Rationale for Deep Brain Stimulation (DBS) Targets Used for Psychiatric Conditions

DBS for intractable OCD: Population, outcomes, and "RDoC-ian" mechanisms

Darin Dougherty, MD and Benjamin D. Greenberg, MD PhD.Psychiatry and Human Behavior, Alpert Medical School of Brown University, Butler Hospital, Providence, RI USA.

Background: Open-label studies suggest DBS is promising for intractable OCD. Our NIMH-supported research aimed to (i) determine the number of patients meeting selection criteria, (ii) evaluate outcomes, and (iii) study fear extinction as a potential therapeutic target.
Methods: (i) We estimated "DBS candidacy" in a naturalistic, treatment-seeking OCD sample from our Brown OCD Longitudinal Study (N=325). (ii) After rigorous multidisciplinary assessments, 21 (of 30 planned) patients underwent bilateral ventral capsule/striatum DBS. Patients underwent pre-operative imaging, macrostimulation, and masked active or sham DBS for 3 months, followed by open DBS. Yale Brown Obsessive Compulsive Scale (YBOCS) severity was the primary endpoint. (iii) OCD patients (DBS-treated and not) underwent a fear conditioning and extinction paradigm.
Results: (i) Of treatment-seeking patients only 0.6% met DBS criteria, usually because behavioral and medical therapies were not exhausted (S. Garnaat et al, 2014), (ii) While masked phase data remain coded, open phase YBOCS OCD severity 6 months after implantation showed a 34% reduction in YBOCS scores; at 12 months the reduction was 39%. Median YBOC improvements were 30 and 31% at 6 and 12 months, respectively. Adverse effects were generally expected, but also included new-onset psychotic symptoms in a 19 y.o. patient and a probable motor apraxia. (iii) OCD patients receiving conventional treatment had deficits in extinction recall (ER), plus lack of recruitment of ventromedial prefrontal cortex on functional MR imaging during ER testing. In contrast, preliminary fear extinction data (N=4) suggest DBS reduced fear expression generally.
Conclusions: DBS may benefit intractable OCD. Open phase results are similar to those after lesioning the same circuitry. Fear extinction retention in OCD appears defective, while in DBS-treated patients, fear expression might be reduced more generally, consistent with effects of DBS-like stimulation in rodents.

SGC-DBS for refractory depression: optimizing stimulus parameters

Rajamannar Ramasubbu MD, FRCPC Assoc. Professor of Psychiatry and Clinical Neurosciences, Faculty of Medicine, University of Calgary, Hotchkiss Brain Institute, Mathison Centre for Mental Health Research and Education, Calgary, Alberta, Canada.

Background: Deep brain stimulation (DBS) of subgenual cingulate cortex (SGC) is an emerging treatment option for treatment resistant depression (TRD). However evidence

based information on stimulus optimization is limited. This study investigates the effects of different stimulus parameters on clinical outcome in SGC-DBS treatment for TRD.
Methods: In a pilot study, 4 patients with TRD underwent SGC-DBS surgery. In the double-blind stimulus optimization phase, frequency and pulse widths were randomly altered weekly and corresponding changes in mood and depression were evaluated using visual analogue (VAS) and Hamilton Depression Rating Scales (HDRS-17). In the open-label post-optimization phase, depressive symptoms were evaluated bi-weekly for 6 months to determine long-term clinical outcomes.
Results: Longer pulse widths (270-450 µs) were associated with reductions in HDRS-17 scores in 3 patients and maximal happy mood VAS responses in all four subjects. After 6 months of open label therapy, two patients responded and one patient partially responded. Based on this data, we have launched a larger study i) to investigate the efficacy and safety of long pulse width (LPW) versus short pulse width (SPW) stimulation ii) to elucidate fiber tracts involved in the two types of stimulation and associated clinical response to optimize preoperative electrode implantation iii) to determine the predictive value of imaging markers for the selection of patients.
Conclusions: LPW may have a role in stimulus optimization for SCC-DBS in TRD. Evidence based information on optimal stimulation parameters and optimal target are required prior to embarking on large scale randomized sham controlled trials.

DBS for psychiatry: insights from mechanistic preclinical studies

Clinton McCracken[1] and Anthony Grace[2]. Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada[1] and Departments of Psychiatry and Psychology, University of Pittsburgh, Pittsburgh, PA, USA.[2]

Introduction: Deep brain stimulation (DBS) of the nucleus accumbens (NAC) region is a promising therapy for refractory psychiatric disorders such as treatment-resistant depression and obsessive-compulsive disorder. While clinical benefits are documented, little is known regarding the mechanism of action by which DBS produces beneficial effects.
Methods: We examined the effects of NAC DBS in the anesthetized rat on single-unit activity in the orbitofrontal cortex (OFC), as well as on spontaneous and evoked LFP activity recorded simultaneously from a number of regions, including medial prefrontal cortex (mPFC) and mediodorsal thalamus (MD).
Results: NAC DBS suppressed neuronal firing in OFC, likely through antidromic activation of recurrent axon collaterals, increasing drive onto inhibitory interneurons. Stimulation at clinically effective frequencies (HF; 130 Hz) potentiated NAC-evoked short-latency LFP responses and enhanced slow oscillation power in OFC, but not in mPFC or MD. Stimulation at 10 Hz (LF) failed to produce these effects. HF DBS also produced widespread increases in spontaneous beta and gamma power and enhanced coherent beta activity between MD and all other regions. Analysis of acute NAC-induced oscillations showed that HF DBS increased induced gamma coherence compared to sham DBS, whereas LF DBS did the opposite.

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Discussion: These data suggest that HF and LF NAC DBS are associated with distinct patterns of region-specific and frequency band-specific changes in synchronous LFP activity. NAC DBS may produce therapeutic effects by enhancing rhythmicity and synchronous inhibition within and between afferent structures, normalizing function of a neural circuit showing aberrant activity in obsessive-compulsive disorder and depression.

Animal models of depression and DBS

Clement Hamani. Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario M5T 1R8

Introduction: DBS is being investigated for the treatment of depression, with promising early results. However, the mechanisms responsible for benefit are unknown. We investigated the effects of ventromedial prefrontal cortex (vmPFC) DBS in rats.
Methods: The outcome of vmPFC stimulation alone or combined with different types of lesions, including serotonin (5-HT) or norepineprhine (NE) depletion, was characterized in different animal models.
Results: DBS induced a significant antidepressant-like response in the forced swim test and sucrose preference in the chronic mild stress model. Data from our studies suggest that the modulation of fibres near the electrodes could play a role in these responses. Also important was the integrity of the serotonergic system, as the effects of DBS were completely abolished in animals bearing 5-HT depleting lesions.
Discussion: In this symposium, I will review behavioral findings of DBS applied to different brain targets in rodents, with a particular focus on the ventromedial prefrontal cortex. Mechanisms and substrates involved in the antidepressant-like effects of DBS will be discussed.

FRIDAY JUNE 20th

15:30 – 16:30

Heinz Lehmann Award Lecture

Kinnear Centre Room 203

Heinz Lehmann Award Lecture

Cognitive Dysfunction in Patients with Mood Disorders: Psychiatry Needs Help

Dr. Glenda MacQueen

Glenda MacQueen, MD, PhD, FRCPC
Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

Cognitive deficits in patients with mood disorders are now well-recognized aspects of these illnesses. A relatively large number of studies have documented that patients experience cognitive problems. Fewer studies have been able to delineate the factors that predict why some patients have persistent inter-episode difficulties with cognition while others have minimal or no persistent deficits. It has also been difficult to estimate reliably the impact of cognitive deficits on various domains of social function. Some of the difficulty in delineating the nature, contributing factors and significance of cognitive deficits in patients with mood disorders may arise from limitations in the methods often used to assess cognition in clinical settings. This presentation will outline some approaches used in cognitive neuroscience to examine elements of cognitive function and discuss the barriers to implementing these in clinical practice. The role of neuroimaging in understanding cognitive dysfunction in patients with mood disorders will also be discussed.

FRIDAY JUNE 20th

20:00 – 20:30 (approximately)

Special Guest Speaker

Kinnear Centre Room 101

Special Guest Lecture

The Mental Health of First Nations and Metis Peoples of Canada: What Role Does Intergenerational Trauma Play?

Dr. Caroline Tait

Caroline L. Tait, PhD, Department of Psychiatry, University of Saskatchewan
Saskatoon, SK, Canada

This presentation discusses intergenerational trauma as a lived experience of Indigenous individuals and communities. Drawing upon the work of the Aboriginal Healing Foundation and the Truth and Reconciliation Commission of Canada, the importance of linking micro and macro "reconciliation" that implicates all Canadians, and specifically in this discussion mental health care stakeholders, in the Indigenous "healing journey" will be explored.

SATURDAY JUNE 21st

08:30 – 10:00

Presidential Plenary Lecture

Kinnear Centre Room 203

Presidential Plenary Lecture

Antidepressant Effects of RNAi Strategies: Focus on 5-HT Genes

Dr. Francesc Artigas

Francesc Artigas PhD, Dept. of Neurochemistry and Neuropharmacology, Institut d'Investigacions Biomèdiques de Barcelona, CSIC-IDIBAPS, CIBERSAM, Barcelona, Spain

Major depression is a high-prevalence disease lacking appropriate treatment. SSRIs and SNRIs show delayed and limited clinical action, leaving a large proportion of patients with recurrent or chronic depression. 5-HT1A autoreceptors largely contribute to this scenario by preventing adequate responses of 5-HT neurons to stress. Moreover, the indirect activation of 5-HT1A autoreceptors by SSRIs and SNRIs limits their clinical effects. Recently, we examined the validity of RNA interference (RNAi) strategies to evoke antidepressant-like responses in rodents. The intra-dorsal raphe (DR) application of small interfering RNA (siRNA) targeting 5-HT1A autoreceptors selectively reduced their expression and function and evoked antidepressant-like responses in mice. Similarly, the intra-DR application of a siRNA targeting the 5-HT transporter modified mouse brain variables considered to be key markers of antidepressant action: enhanced forebrain 5-HT function, increased hippocampal neurogenesis and increased expression of plasticity-related genes. A major limitation of RNAi strategies is the difficulty to deliver oligonucleotides to selected brain neurons/systems. We developed a conjugated siRNA targeting 5-HT1A autoreceptors, covalently bound to the SSRI sertraline, for its selective delivery to 5-HT neurons after i.c.v. or intranasal administration. Short-term administration of this conjugated siRNA by both routes reduced the expression and function of 5-HT1A autoreceptors and evoked robust antidepressant-like responses in mice. We are currently exploring novel targets linked to monoamine function such as the TASK3 K+ channel, which controls neuronal excitability, also with promising results. Overall these data suggest that siRNA-based strategies targeting 5-HT-related genes may have an important therapeutic potential in the treatment of major depression.

SATURDAY JUNE 21st

10:30 – 12:30

Symposium 7

Kinnear Centre Room 205

Symposium 7:

Mental Health & Comorbidity Research – "Eureka Discovery" Through Stakeholder Internetwork Collaboration

Chair: Dr. Zul Merali

10:30	Depression and co-occurring illnesses: collaborative research as a pathway to personalized medicine *Zul Merali*
11:00	Substance abuse – a concurrent disorder to treat with mental health disorders *Marco Leyton*
11:30	Depression and the road to Alzheimer pathology: will it eventually direct us to an effective treatment? *Darrell Mousseau*
12:00	The workplace and mental health – a focus on the military milieu *Alice Aiken*

Saturday, June 21st

Symposium 7: Mental Health & Comorbidity Research – "Eureka Discovery" Through Stakeholder Internetwork Collaboration

Depression and co-occurring illnesses: Collaborative Research as a Pathway to Personalized Medicine

Zul Merali, University of Ottawa Institute of Mental Health Research, The Royal, Ottawa, ON, Canada.

Depression is the leading burden of illness in Canada, and travels in expensive company. It very often co-occurs with various mental- and physical-illnesses (e.g. anxiety disorders, substance misuse, PTSD, obesity, cardiovascular disease, dementia/Alzheimer's disease, etc.).

There is a high need to customize interventions tailored to various co-occurring conditions, rather that the conventional silo-based approach targeting individual conditions in isolation. This requires an integrative approach, where researchers focused on specific conditions seek to collaborate with researchers focused on other co-occurring condition(s). A useful collaborative research tool could be the recently launched NIMH initiative called the Research Domain Criteria project (RDoC). This defines basic dimensions of functioning (such as fear circuitry or working memory) to be studied across multiple units of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined. The intent is to translate rapid progress in basic neurobiological and behavioral research to an improved integrative understanding of psychopathology and the development of new and/or optimally matched treatments for mental disorders.

Tremendous progress has been made for specific illnesses based on networks of experts with a focus on specific illnesses (e.g. Cancer, Stroke or Obesity networks). Recently, the Canadian Depression Research and Intervention Network (CDRIN) was launched, to address depression and related conditions. We would like to propose a 'network of networks' concept, fostering more integrative approaches across diverse coexisting conditions, with a focus on the whole patient rather than isolated or compartmentalized approach currently in place. We propose using CDRIN to provide a mechanism for novel collaborative opportunities.

Substance abuse – a concurrent disorder to treat with other mental health problems

Marco Leyton[1] & Franco Vaccarino[2]
[1] Department of Psychiatry, McGill University, Montreal
[2] Department of Psychology, University of Toronto, Scarborough, Toronto

Substance use disorders (SUDs) are commonly presaged by problems in childhood and adolescence. Comorbidity, twin and adoption studies indicate that this reflects

overlapping heritable traits and common environmental factors (*e.g.,* childhood physical, sexual, and emotional abuse). Two primary trajectories have been identified. One reflects the early expression of externalizing behaviors and disorders (*e.g.,* conduct disorder), the other reflects internalizing traits (*e.g.,* fear, anxiety, depressed mood). As emerging adults, these tendencies can come to express themselves as SUDs with comorbid psychopathology. Although comorbidity is well established, most work proceeds as if the problems are separate. Dual-diagnosed patients are excluded from clinical trials; the odds ratio of unmet needs is over three times that for those with single disorders; and outcomes are worse. The problem is non-trivial. Two of the top three leading causes of disease burden are related to substance misuse yet the degree to which recommended practices for basic care are adhered to varies from a high of 79% for senile cataracts to 10% for alcohol dependence. These features were summarized in two recent reports from the Canadian Center on Substance Abuse (CCSA). The CCSA calls for increased recognition of comorbidity issues, institution of the infrastructure necessary to facilitate the wider adoption of best practices, and the implementation of trait specific and other prevention strategies showing evidence of effectiveness. Treatment interventions are 10 times more cost-effective than, for example, enforcement. We can and should do better.

Depression and the road to Alzheimer pathology: will it eventually direct us to an effective treatment?

Darrell D. Mousseau: Cell Signalling Laboratory, Department of Psychiatry, University of Saskatchewan

Introduction: Depression has been shown to be strongly associated with the prodromal phase of Alzheimer disease (AD). We aim to define cross-disorder mechanisms that would concurrently provide insight into disease mechanism and therapeutic targets for both disorders. Inter-patient variability in risk implicates several mechanisms. We have reported that AD-related variants of the presenilin-1 (PS-1)/gamma-secretase (PS-1/GS) complex negatively regulate the function of the depression-related monoamine oxidase-A (MAO-A). We have found that disruption of the PS-1/MAO-A complex increases both MAO-A activity as well as amyloidogenic processing of the Amyloid Protein Precursor (APP). These observations provide the basis for the current discussion.
Methods: We used cell and animal models of AD, and human autopsied AD brain samples.
Results: Incubation of AD brain samples with a PS-1/GS inhibitor increased MAO-A activity in certain samples, suggesting disruption of a PS-1/MAO-A complex. Sequencing revealed the presence of a polymorphism. This allelic variant is negatively correlated with MAO-A activity in human cortex, and overexpression of PS-1 carrying this variation inhibits MAO-A in neuronal cultures. In contrast, the overexpression of an age-related, secretase-mediated fragment of APP induces MAO-A mRNA, protein and function in neuronal cells, and this is associated with an increase in activity of the *MAO-A* promoter.

Saturday, June 21st

Matters for discussion: Could PS-1/GS inhibitors inadvertently trigger MAO-A activity and promote a depressive phenotype? In contrast, if the PS-1/MAO-A complex is naturally disrupted, could PS-1/GS inhibitors be used to regulate APP processing and indirectly (and paradoxically) be used to inhibit MAO-A and inhibit a depressive phenotype?

The workplace and mental health – a focus on the military milieu

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The Canadian Institute for Military and Veteran Health Research (CIMVHR) is an innovative organization that engages existing academic research resources and facilitates the development of new research, research capacity and effective knowledge translation. With a network of academic researchers from across Canada, it serves as a focal point for 30 Canadian universities who have agreed to work together in addressing the health research requirements of the Canadian military, Veterans and their families. The institute serves all Canadian stakeholders interested in military and Veteran health research and acts as a conduit between the academic community, government organizations (eg. National Defence and Veterans Affairs Canada), industry and similar international organizations. The CIMVHR research program ensures sustainability through increased public awareness and public-private funding.

SATURDAY JUNE 21st

10:30 – 12:30

Symposium 8

Kinnear Centre Room 202

Symposium 8:
Are Clinical Trials Still Feasible in Psychiatry?
Chair: Dr. Thomas Raedler

10:30	Are clinical trials in psychiatry ethical? *Stacey Page*
11:00	Clinical trials from the perspective of a principal investigator *Thomas Raedler*
11:30	Clinical trials from the perspective of the pharmaceutical industry *Nita Arora*
12:30	Clinical trials from the perspective of a contract research organisation (CRO) *Sandra Harris-Diotte*

Saturday, June 21st

Symposium 8: Are Clinical Trials Still Feasible in Psychiatry?

Are clinical trials in psychiatry ethical?

Stacey A. Page PhD Assistant Professor, Department of Community Health Sciences, Chair, Conjoint Health Research Ethics Board University of Calgary, Calgary, Alberta, Canada

The cost and burden of mental illness in Canada is significant; an estimated 1/5 Canadians will suffer from a mental health issue in their lifetime and over 25% of all disability claims in Canada are due to mental illness. The prevalence of mental illness has made research into its causes, treatment and prevention imperative. Clinical trials generate efficacy and safety data on new biomedical or behavioural interventions. The conduct of clinical trials and advancement of knowledge would not be possible without the participation of people with mental illness and other volunteers. People struggling with mental illnesses are particularly vulnerable as research participants, as history has shown. The mandate of research ethics boards is to review the ethical acceptability of research proposals. This involves balancing the pursuit of knowledge while ensuring participants are respected and protected. Clinical trials in psychiatry give rise to several ethical considerations, such as the dual role of the clinical investigator and those relating to informed consent including competence, surrogate consent and research directives. This presentation will describe ethical considerations in clinical trials in psychiatry and will present some approaches to mitigating concerns.

Clinical Trials from the Perspective of the Principal Investigator

Thomas J Raedler, MD
University of Calgary, Faculty of Medicine, Department of Psychiatry
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I have participated as a rater in multiple clinical trials over the past decade. It has been my honor to serve as Medical Director of the Psychopharmacology Research Unit (PRU) of the University of Calgary since 2012 (http://www.ucalgary.ca/pru). Due to the small size of our unit I currently serve as Principal Investigator on all our studies. Traditionally our unit has focused on studies in schizophrenia. Over the last months we have been expanding the scope of our unit to include additional indications.
Our work is complicated by a variety of problems, including administrative, legal, regulatory and financial aspects. However, the biggest difficulty remains the recruitment of suitable participants for our studies.
This presentation will review the challenges of conducting clinical trials as a Principal Investigator. The discussion will focus on how to overcome these challenges.

Saturday, June 21st

Clinical trials from the perspective of the pharmaceutical industry

Nita Arora, MD, Vice-President, Clinical Research, Hoffmann-La Roche Canada, Toronto, ON, Canada.

Clinical trials are an essential part of the drug development process. Although expensive and labor intensive, clinical trials are required by every regulatory body around the world as part of the approval process for new drugs. Clinical trials continue to grow more complex to satisfy the increasing expectations of not only regulatory bodies, but also physicians, payers and patients. Currently, Phase 3 clinical trials make up approximately 90% of all drug development costs. Despite these complexities, global clinical trials testing innovative compounds are still in great demand by the international scientific community. The Canadian government and institutions are partnering with pharmaceutical companies to streamline the process and decrease the administrative burden that comes along with the conduct of clinical trials. Pharmaceutical companies are re-examining protocol designs, developing innovative patient recruitment practices and streamlining data collection, in an effort to bring down costs and increase speed to market. There is also an effort to increase the cooperation amongst pharmaceutical companies to create more globally standardized processes and mutually recognize each other's training to eliminate duplication of effort. Without another alternative, it is in the best interests of patients, pharmaceutical companies, and the scientific community, to make clinical trials as effective and efficient as possible.

Clinical Trials from the Perspective of a CRO

Sandra Harris-Diotte, Project Management, Stiris Research Inc., London, ON, Canada.

The Contract Research Organization (CRO) has an ever changing perspective on research. This perspective is based on the needs and requirements of the client. The CRO role may be to run an entire study or to have a specific defined function within a clinical program. Research that is Canadian based poses some challenges. The challenges include the identification of appropriate qualified investigators, the length of time required to negotiate budgets and contracts, and the time required for ethics approval. For psychiatric research there is also the potential complication of outcome measures and personnel completing safety evaluations. None of the issues create unbreakable barriers but do need to be addressed by sites and sponsors/CROs. Taking the time to review the challenges and to plan for upcoming trials at a site level will facilitate research in Canada.

THURSDAY JUNE 19th

17:30 – 19:00

Poster Session I

Kinnear Centre Room 201

POSTER SESSION I

Changes in dopamine in the dorsolateral striatum during the augmentation of heroin seeking in chronically food restricted rats

Tracey M. D'Cunha, MA; Audrey Bishop; Uri Shalev, PhD. Center for Studies in Behavioral Neurobiology, Concordia University, Montreal, Quebec, Canada

Introduction: Dieting, or food restriction, during drug abstinence increases the risk for relapse. We recently reported that chronic food restriction augmented heroin seeking in rats with a history of heroin self-administration. The mechanisms underlying this augmentation still remains unclear. Previous research on chronically food restricted rats has found alterations in the dopaminergic system, a critical component of the reward system. We examined the changes in extracellular dopamine in the dorsolateral striatum (DLS), a region implicated in addiction and relapse, during the heroin seeking test following chronic food restriction.
Methods: Rats were trained to self-administer heroin for 10 days. Rats were then returned to the animal colony for 14 days and given either free access to food, or underwent a mild chronic FDR that maintained them at 90% of their baseline body weight. Rats were then returned to the operant chambers for a drug seeking test under extinction conditions. We assessed extracellular dopamine in the DLS during baseline conditions and during the 3 hour heroin seeking test.
Results: FDR rats demonstrated a robust increase in cue-induced heroin seeking compared to sated controls. Dopamine in the DLS increased at the onset of the heroin seeking test, but only in the sated rats. There was an interaction in DLS dopamine between FDR and sated rats over time, however this did not mirror drug seeking.
Conclusions: Our findings suggest that changes in dopamine release in the DLS are not involved in the augmentation of drug seeking in food restricted abstinent rats.

Auditory Gating Deficiency in Schizophrenia: Modulation by Nicotinic Pharmacology

Joelle Choueiry[1], PhD (candidate), Crystal M. Blais[2], PhD, Canada Dhrasti Shah[3], MA, Alain Labelle[4], MD, FRCPC, CSPQ, Verner Knott[5], PhD, C.Psych.,
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University of Ottawa Institute of Mental Health Research, and The Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada

It's been long hypothesized that schizophrenia patients self-medicate with nicotine (smoking rates: schizophrenia ~80% vs. ~15 % in the healthy population). Accordingly, studies in healthy controls and patients have shown nicotine mediated sensory gating improvements. However, alpha 7 nicotinic acetylcholine receptors (α7 nAChRs) desensitize quickly upon nicotine exposure. Hence, an α7 nAChR treatment limiting the desensitized state while prolonging the activated state might express an optimal ameliorating effect on sensory gating in patients. The objective of this study was to examine the effects of a nicotinic treatment comprised of galantamine (a positive nAChR allosteric modulator that enhances neurotransmission and increases the receptor's affinity to agonists) and CDP-choline (a specific α7 nAChR agonist) on sensory gating. We hypothesized that galantamine and CDP-choline will mimic the nicotinic effect and alleviate sensory deficits measured by an auditory sensory gating paradigm (P50). This paradigm employs a conditioning auditory tone that elicits a P50 auditory event-related potential (ERP) wave, while a testing tone, presented 500 ms later, elicits a diminished P50 wave inhibited by the sensory gating system. P50 ERPs of 24 Schizophrenia patients were measured within two randomized, double-blinded, and counter balanced testing sessions (placebo; nicotinic treatment – 16 mg galantamine & 500 mg CDP-choline). Preliminary findings demonstrated that the nicotinic treatment (vs. placebo) enhanced sensory gating by decreasing the response to the testing tone. CDP-choline and galantamine effects on P50 sensory gating have not been previously examined. Alleviating sensory gating deficits may alleviate sensory overload and hence better the functional outcome of patients.

Targeting on oligodendrocyte repair and development: a new feature of atypical antipsychotic drugs and beyond?

Yanbo Zhang[1], MD, PhD; Handi Zhang[2], PhD; Junhui Wang[2], PhD; Xiaoying Bi[3],MD, PhD; Shenghua Zhu[4], MA; Haiyun Xu[2], PhD; Lan Xiao[5], PhD; Qingrong Tan[6], MD, PhD; Zhijun Zhang[7], MD, PhD; Jue He[8], PhD; Dai Zhang[9], MD, PhD; Jiming Kong[4], PhD; Xin-Min Li[8] MD,PhD. [1]Department of Psychiatry, University of Saskatchewan, Saskatoon, SK, Canada, [2]Mental Health Center, Shantou University, Shantou, Guangdong, China [3]Department of Neurology, Shanghai Changhai Hospital, Secondary Military Medical University, Shanghai, China,[4]Department of Human Anatomy and Cell Science, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada,[5]Department of Histology and Embryology, Faculty of Basic Medicine, Chongqing Key Laboratory of Neurobiology, Third Military Medical University, Chongqing, China,[6]Department of Psychiatry, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, China [7]Department of Neuropsychiatry, Institute of Neuropsychiatry of Southeast University, Nanjing, China, [8]Department of Psychiatry, University of Alberta, Edmonton, AB, Canada, [9]Institute of Mental Health, The Sixth Hospital, Peking University, Beijing, China

Objective: Neuroimaging and microarray studies have indicated that oligodendrocyte and myelin abnormalities are important pathological changes of schizophrenia. Antipsychotic drugs (APDs) are effective in treatment of schizophrenia, but the underlying mechanism remains unknown. Our previous studies suggested that quetiapine, an atypical antipsychotic drug, promoted neural progenitor cells to differentiate into oligodendrocyte lineage cells and alleviated cuprizone (CPZ)-induced demyelinating pathology. In this project, we further investigated the effect of different antipsychotic drugs on oligodendrocytes in vitro.
Methods: A well-established oligodendrocyte-lineage cell line, CG4 cells, were used to examine the effect of three antipsychotic drugs: haloperidol, quetiapine and olanzapine. The antipsychotics showed no effects on proliferation of CG4 cells evaluated by the CCK-8 proliferation assay. However, all of the drugs promoted differentiation of CG4 cells into mature oligodendrocytes when evaluated by the expression of CNPase, a maker of mature oligodendrocytes. When further investigating the mechanism of antipsychotic drugs, we found the expression of oligodendrocyte transcription factors olig1 and 2 were distinctly regulated by the drugs.
Results: The expression of olig2 was up-regulated by that the drugs tested and olig1 was increased by quetiapine and olanzapine, but not by haloperidol. These data suggested olig1 and olig2 may play a key role in the regulation of APDs on oligodendrocyte development and there may be some differences between the action of typical and atypical antipsychotics.
Conclusions: Our results indicate APDs promote the differentiation of the CG4 oligodendrocyte cell line in vitro and oligodendrocytes/myelin may be a novel target for APDs.

The effect of chronic stress on depressive-like behaviour and prefrontocortical small conductance calcium-activated potassium (SK) channel function is rapidly reversed by muscarinic receptor antagonists

Francis R. Bambico, PhD; Zhuoliang Li, BS; Roger Raymund, MS; José N. Nobrega, PhD Research Imaging Centre, Centre for Addiction and Mental Health (CAMH) and University of Toronto, Toronto, ON, Canada

Introduction: The muscarinic antagonist scopolamine (SCP) elicits antidepressant activity, but the exact mechanism for this is not fully understood. Because SK channels may be activated by muscarinic M1 receptors via calcium release from intracellular stores, we examined whether SCP's antidepressant action is mediated by a blockade of an M1-SK pathway.
Methods: In the chronic unpredictable stress (CUS) model, rats were exposed to stressors for at least 4 weeks. Sucrose preference (SP) and passive coping (forced swim test/FST) were repeatedly measured. Electrophysiological recordings of prefrontal pyramidal and raphe serotonin neurons were then conducted. The expression of SK1/SK2 channels (in situ hybridization) and BDNF (ELISA) were also assessed.
Results: CUS increased SK expression in the prefrontocortical prelimbic area (PrL), which was associated with a progressive decrease in SP. This anhedonia-like reactivity was rapidly reversed by a low dose of SCP, detected within 24 hours of injection and

maintained at normal levels for another 24 hours. SCP also reversed CUS-induced increase of immobility in the FST. Co-treatment with the SK agonist 1-EBIO abrogated these effects. Intra-PrL infusions of SCP, the M1 antagonist pirenzepine or the SK antagonist apamin mimicked the antidepressant-like effects. SCP significantly enhanced PrL pyramidal excitability, without altering serotonergic activity. These effects did not depend on BDNF since SCP did not alter BDNF expression in the PrL.
Conclusion: These suggest that the rapid onset antidepressant activity of SCP may be mediated by activity-dependent mechanisms via inhibition of M1 and SK channel activity in the PrL.

Hippocampal Activity During a Word-Pair Association Task in Young Adults with Major Depressive Disorder

Elisea De Somma, BSc., Natalia Jaworska, and Glenda MacQueen, MD, PhD, FRCPC. Department of Psychiatry, University of Calgary, Calgary, Alberta

Introduction: Exercise is increasingly promoted as a key component of treatment for mild to moderate depression, yet the mechanisms through which exercise exerts its positive effects are largely unknown. This study assessed hippocampal activity, using functional magnetic resonance imaging (fMRI), in young adults with depression; depressed patients were expected to exhibit altered hippocampal activity compared to healthy controls prior to an aerobic exercise treatment, and no activation differences post-treatment.
Methods: The fMRI Word-Pair Association task assesses habit and recollection memory and was completed by young adult (18-24 years) patients with major depressive disorder (MDD), before and after 12-weeks of exercise (3X/week). Activity was assessed in the bilateral hippocampus and parahippocampal complex (primary measure of interest) as whole-brain analyses during habit and recollection memory trials, as well as during encoding.
Results: At baseline, greater left hippocampal activity was observed in MDD patients compared to controls, who did not complete the exercise protocol, during recollection trials (vs. encoding; $p=.043$). A similar pattern was apparent in the left inferior parietal lobule ($p<.001$). No differences were observed between MDD and control participants at week 12.
Conclusion: These results suggest a deficit in hippocampal activity for encoding verbal information in MDD. Young adults with depressive symptoms may have recruited greater resources during habit and recollection memory to compensate for deficient information encoding, as performance did not differ between groups. Post-exercise training, baseline differences in hippocampal activity between patients and controls were no longer present, suggesting a functional change with aerobic exercise training.

Ahi1 knockout affects neurotransmitter release and causes depression-like behaviors in mice

Liyan Ren BS, Xuanchen Qian BS, Lijing Zhai BS, Zhigang Miao MS, Xingshun Xu PhD. The institute of Neuroscience, Soochow University, Suzhou City, Jiangsu Province, China

Introduction: Major depression is becoming one of the most prevalent forms of psychiatric disorders. However, the mechanisms of major depression are still not wellunderstood. Most antidepressants are only effective in some patients and produce serious side effects. Animal models of depression are therefore essential to unravel the mechanisms of depression and to develop novel therapeutic strategies. Our previous studies showed that Abelson helper integration site-1 (Ahi1) deficiency causes depression-like behaviors in mice.
Methods: In this study, we characterized behavioral changes in Ahi1 knockout (KO) mice by the forced swimming test, tail suspension test, and glucose preference test. Neurotransmitters in different brain regions were evaluated by high performance liquid chromatography (HPLC).
Results: In Ahi1 KO mice, neurotransmitters including serotonin and dopamine were significantly decreased in different brain regions. However, glutamate and GABA levels were not affected by Ahi1 deficiency. The antidepressant imipramine attenuated depressive behaviors and partially restored brain serotonin level in Ahi1 KO mice.
Conclusion: Our findings suggest that Ahi1 KO mice can be used for studying the mechanisms of depression and screening therapeutic targets.

Behavioral and neurochemical alterations in mice exposed to chronic defeat stress during the adolescent period: an in vivo 1H-MRS study at 7T

Handi Zhang, MD, PhD; Gen Yan, MD, PhD; Zeman Fang; Yinghua Xuan, PhD; Renhua Wu, MD, PhD; Haiyun Xu, PhD; Xin-Min Li, MD, PhD; Jiming Kong, PhD; Qingjun Huang, PhD Zhang, Fang, Xuan, Xu, Huang - Mental Health Center, Shantou University, Shantou, Guangdong, China; Yan, Wu - Department of Medical Imaging, the Second Affiliated Hospital, Shantou University, Shantou, Guangdong, China; Li - Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada; Kong - Department of Human Anatomy and Cell Science, University of Manitoba, Winnipeg, Manitoba, Canada

Introduction: Chronic psychosocial stress during the adolescent period is a risk factor for the emotion related disorders such as depression, anxiety and post-traumatic stress disorder. The disturbance of adolescent brain development may be the underlying mechanism for the onset of these disorders. We aimed to dynamically examine both the behavior and neurochemical alterations in the mice exposed to chronic stress during adolescent period.
Methods: Adolescent Balb/c mice were divided into control and stress groups. Mice in the stress group were administered intermittent chronic social stress for 2 weeks. Behaviors including locomotor activity, anxiety status and social interaction were evaluated after the stress and 3 weeks later. At both time points, neurochemical changes were assessed in the frontal cortex of mice by 1H-MRS at 7T.
Results: Mice in the stress group showed hypoactivity and decreased social interaction with novel CD1 mice which they had been beaten by during a previous stress process. They displayed comparative locomotor activity 3 weeks later but still had impaired social interaction. Anxiety status and social interaction with a novel Balb/c mouse was not changed at either time point. The concentrations of Cr+pCr and Glu+Gln were lower

after stress in these mice, but not 3 weeks later. However, the concentrations of NAA decreased and NAAG increased only 3 weeks after stress.

Conclusion: These results indicated that adolescent chronic stress leads to both short-term and long-term behavioral and neurochemical changes which may be relevant to the pathophysiology of emotion related disorders.

Effect of Escitalopram on cognitive function in depression:A mismatch negativity potentials study

Zhenhe Zhou, Department of Psychiatry, Wuxi Mental Health Center of Nanjing Medical University, Wuxi, Jiangsu Province, China.

The clinical symptoms of depression are paralleled by typical neurocognitive deficits,including verbal memory, attentional processing and executive function. The event-related potential (ERP) mismatch negativity (MMN) is an effective measure of preattentive information processing by auditory change detection. MMN is a negative ERP component elicited by deviant stimulus, i.e. the standard sounds changed frequency, duration, intensity or location. 30 subjects were recruited as the depression group. 30 healthy persons matched for age, gender and education were recruited as the control group. MMN values were recorded at baseline and after 8 weeks of Escitalopram treatment and severity was rated in patients with the Hamilton Depression Rating Scale (HAMD). Results showed that Escitalopram decreased HAMD scores; Patients showed smaller mean amplitudes of frequency and duration MMN at baseline than did controls; MMN amplitudes at 8 weeks were higher than those at baseline. These results revealed that patients with depression present abnormalities of early auditory processing; MMN may be a tool of evaluation for cognitive function and treatment effect.

Response to placebo in children with ADHD: Multidimensional evaluation and exploration of its determinants

Weam Y. Fageera, [1,2] Marie-Eve Fortier, [1,2] Natalie Grizenko, [1,3] Zia Choudhry, [1,2] Sarojini M. Sengupta, [1,3] and Ridha Joober [1,2,3]. [1] Douglas Mental Health University Institute, Montreal, Quebec, Canada, [2] Department of Human Genetics, McGill University, Montreal, Quebec, Canada, [3] Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Placebo (PBO) response is critical to determine whether a medication is effective or not in clinical trials. In this study we evaluated placebo response (PR) as assessed by several observers and explored its correlates in children with ADHD.

Method: 614 ADHD children (6-12 years) were recruited and completed the Restricted Academic Situation Scale (RASS). Of these, 539 were assessed by parents (Conners Parents rating scale) and 528 were assessed by teachers (Conners Teacher rating scale) while treated for a week with methylphenidate (MPH) or PBO.
Results. A highly significant PR was identified according to parent and teacher ratings. In contrast, the children's behavior as assessed by RASS deteriorated significantly after PBO, suggesting a reverse placebo effect [all Ps<0.001]. Parental income, marital

status, mother's education level, and maternal smoking during pregnancy showed a significant effect on PR as assessed by parents. Ethnicity showed significant effects as assessed by teachers. Prior exposure to psychostimulant (PEP) was significantly associated with PBO response according to the parent and teacher rating scales. Further analysis revealed 2 patterns of PR and showed the independent contribution of ethnicity on PR as assessed by the teacher rating scale [p= 0.055] and PEP as assessed by parents and teachers.
Conclusion: These results suggest that PR as observed in the parent and teacher rating scales is mainly due to expectations rather than any "objective" improvement in the child behavior. Many factors modulated PR, including ethnicity in school setting, suggesting that clinical trials should be cognizant of this dimension.

Association of the catechol-O-methyltransferase (COMT) gene with the reverse placebo effect in children with ADHD

Weam Y. Fageera, [1,2] Zia Choudhry, [1,2] Sarojini M. Sengupta, [1,3] Marie-Eve Fortier, [1,2] Natalie Grizenko, [1,3] and Ridha Joober [1,2,3]. [1] Douglas Mental Health University Institute, Montreal, Quebec, Canada, [2] Department of Human Genetics, McGill University, Montreal, Quebec, Canada, [3] Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Placebo response (PR) is the subjective improvement while taking a non-active agent. The literature suggests that PR is modulated by specific brain circuits, especially the brain dopamine (DA) system.Thus, genetic factors coding for proteins involved in DA neurotransmission may modulate PR. Variations within the Catechol-O-methyltransferase (COMT) gene, a major catabolizing enzyme for DA, may therefore be implicated in modulating PR.
Methods: Four SNPs (rs6269, rs4633, rs4818, and rs4680) in the COMT gene were genotyped in 371 Caucasian children with ADHD (6-12 years). COMT genotypes and diplotypes were tested for association with Placebo and methylphenidate response (MR) using ANOVA. PR and MR were calculated as the difference in Restricted Academic Situation Scale score (RASS) before and after PBO and methylphenidate(MPH) respectively in a two-week double-blind, placebo-controlled MPH trial.
Results: Children's performance on the RASS deteriorated after PBO administration, suggesting a reverse placebo effect (RPE). This RPE was completely reversed by methylphenidate. Two SNPs, rs6269 [P = 0.011] and rs4818 [P = 0.008], and the haplotypes [P = 0.046], were significantly associated with the RPE in children with ADHD but response to methylphenidate was not. Both homozygous genotypes, putatively associated with suboptimal levels of DA in the PFC, were associated with higher RPE compare to heterozygous children.
Conclusion: These results suggest that DA system and COMT gene variation are involved in RPE in ADHD.

Effects of chronic food restriction-induced augmentation of cocaine seeking in rats under withdrawal

Janie Duchesneau, BA; Leon Mayers; Stacy Pollack; and Uri Shalev, PhD.
CSBN/Psychology, Concordia University, Montreal, Quebec, Canada

Introduction: Recently, our laboratory has reported augmented heroin seeking in chronically food restricted rats under withdrawal. The effects of prolonged food restriction across different drug classes, and the effect of pre-exposure to food-restricted conditions prior to drug training have yet to be elucidated. Thus, the present study investigated cocaine seeking, following prolonged withdrawal, in rats that were exposed to chronic food restriction before (pre-FDR) and after (post-FDR) cocaine self-administration (SA) training.
Methods: Thirty male Long-Evans rats were divided into two groups (pre-FDR, pre-sated). The pre-FDR group was restricted to 90% of their baseline bodyweight over 7 days while the pre-sated group was allowed free access to chow. Following a 3-day recovery period rats were implanted with intravenous catheters to allow for cocaine SA. Rats were trained to SA cocaine (0.5 mg/kg/infusion) on a FR1 schedule of reinforcement during 4-hour daily sessions over 10 days. Following SA training, rats were removed from their drug-taking environment, divided into two groups (post-FDR, post-sated) and exposed to a 14-day withdrawal phase. On day 14 of withdrawal, rats were returned to their training chambers and tested for cocaine seeking under extinction conditions.
Results: Exposure to chronic food restriction, during withdrawal, augmented cocaine seeking. Interestingly, pre-exposure to food restriction augmented cocaine seeking on test day, under both feeding conditions.
Conclusion: Chronic food restriction during withdrawal robustly augments cocaine-seeking behaviour in rats, reflecting the generalizability of the food restriction effect. In addition, pre-drug history of food restriction may sensitize cue-induced drug seeking.

Sex, drugs, and food: the role of sex hormones in chronic food restricted-induced augmentation of heroin seeking in female rats under withdrawal

F. Sedki, MA; A. Luminare; and U. Shalev, PhD. CSBN/Psychology, Concordia University, Montreal, Quebec, Canada

Introduction: Food restriction enhances drug seeking following prolonged abstinence from drug taking. Recently, we reported augmented heroin seeking in chronically food restricted male and female rats, under withdrawal. It is thought that, in females, progesterone and estradiol play opposing roles in drug seeking. Estradiol may enhance drug seeking, while progesterone may attenuate drug seeking. Previous studies have investigated the effects of such sex hormones on cocaine trained, but not heroin trained rats. Thus, we investigated the role of progesterone and estradiol in the augmentation of heroin seeking in chronically food restricted female rats, under withdrawal.
Methods: Female Long-Evans rats were trained to self-administer heroin for 10 days in operant conditioning chambers. Next, rats were moved to the animal colony and

maintained on free access to food (sated group) or subjected to 14 days of mild chronic FDR (FDR group), which sustained their body weight at 90% of their baseline body weight. On day 14, rats underwent a 3 h heroin-seeking test under extinction conditions, in the operant conditioning chambers. Progesterone injections (0.0, 2.0 mg/kg) were administered 24 h and 2 h prior to testing.
Results: Food restriction resulted in augmented heroin seeking in the FDR group, compared to sated controls. Injections of progesterone however did not attenuate this augmented seeking.
Conclusions: Generally, the effect of FDR on heroin seeking in female rats under withdrawal is as robust as in males. However, results indicate that progesterone does not modulate heroin seeking in female rats.

Is high fructose corn syrup addictive? Studies of operant intraoral self-administration in rats

Anne Marie Levy and Francesco Leri. Department of Psychology University of Guelph, Guelph, Ontario, Canada

Introduction: The numerous similarities between obesity and drug dependence suggest that some foods and drugs of abuse may share the ability to reinforce behavior. The current experiments in rats employed operant intraoral self-administration and taste reactivity to study and compare the hedonic and reinforcing effects of high fructose corn syrup (HFCS), saccharin and sucrose.
Methods: Animals surgically implanted with intraoral cannulas were tested for orofacial reactions to different sweet solutions and allowed to press a lever to receive infusions of these solutions on continuous ratio (CR) and progressive ratio (PR) schedules of reinforcement.
Results: Experiment 1 revealed that self-administration of HFCS on a CR schedule is sensitive to changes in concentration/infusion (10%, 25% and 50%), and that higher concentrations maintain higher breakpoints (BPs) on the PR schedule. Experiment 2 indicated that intake of HFCS escalates over 3 weeks of self-administration (3 hours a day) because rats develop binge-like patterns of intake. Experiments 2 and 3 clearly indicated that various concentrations of saccharin do not substitute for HFCS, even when hedonic orofacial reactions are equated. Finally, Experiments 4 and 5 revealed that HFCS produces higher hedonic reactions than sucrose, and that at equicaloric concentrations, HFCS is more potent than sucrose (lowers responding on the CR schedule, and supports higher BPs on the PR schedule).
Conclusion: These data in rats suggest that HFCS has unique hedonic and reinforcing characteristics that may cause addictive-like consumption of foods/drinks that contain it.

Use Of Structural MRI And Machine Learning To Identify Subjects At High Genetic Risk For Bipolar Disorders

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Introduction: Neuroimaging has not yet provided biomarkers for diagnostic use in psychiatry. Machine learning (ML) may better translate neuroimaging to the level of individual subjects. Studying the unaffected offspring of bipolar parents (high-risk design) minimizes clinical heterogeneity and increases sensitivity for detection of biomarkers. This is the first neuroimaging study using ML to identify subjects at high risk for BD.
Methods: We included 45 asymptomatic offspring of BD probands with no personal history of psychiatric disorders (HR subjects) matched by age and sex to 45 controls with no personal or family history of psychiatric disorders recruited from 2 sites (Halifax, Canada; Prague, Czech Republic). We utilized ML of structural MRI with support vector machines (SVM) and Gaussian process classifiers (GPC).
Results: The SVM of white matter distinguished HR from control subjects in the combined dataset (sensitivity= 75.6%, specificity=62.2%, accuracy=68.9%, p=0.001), with similar accuracy for the GPC (65.6%, p=0.002) or when analyzing data from each site separately. Machine learning applied to grey matter was not able to distinguish subjects at high versus low genetic risk. The regions, which most contributed to the discrimination of the two groups included white matter of the inferior frontal gyrus, cingulate gyrus, cerebellum, precuneus.
Conclusions: Machine learning of white but not grey matter was able to accurately and significantly distinguish unaffected subjects at high and low genetic risk for BD. The regions which most contributed to the discrimination maps (inferior frontal gyrus, cingulate gyrus, precuneus, cerebellum) have previously been implicated in the pathophysiology of BD.

Attenuation of acrolein toxicity by the monoamine oxidase inhibitor phenelzine and its active metabolite ß-phenylethylidenehydrazine

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Introduction: The antidepressant/anxiolytic monoamine-oxidase inhibitor phenelzine has been shown to possess neuroprotective properties in animal models of global ischemia, multiple sclerosis and traumatic brain injury. It appears that a metabolite of phenelzine, ß-phenylethylidenehydrazine (PEH), shares some of its neuroprotective mechanisms. Since phenelzine and PEH possess a hydrazine group, it has been suggested that they can sequester aldehydes by a direct chemical reaction. Acrolein is a toxic reactive aldehyde generated endogenously by lipid peroxidation and polyamine metabolism. There are numerous reports of increased acrolein levels in pre-clinical and late-stage Alzheimer's disease (AD) brains. Acrolein was shown to induce tau phosphorylation and induce AD-like pathologies in rats. We have investigated the ability of phenelzine and PEH to sequester acrolein and attenuate acrolein toxicity in mouse cortical neurons.
Methods: Acrolein sequestration by phenelzine and PEH in vitro was quantified by GC-MS following a 30-minute incubation with each drug. Mouse cortical neurons were co-treated with acrolein and phenelzine or PEH for 24 hours, followed by assessment of cell viability with the MTT colorimetric assay.

Results: Phenelzine and PEH sequestered acrolein in a dose-dependent manner, with both drugs reducing free acrolein content by 80-90% when incubated at equimolar concentrations with acrolein. Acrolein was toxic to mouse cortical neurons, reducing cell viability to 20% of controls at 50µM. Cell viability was significantly increased when 50µM acrolein was co-treated with 25-100µM phenelzine or 50-100µM PEH.
Conclusion: These results suggest that phenelzine and PEH are protective against acrolein toxicity and may be useful as adjunctive treatments in AD.
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Neuroprotection by improved mitochondrial performance
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Habitual consumption of dietary flavonoids known to reduce the excessive production of reactive oxygen species by improving mitochondrial function decreases the risk of Parkinson's disease, stroke and dementia. In view of these findings, we have developed a flavonoid-enriched extract from apple peel termed AF4 that dramatically reduces neuronal cell loss, neuroinflammation and motor deficits in our mouse models for stroke and multiple sclerosis. We report here for the first time that quercetin and epicatechin, the two most abundant flavonoids in AF4, are primarily responsible for the neuroprotective effects of this flavonoid-enriched extract. Combining quercetin with epicatechin resulted in supra-additive reductions in the death of primary cultures of mouse cortical neurons exposed to a lethal period of oxygen glucose deprivation. This was accompanied by synergistic increases in the expression of mitochondrial genes encoding members of the electron transport chain. Furthermore, neuroprotection produced by quercetin and epicatechin was accompanied by increases and decreases in mRNA levels for bcl-2 (anti-apoptotic) and p53 (pro-apoptotic), respectively. Confocal microscopy revealed that combining epicatechin with quercetin markedly increased oscillations in intracellular and mitochondrial calcium concentrations indicative of increased neuronal activity. These findings suggest that the synergistic increases in neuronal cell survival produced by combining quercetin with epicatechin are mediated by activity-dependent increases in mitochondrial performance.

Behavioural effects of chronic prenatal MK-801 treatment in adult male offspring
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Introduction: Patients with schizophrenia show increased sensitivity to psychomimetic drugs, impaired executive functioning, and increased social withdrawal. The neurodevelopmental hypothesis of schizophrenia suggests that disruption of the developing brain predisposes neural networks to structural and functional abnormalities. Given the critical role of the glutamatergic system in early brain development, we investigated whether chronic prenatal exposure to the glutamate NMDA receptor antagonist, MK-801, induces behavioural impairments in adult offspring.
Methods: Pregnant Long-Evans rats were administered saline or MK-801 (0.1 mg/kg;

s.c.) at gestation day 7-19. Locomotor-activating effects of acute amphetamine (0.75, 1.0, 1.5 mg/kg) and MK-801 (0.1, 0.4 mg/kg) were assessed in adult male offspring. Object recognition memory and cognitive flexibility were assessed using a novel object preference task and a maze-based set-shifting procedure, respectively. Social behaviour was assessed in pairs of rats interacting in an open-field box.
Results: Although there were no significant differences following acute amphetamine challenge, MK-801-induced locomotor activity in MK-801 rats was lower compared to controls. MK-801 rats showed impaired object recognition following a 90 min delay. The set-shifting task revealed impaired acquisition of a new rule in MK-801 rats compared to controls. This deficit appeared to be driven by regression to the previously learned behaviour. In the social interaction task, MK-801 rats spent less time sniffing and more time wrestling with a novel rat compared to controls.
Conclusions: These findings suggest that glutamate dysfunction during early development may mediate behavioural deficits in adulthood and therefore may help explain the role of glutamate in symptoms of schizophrenia.

Inflammatory profile of microglia varies between microglia derived from different regions of the central nervous system

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Introduction: Microglia are the innate immune cells of the CNS and are important for maintenance of homoeostasis in the central nervous system (CNS) as well as the inflammatory response to brain insult. Isolated microglial cultures can be used to study the inflammatory phenotype of microglia derived from different regions of the CNS. Interestingly, microglia from different regions of the CNS (cortex, brainstem, striatum, etc.) have different phenotypes upon activation in culture. We recently demonstrated that microglia can be isolated from rat neo-natal primary mixed glial cultures derived from the spinal cord. Our experiments showed that spinal microglia had a reduced inflammatory profile compared to brain derived microglia after activation with lipopolysaccharide (LPS, a bacterial endotoxin). Notably, release of inflammatory cytokines tumor necrosis factor alpha (TNFα) and interleukin-1beta (IL-1β) was reduced in spinal cord microglia compared to brain microglia. However, we found that yield and purity of spinal microglia was inconsistent between independent culture preparations. To improve our culture preparation for isolated spinal microglia, we have now optimized techniques to isolate microglia from the spinal cord, and are now performing activation studies with LPS or the excitatory neurotransmitter (and gliotransmitter) glutamate.
Methods: Several methods for isolation of brain and spinal microglia were assessed. Optimal results for spinal microglial cultures were obtained with the “shaking method” (after incubation with 15 mM lidocaine) for isolation of microglia. Primary mixed glial cultures were seeded on poly-L-lysine coated flasks. After 2-3 weeks in culture the primary mixed brain and spinal cultures were treated with 15 mM lidocaine for 5 minutes and gently shaken (using an orbital shaker for an additional 10 minutes) to separate microglia from other glial cells. These microglia were then seeded in equal density on to

48 well poly-L-lysine coated culture plates. After 24 hr recovery from lidocaine treatment, the inflammatory phenotype of the brain and spinal cord microglia, including release of TNFα and IL-1β, was assessed in response to activation with LPS and/or glutamate (24 hr treatment).
Results and Conclusion: The purity of microglia obtained by shaking (with 15 mM lidocaine) was > 98% with marked reduction in fibroblast-like cells that contaminated spinal microglial cultures isolated by mild trypsinization. Notably, while purity was improved, activation data show a similar trend in release of TNFα and IL-1β (reduced in spinal microglia relative to brain) after LPS activation. Microglial activation has been implicated in neurodegenerative diseases such as Alzhemier's, Huntington's, Parkinson's disease and Multiple Sclerosis, as well as neuropsychiatric diseases such as depression, autism and schizophrenia. Region specific heterogeneity in microglial inflammatory phenotype across different CNS regions may be an important consideration for immunomodulatory therapies for these disorders.

Organotypic slice cultures of basolateral amygdala: A model for stress-related circuitry

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Introduction: The amygdala is a chief regulator of emotional processing in the mammalian brain and is the seat of anxiety, a very prevalent psychiatric disorder. A key component, the basolateral amygdala (BLA), receives an array of inhibitory and excitatory inputs, and its activity is regulated by several neuromodulators, including the anxiolytic neuropeptide Y (NPY). While we have established that the acute anxiolytic effect of NPY results partly from inhibition caused by a Y1 receptor-mediated reduction in the activity of the H-current (Ih), which excites resting pyramidal cells, NPY also can induce long-term stress resilience. Rats receiving 5 daily intra-BLA injections of NPY not only show acute increases in social interaction (SI), but this effect also lasts up to 8 weeks. We have developed novel in vitro organotypic slice cultures (OTCs) of the BLA to investigate this mechanistically.
Methods: BLA OTCs were prepared from P14 rats using the interface method. Age-matched cultures were incubated with varying concentrations of NPY for 5 days then OTC pyramidal cells were characterized electrophysiologically. Dendritic arborization was analysed with confocal microscopy coupled with Sholl analysis.
Results: Electrophysiological results suggest that prolonged exposure to NPY does not reduce Ih, however, pyramidal cell capacitance, directly proportional to cell surface area is reduced. Visual inspection and Sholl analysis revealed a reduction in total dendritic length, limited to the distal dendrites, caused by NPY.
Conclusions: This model culture system has provided a potential mechanism for NPY-mediated stress resilience and should further our understanding of the signalling mechanisms downstream of NPY receptor activation.

FRIDAY JUNE 20th

11:00 – 13:00

Poster Session II

Kinnear Centre Room 201

POSTER SESSION II

Assessment of Social Cognition in Bipolar Disorder

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Introduction: Impairment in social cognition may contribute to deficits in social functioning in patients with bipolar disorder (BD). Through the use of a behavioral social cognition task, and functional magnetic resonance imaging (fMRI), it was hypothesized that the behavioral and neural deficits underlying impairment in social cognition in BD would be revealed.
Methods: The task was administered to 25 healthy controls (HC) and 25 patients with depression scores ranging from euthymic to depressed at the time of assessment. The task required participants to evaluate situations that were “enhancing” or “threatening” to self-esteem, directed at either self or at other people. Self-esteem enhancing scenarios involved vignettes of activities such as receiving praise during a sports game. Threatening scenarios involved, for example, receiving criticism at a party. Participants were required to evaluate characters in the scenarios on the basis of positive or negative descriptors. Evaluation classifications ranged from extremely negative to extremely positive. The frequencies of behavioral responses were analyzed using chi-square tests and fMRI data were analyzed using Statistical Parametric Mapping software.
Results: Patients differed from HCs in their evaluation of threatening scenarios, directed at both oneself and at other people ($p<0.001$). Specifically, patients had a lower proportion of responses in the neutral category, and more responses in the positive and negative categories, relative to HCs. Neuroimaging results reveal differential patterns of prefrontal-cortical and limbic-subcortical activation in BDs throughout the task ($p<0.05$).
Conclusion: Findings may contribute to understanding difficulty in interpersonal functioning in patients with BD.

Oligodendrocyte dysfunction in schizophrenia: a mechanism and target for treatment

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Introduction: Schizophrenia is characterized by disturbances of perception, emotion, social functioning and cognition. Although its pathophysiology is largely unknown, a deficit in information integration as a result of abnormal neural connectivity has been suggested. Increasing evidence supports a role of oligodendrocytes (OL), the myelin-forming cells in the brain, in the pathogenesis of schizophrenia. Genome-wide gene expression analysis has found a deregulation of myelination-related genes in schizophrenia. Neuropathological and neuroimaging studies demonstrated loss of oligodendrocytes and myelin abnormalities in the brains of schizophrenic patients. Furthermore, patients with various demyelination disorders have psychotic symptoms, indicating a correlation between demyelination and schizophrenia.
Methods and Results: In an animal model of chemically (cuprizone)-induced demyelination we found that the number of mature OLs was significantly reduced, particularly in the prefrontal cortex. Mice with demyelination presented a host of schizophrenia-like behaviors, e.g., disrupted sensory gating in a prepulse inhibition test, decreased social interaction, and impaired working memory. Importantly, the cuprizone-induced schizophrenia-like behaviours were associated with the severity of demyelination and could be attenuated by the atypical antipsychotic drug quetiapine through an action of neuroprotection, but not by the typical antipsychotic haloperidol.
Conclusion: Oligodendrocytes are the most vulnerable cells in the brain and susceptible to even mild stimuli such as an episode of transient ischemic preconditioning or psychosocial stress. Detailed analysis suggests that inefficient energy metabolism due to low levels of monocarboxylate-transporter 1 expression makes oligodendrocytes more vulnerable than neurons and astrocytes. Collectively, these data suggest that oligodendrocytes are involved in the pathogenesis of schizophrenia and should be considered as a new therapeutic target.

Translational Behavioral Analysis of Acute L-Arginine and Antipsychotic Treatment in a Phencyclidine Model of Psychosis

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Introduction: It is important to identify safe and well-tolerated treatments that can be used with antipsychotic medications to improve treatment response in schizophrenia. Glutamate/nitric oxide (NO)-based therapies may offer an alternative approach for drug development. A recent clinical study indicated that the NO-donor sodium nitroprusside caused a rapid improvement of symptoms in treated patients with schizophrenia. We recently examined the effects of L-arginine (a NO precursor), the antipsychotic medications clozapine and risperidone, alone and in combination, on phencyclidine (PCP)-induced hyperlocomotion in rats.

Methods: Twelve treatment groups of adult male Sprague Dawley rats (n=6) were used. Locomotor activity was recorded with the San Diego Instruments Photobeam Activity System-Home Cage (PAS-HC) apparatus. The antipsychotics alone or in combination with L-arginine (500, 1000, 1500 mg/kg ip) were admininistered to the rats 30 minutes prior to the injection of PCP (5 mg/kg ip) and locomotor activity was measured for 60 min after PCP administration.
Results: Both antipsychotics reduced hyperlocomotor activity produced by PCP, but L-arginine alone had no effect and it did not enhance the locomotor-reducing effects of either antipsychotic.
Conclusion: These results are consistent with results from a previous clinical trial where we found no significant changes in the Positive and Negative Syndrome Scale (PANSS) positive symptom scores at the end of augmenting L-arginine treatment in patients with schizophrenia taking antipsychotics. At the doses and times tested, treatment with the NO precursor L-arginine does not appear to be an effective augmentation strategy when treating psychoses. (Funds provided by Alberta Health Services).

Cocaine Cue-Induced Dopamine Release in the Human Prefrontal Cortex

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Introduction: The prefrontal cortex (PFC) integrates sensory information to direct attention and plan actions based on experience. In people with cocaine use disorders, the PFC is engaged during cue-elicited craving for the drug. One transmitter plausibly contributing to this effect is dopamine, but this has yet to be tested.
Methods: Here we used high-resolution positron emission tomography (HRRT PET) with [18F]fallypride to measure PFC D2/3 receptor availability in the presence vs. absence of drug related cues in volunteers meeting DSM-IV criteria for current cocaine dependence (n=12).
Results: Exposure to cocaine cues significantly decreased BPND values across the PFC in subjects with a high craving response (16-20% magnitude of [18F]fallypride displacement). Individual differences in the magnitude of craving correlated with dopamine release in the medial orbital cortex ($r = 0.57$, $p = 0.054$) and anterior cingulate ($r = 0.58$, $p = 0.045$). Midbrain D2 levels significantly correlated with dopamine release in the striatum but not the cortex. The lower the midbrain D2 receptor levels, the higher the striatal dopamine release ($ps < 0.05$) and craving ($r = -0.64$, $p = 0.024$).
Conclusions: Consistent with evidence that somatodendritic autoreceptors are present on meso-striatal but not meso-cortical dopamine cells, midbrain D2 levels correlated with striatal dopamine release only. Both striatal and PFC dopamine release covaried

with craving, suggesting that both influence drug focused incentive motivational states in people with severe cocaine use disorders. This mechanism, possibly involving the interplay of multiple cognito-affective processes, might contribute to the perpetuation of pathological drug seeking.

Baseline oxytocin levels predict change in anxiety post-clubbing

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Introduction: Oxytocin is known to reduce anxiety and modulate social interactions. We looked at the relationship between pre-clubbing oxytocin level and change in anxiety post clubbing. Method: This study sampled 48 regular 'clubbers'. Oxytocin levels were measured before and after clubbing. The State-Trait Anxiety Inventory (STAI, Spielberger et al) was used to measure levels of anxiety before clubbing, 3 and 5 days post-clubbing (data available on 19 and 18 respectively). Baseline oxytocin level was explored as a predictor for change in STAI score on days 3 and 5 using linear regression analysis.
Results: Linear regression analysis showed that pre-clubbing oxytocin level was a significant predictor of change in anxiety scores on the STAI on Tuesday and Friday ($p=0.013$ and $p=0.019$ respectively). Conclusion: Pre-clubbing oxytocin in this sample of regular clubbers is a significant predictor for change in anxiety level experienced during the week following the "rave." Further data analysis including relevant covariates is underway. It is possible that the baseline higher oxytocin level is a marker for a more reactive posterior pituitary axis, which is associated with a greater change in anxiety level in the week following clubbing.
Acknowledgement: This study was carried out with support from Fulcrum TV productions Ltd. Dr Aitchison holds a Government of Alberta funded Alberta Centennial Addiction and Mental Health Research Chair.

References: Wolf K, et al (2006). Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population. *J. Psychopharmacol 20(3), 400-410*

Quetiapine Ameliorates the Cuprizone-induced Changes in 1H-MRS Metabolites in C57BL/6 Mouse Brain via an Antioxidant Capacity

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Cuprizone (CPZ) is a copper-chelating agent and was shown to selectively (at a low dose of 0.2%) induce oligodendrocyte loss and demyelination in C57BL/6 mouse brain by inhibiting cellular respiration. Recent studies have used the CPZ-fed mouse as an animal model of schizophrenia for the CPZ-induced white matter damage and behavioral changes can be ameliorated or prevented by some of antipsychotic drugs such as quetiapine (QTP). The aims of this study were to check the possible changes in oxidative stress relevant indices and brain metabolites of CPZ-fed mice and to examine the potential effects of QTP on these changes. CPZ-feeding for four weeks decreased the proton magnetic resonance spectroscopy (1H-MRS) signals of N-acetyl-L-aspartate, creatine, phosphocreatine, phosphorylcholine, and glycerophosphorylcholine, suggesting the existence of mitochondrial dysfunction in brain cells. The treatment increased levels of malondialdehyde and H_2O_2, but decreased activities of catalase and glutathione peroxidase in the brain tissue, indicating the presence of an oxidative stress. More significantly, these CPZ-induced changes were effectively ameliorated in the mice co-administered with CPZ and QTP, although the antipsychotic alone showed no effect in terms of these indices. These findings suggest that QTP ameliorates the CPZ-induced mitochondrial dysfunction of brain cells via its antioxidant capacity.

Changes of proinflammatory cytokines and white matter in rats exposed to chronic unpredictable mild stress

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Introduction: Alteration of the proinflammatory cytokine contents and white matter lesions are both important pathophysiological changes in patients with depression. The aim of this study was to investigate the relationship between proinflammatory cytokines changes and white matter lesions in the brain of rats exposed to chronic stress and their correlations with the depressive-like behaviors.
Methods: male SD rats were divided into control and stress groups. Rats in the stress group were subjected to chronic unpredictable mild stress (CUMS) for 4 weeks while controls were raised at the same living conditions without CUMS. Anxiety-like and depressive-like behaviors were assessed and the content of proinflammatory cytokines and the white matter status were examined by immunohistochemistry staining after stress.
Results: Stressed rats showed lower locomotor activity and spent less time in the central zone in the open-field test. They consumed less sucrose solution in the sucrose intake test and showed more immobility time in the forced swimming test. The levels of proinflammatory cytokines (IL-6, IL-1ß and TNF-a) were much higher in stressed rats than those in the control rats. While no myelin breakdown was identified by Luxol fast blue staining and immunohistochemical staining for myelin basic protein, loss of oligodendrocytes in prefrontal cortex was found in stressed rats.
Conclusion: These results indicated a putative role of white matter abnormality and abnormal levels of proinflammatory cytokines in the pathophysiology of depression. Further research is needed to investigate the exact connection between proinflammatory cytokines and white matter lesions in depression.

Quetiapine decreases cerebral microglial activation in an APP/PS1 double transgenic mouse model of Alzheimer's disease

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Introduction: Previous studies have suggested that cerebral microglia activation was associated with Aß senile plaques, and quetiapine, an atypical antipsychotic drug, decreased Aß levels in Alzheimer's disease (AD) mice. The aim of the present study was to evaluate the effects of quetiapine on microglial activation that could be involved in the AD pathogenesis in an amyloid precursor protein (APP)/presenilin-1 (PS1) double transgenic mouse model of AD.
Methods: Non-transgenic and transgenic mice were treated with quetiapine (0 or 5 mg/kg/day) in drinking water from the age of 2 months. After 10 months of continuous quetiapine administration, the mice were sacrificed, and hippocampal microglial activation and total ß-amyloid peptide levels were measured.
Results: The results showed quetiapine significantly decreased microglial activation and ß-amyloid peptide levels in the hippocampus of transgenic mice.
Conclusion: These suggest that quetiapine can reduce microglia activation in an APP/PS1 transgenic mouse model of AD, and indicate that suppression of microglial activation may be a useful strategy to slow the progression of AD.

Neurotensin potentiates GABAA-mediated transmission and is anxiogenic in the oval Bed nucleus of the Stria Terminalis

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Introduction: Anxiety involves neuronal activity in the Bed Nucleus of the Stria Terminalis (BNST). Neurotensin (NT) plays a role in anxiety and the ovBNST is rich in NT-positive neurons and fibers. Therefore, this study investigated how ovBNST NT modulates synaptic transmission and contributes in anxiety.
Methods: We combined brain slice neurophysiology and behavioral pharmacology in Long Evans rats. ovBNST GABAA-IPSC and AMPA-EPSC were electrically-evoked at 0.1 Hz. NT (1µM) was exogenously applied for 5 mins or endogenously released using repetitive depolarization (0mV, 100msec, 2Hz, 5 mins). Another contingent of rats was subjected to a chronic unpredictable stress (CUS) paradigm for 4 weeks. They were then tested for locomotion and exploratory activity in the open-field test and anxiety in the elevated plus maze and acoustic startle while receiving intra-ovBNST microinjections of saline or the NT non-selective antagonist SR-142948 (2ng/300nl/side) 30 mins before paradigm.
Results: Exogenous or endogenous NT reversibly and pre-synaptically increased (+50-70%) ovBNST GABAA-IPSC amplitude. However, NT had no effect on AMPA-EPSC and did not significantly modulate GABAA transmission in the adjacent anteromedial

BNST or in the NT-rich nucleus accumbens shell. 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 or acoustic startle response.
Conclusion: Our data show localized potentiation of GABAA synaptic transmission in the ovBNST. Blockade of ovBNST NT receptors reduced anxiety in stressed rats. Therefore, our study expands understanding of the neural underpinnings of anxiety.

A new method of evaluating the neurobiological effects of a psychotropic medication: Combining machine learning, event related potentials and brain source localization in schizophrenic subjects treated with clozapine and in healthy volunteers

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Objective: To develop a method to discover electrophysiological effects of clozapine (CLZ) relevant to therapeutic efficacy. Machine learning (ML) is a method of identifying variables relevant to classification within a large data set. ML was used to discover EEG features that simultaneously 1) distinguish healthy volunteers (HV) from schizophrenic (SCZ) subjects before treatment (BT) with CLZ; 2) distinguish whether EEG originates BT or after treatment (AT) in SCZ subjects most responsive (MR) to CLZ; 3) discriminate HV from least responsive (LR) SCZ subjects both BT and AT; 4) no longer discriminate HV from MR SCZ subjects AT.
Methods: EEG was collected in 66 HV and in 47 SCZ adults both BT and AT with CLZ. SCZ subjects were divided into MR and LR groups based on improvement after CLZ. Using brain source localization analysis of P300 signals, source waveforms were extracted from specified brain regions. ML was then used to search for the smallest set of features satisfying our four conditions.
Results: Five cross-power spectral density (CPSD) features combining brain source activity with connectivity were identified in medial frontal, right temporal, right parietal and right occipital areas. These regions overlap with parts of the default mode network (DMN).
Conclusions: Our findings suggest that i) CLZ normalizes activity in parts of the DMN which are hyperactive and hyperconnected ii) ML can identify regional electrophysiological effects of CLZ relevant to it's therapeutic effect. This strategy may be useful in the search for new pharmaceuticals with CLZ-like efficacy.

Ganciclovir reduced activation of microglia/macrophage in transgenic CD11b thymidine kinase mice following intracerebral hemorrhage

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Microglia become activated following intracerebral hemorrhage (ICH). Monocytes from the circulation migrate into areas of CNS injury to become macrophages. These activated cells are often called “microglia/macrophages”, which can release numerous cytotoxic mediators and some neurotrophic factors. We investigated whether the activated microglia/macrophages promote neuronal injury in the acute period and whether inhibiting their activity attenuates brain injury following ICH by using ganciclovir to treat the transgenic CD11b thymidine kinase (CD11b-TK) mice. Ten-µl of autologous blood obtained from the tail was injected into the right striatum of adult male mice to produce ICH. C57/B6 wildtype mice were used to examine the time course of brain injury from 1-7 day(s). The area of brain damage, the extent of neuronal death and microglia/macrophage activity were evaluated. We used transgenic CD11b-TK mice where proliferating microglia/macrophages were removed by ganciclovir treatment. Mice were killed at 3 days after ICH and their brain sections were evaluated. ICH injury resulted in activation of microglia/macrophages through 1-7 days of insult. The area of brain damage peaked at 2-3 days; the number of dying neurons peaked at 1-3 days, while the activation of microglia/macrophages peaked at days 3-4. The activation of microglia/macrophages, the area of brain damage and the death neurons were significantly reduced when the transgenic CD11b-TK mice were treated with ganciclovir after ICH compared to various control groups. Activation of microglia/macrophages in the early periods after ICH promotes brain injury. These results shed light on the advent of new medications for ICH patients, including microglia deactivators.

White Matter Deficits in High-Risk Adolescents: Findings from DTI

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Introduction: Adverse childhood experiences slow development of white matter axon diameter and microtubule structure, and decrease the ratio of myelinated to unmyelinated fibers in the brain’s white matter tracts. The brain is becoming viewed more as a complex system of networks, with each network relying on white matter integrity to function optimally. Diffusion MRI provides a means of measuring white matter integrity. In this study, Diffusion Tensor Imaging (DTI) scans were used to investigate whether complex psychiatric symptoms are correlated with impaired white matter development.

Methods: Single-scan DTI data from 20 adolescent inpatients from CASA House Edmonton were compared to 20 pair-matched (age/gender/handedness) controls. Patients were diagnosed with at least two Axis-I (DSM-IV TR) disorders; patients with any neurological disorder (e.g., FAS, Tourette’s) at the time of scanning were excluded from analysis. Tract integrity analysis was carried out using Tract-Based Spatial Statistics. This approach extracts Fractional Anisotropy (FA) maps from the brain, which indicate white matter tracts. These are combined by group and compared for

differences at the core of each tract. Differences between groups suggest a significant difference in tract integrity.
Results: Following statistical corrections, we saw decreases in patient white matter integrity, localized to three tracts ($p<0.05$): superior fronto-orbital fasciculus, genu of the corpus callosum, and corticospinal tract.
Conclusion: Adolescent inpatients had significantly impaired white matter development in three tracts compared to control subjects. This suggests underdeveloped white matter could act as a marker for complex psychiatric disorders, and potentially as a target for assessing long-term treatment response.

Evaluating a Fluorinated Analogue of Marsanidine as a potential PET Ligand for Central Alpha-2 Adrenoceptors

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Introduction: Development of a highly selective PET radiotracer labeled with ^{11}C or ^{18}F for imaging central α2-adrenoceptors (α2-AR) has been studied extensively in recent years. In the current study we have chosen marsanidine, a known α2-AR agonist, as the lead compound and synthesized several fluorinated derivatives which were studied in vitro to assess their affinity and selectivity for α2-AR and in vivo to determine their pharmacological effects on extracellular noradrenaline in rat frontal cortex.
Methods: In vitro radioligand binding assays were employed to establish affinities of the compounds for α1- and α2-AR and imidazoline-1 (I1R) and imidazoline-2 receptors (I2R). The most α2-AR-selective derivative was studied further using in vivo microdialysis in freely moving conscious rats (male Sprague-Dawley, n=6 per group) with probes pre-implanted under anaesthesia.
Result: Initial binding assays identified AW-21 to exhibit the highest affinity and selectivity for α2-AR over other receptor types (Ki=31 nM, a2/I2=11263). Repeated measures one way ANOVA showed that intraperitoneal administration of AW-21 at 0.1 mg/kg slightly but non-significantly decreased extracellular noradrenaline by 17% in rat frontal cortex compared to basal level. At a higher dose of 1 mg/kg, AW-21 reduced cortical noradrenaline significantly by 73% compared with basal levels (***$p<0.0001$). In addition, administration of AW-21 at both the doses produced rapid onset of sedation in rats, indicating good brain penetration.
Conclusion: Initial studies show AW-21 to have favourable binding and functional properties at α2-AR. Further experiments must be carried out to explore its potential for imaging central α2-AR in vivo.

Exploring interactions between COMT, BDNF and AKT1 and cannabis consumption in the genesis of psychosis

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Background: Clinical and preclinical genetic studies provide increasing evidence that genes related to dopamine signaling and neuroprotection are implicated in the association between cannabis and psychosis. Such genes in prior reports in Caucasians include COMT, BDNF, and AKT1 (reviewed in O'Tuathaigh et al., 2014). We herein are seeking to investigate these genetic associations in samples from young Canadian patients with a psychotic illness.
Methods: The sample comprises 242 patients with psychosis recruited in Edmonton and Halifax. The markers are rs4680 (Val158Met) in COMT, rs2494732 in AKT1, and rs6265 (Val66Met) in BDNF. Data on substance use and other relevant variables including cognition have been collected.
Results: The proportion of our sample that has used cannabis in their lifetime is approximately 70%, with a smaller proportion having problematic substance use. The COMT and BDNF genotypes are in Hardy-Weinberg equilibrium.
Conclusions: It will be interesting to see whether or not findings identified in European Caucasians hold up in our Albertan and Nova Scotia samples, while the analysis of genetic moderation of the particular cognitive phenotypes available in this dataset in the context of cannabis use is novel. Funding and Acknowledgements: This study was funded by the Canadian Institutes of Health Research (CIHR): Dr Aitchison holds an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta (Canada). Genotyping of NPAS3 and COMT was conducted in TAGC, University of Alberta. Reference: O'Tuahaigh et al. (2014) Progress Neuro-Psychopharmacology and Biological Psychiatry 52: 33-40.

Raphe-specific Freud-1 Knockout in Adulthood induces 5-HT1A Autoreceptor Overexpression, Leading to Depression/Anxiety Phenotype

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Altered expression of the serotonin-1A receptor (5-HT1A) during early post-natal development has been implicated in adult anxiety phenotype in mouse models. However, it remains unclear whether altered 5-HT1A receptor expression during adulthood is sufficient to induce an anxiety phenotype. Additionally, the underlying mechanisms of transcriptional regulation of serotonin genes such as HTR1A (5-HT1A gene) remain to be clarified to understand how these genes become dys-regulated in mental illness. Previously, we identified Freud-1 (5' repressor element under dual repression binding protein 1) as an important repressor of 5-HT1A transcription that is

strongly expressed in raphe 5-HT neurons and displays predominant repressor activity in 5-HT1A-positive 5-HT neuronal cells in culture. To test the hypothesis that alteration in Freud-1 induces dysregulation of 5-HT1A autoreceptors in vivo, we generated Freud-1 conditional knockout mice bred to a C57BL/6 background and induced raphe-specific Freud-1 knockout at 7-8 wks of age. At the age of 10-12 weeks deletion of Freud-1 induced expression of functional 5-HT1A receptors in 5-HT neurons of the dorsal raphe. Knockout of Freud-1 in adult was associated with a depression/anxiety-like phenotype. These preliminary studies provide important evidence to validate that alteration in Freud-1 expression or activity in adulthood leads to depressive/anxiety phenotype.
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A common target in Type 2 diabetes mellitus and Alzheimer's disease (AD)
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Objectives: AD is characterized by the presence of senile plaques, neurofibrillary tangles, and neuronal loss in defined regions of the brain. Type 2 Diabetes Mellitus (T2DM) has been shown to be highly correlated with AD development. Pathologies common to both diabetes and AD include vascular impairment, neurodegeneration and plaque accumulation, and these AD symptoms may be exacerbated by T2DM. However, the precise mechanism by which T2DM is associated with AD remains unclear. To address this question, we induced a diabetic complication, using a pharmacological drug, streptozotocin (STZ) to study the mechanisms of insulin signaling impairments in the context of how T2DM may contribute to AD pathologies. We further targeted insulin-related potential signaling molecules, PI3K/AKT and glycogen synthase kinase 3 beta (GSK3β) in addition to altered expression of insulin receptor.
Materials and Methods: Peritoneal injection of STZ was performed to induce T2DM in APP/PS1 mice. Blood glucose level was measured using ELISA for validation of STZ-induced diabetes, and immunohistochemistry and microscopic methods were used for characterizing cerebrovascular integrity, neurodegeneration and glia-induced inflammation.
Results: Cerebrovascular impairment was associated with plaques in APP/PS1 mouse brains, while there were no signs of comparable damage in WT mice. This impairment was accompanied by excessive activation of astrocytes, a sign of inflammation. Our immunoblotting data showed that the expression of glucose transporter (GLU-T), a marker for blood vessel integrity, was decreased in APP/PS1 mouse brain. This measure of reduced GLU-T levels associated with a damaged cerebrovascular system was supported by GLU-T immunohistochemistry. We suggest that these pathologies are accelerated by STZ-induced diabetes and alteration of insulin signaling, demonstrating the potential links between diabetes and AD.
Conclusion: Our data indicate that vascular damage is accompanied by excessive activation of glia, associated with accumulated plaques. STZ-induced diabetes provides a valid animal model to study diabetes-associated AD, and as a model for sporadic cases of AD.
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Phosphorylation of the insulin receptor substrate-1 regulates monoamine oxidase-A in primary and immortalized neuronal, but not glial, cultures

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Introduction: The mechanism underlying the significant comorbidity between diabetes and depression remains unexplained.
Methods: We used tissues from db/db mice, a preclinical model of Type II diabetes, and primary and immortalized neuronal and glial cultures to determine the effect of insulin (INS) receptor signalling on the function of the depression-related enzyme, monoamine oxidase-A (MAO-A).
Results: In db/db mouse, circulating levels of INS are increased, whereas cortical levels of INS are similar to levels in the 'lean' control mice. In db/db mouse cortex, serotonin turnover is decreased and dopamine turnover remains unchanged. An increase in MAO-A activity and protein expression in these same tissues parallels an increase in immunodetection of the INS receptor as well as the phosphorylation of its major effector protein, the INS receptor substrate-1 (IRS-1). Treatment of primary neuronal cultures (C57BL/6 mouse brain) and mouse HT-22 neuronal cells with INS alters MAO-A activity and protein expression. This is positively correlated with the expression of the INS receptor and IRS-1 phosphorylation. In contrast, INS-induced changes in MAO-A activity and protein expression are independent of IRS-1 phosphorylationin in primary astrocytes and in C6 glioblastoma cells. These observations are corroborated by overexpression of IRS-1 variants containing targeted Serine-to-Alanine substitutions in HT-22 and in C6 cell lines.
Conclusion: INS influences cell type-dependent IRS-1 signalling that contributes to regulation of MAO-A function. Given the potential negative health consequences associated with comorbid diabetes and depression, knowledge of this molecular mechanism could benefit patients being treated for either pathology.

Illicit and Prescription Opiate Abuse: Understanding Treatment Failure And Improving Outcomes

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Introduction: Dependence on opiates is a major health issue in North America. The recent increases in both prescription and illicit opiate abuse have exacted enormous tolls in terms of health care, mental illness, quality of life, unemployment, and crime, while the difficulty in treating opioid dependent patients with standard abstinence-based therapies is not well understood. The objective of this study was to provide a novel approach to understanding the poor outcomes of opiate dependent patients by focusing on identifying predictors of treatment failure.
Methods: This study was conducted at the Addictions Unit of the McGill University

Health Center in Montreal. Patients were prospectively monitored during inpatient detoxification for opiate dependence or sedative-hypnotic dependence in terms of craving, mood, withdrawal symptoms, vital signs, subjective experiences of pain, and objective measures of hyperalgesia and allodynia. Patient psychiatric comorbidity (Axis I and Axis II disorders), chronic medical conditions (pain syndromes), and severity of substance dependence were also considered.
Results: Results indicated that during treatment patients with cluster B personality disorders reported more negative mood symptoms (anger, anxiety, depression) and greater scores on objective measures of withdrawal. Opiate dependent patients were more likely to have chronic pain conditions, and demonstrate increased physical sensitivity and lower pain thresholds.
Conclusions: Together these findings suggest that hyperalgesic, highly sensitive opiate-dependent patients with cluster B personality disorders may have substantial difficulties tolerating both the physical and emotion symptoms of withdrawal, and may benefit from the development of targeted interventions.

GANGLIOSIDE GM1 AMELIORATES NON-MOTOR SYMPTOMS IN MOUSE MODELS OF HUNTINGTON DISEASE

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Huntington disease (HD) is a neurodegenerative disorder that results in motor, cognitive and psychiatric deficits. The disease is caused by the expansion of a polyglutamine stretch in huntingtin, a ubiquitous protein with still unclear functions.
The molecular mechanisms underlying neurodegeneration in HD are complex and include transcriptional dysregulation, mitochondrial dysfunction, impaired intracellular and axonal transport, as well as aberrant signaling and neurotransmission.
We recently demonstrated that the synthesis of ganglioside GM1, a lipid highly enriched in the brain, is also impaired in HD models. We further demonstrated that chronic intra-ventricular infusion of GM1 reverts the pathological motor phenotype and slows down the neurodegenerative process in already symptomatic transgenic models of HD. The dramatic therapeutic effects of GM1 are accompanied by phosphorylation of mutant huntingtin at Ser13 and Ser16, a post-translational modification that has been shown to decrease mutant huntingtin toxicity. These findings suggest that GM1 might be able to modify the course of HD and correct non-motor symptoms of the disease in addition to motor dysfunction.
To analyze the effects of GM1 on non-motor behaviour (cognitive and psychiatric symptoms) we used two well-characterized mouse models of HD with different genetic background, the transgenic YAC128 model and the knock-in Q140 model. After intracerebroventricular infusion with GM1, significant attenuation of cognitive and psychiatric-like symptoms was observed in both models. YAC128 mice returned to wild-type performance levels on tests of anxiety (elevated plus maze and novelty-induced hypophagia), cognition (social approach test) and depression (forced swim test) after 14

days of treatment with GM1. Similarly, Q140 mice treated with GM1 became indistinguishable from wild-type littermates on motor, anxiety (light-dark box test) and cognition (Y-maze) tests.
Overall, our data show that the therapeutic effects of GM1 extend beyond amelioration of motor symptoms and support the hypothesis that GM1 has disease-modifying properties in HD models.
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