



UNIVERSITY OF  
ALBERTA

*Department  
of  
Psychiatry*

*University of Alberta  
Edmonton, AB, Canada*

**Wednesday June 5<sup>th</sup>, 2013**

**12<sup>th</sup> Annual Research**

# CHAIR'S WELCOME

## Welcome to the 12<sup>th</sup> Annual Psychiatry Research Day at the University of Alberta!

Our department has an internationally recognized record of research going back to the early days of Dr. Bill Dewhurst's chairmanship. A psychiatrist and neurochemist, Dr. Dewhurst recognized the importance of having basic science researchers included in clinical departments and of encouraging collaborative research between basic science and clinical researchers. As cofounder of the Neurochemical Research Unit, Dr. Dewhurst was a pioneer in the area of "trace amines" and suggested in the 1960s, after conducting a series of elegant studies which resulted in a number of seminal publications including a major paper in *Nature*, that these compounds had an important role to play in psychiatric disorders. Since those early days, the number of basic science and clinical researchers in our Department has grown significantly, and we now have active programs in many areas relevant to psychiatry including neurochemistry, neuropsychopharmacology, psychotherapy, neuroimaging, neuropsychiatry and translational neuroscience, with newer programs evolving in other areas. Many of these programs involve collaborative research with colleagues from other departments and institutions locally, nationally and internationally.

Over the years, the Department of Psychiatry has developed very strong MSc and PhD programs to complement our excellent residency program, with some of our residents enrolled in our MSc program. Our graduate students, postdoctoral fellows and residents represent our department exceedingly well by winning many national, provincial, university and faculty scholarships and awards and by disseminating their research at scientific conferences throughout the world. These junior colleagues play an important role in keeping our department on the international stage of psychiatric research.

For this, our 12th Research Day, the **keynote speaker is Dr. Jeffrey Meyer**. Dr. Meyer is internationally known for his work using positron emission tomography imaging to study abnormalities in major depressive disorder and in quantitating the effects of antidepressant treatments. Dr. Meyer is a Canada Research Chair in the neurochemistry of major depressive disorder, a Professor at the University of Toronto and the head of the Neurochemical Imaging in Mood Disorders program at the Toronto PET Centre. His work began with studying monoamine abnormalities in mood disorders and led into mitochondrial markers in mood disorders, with new implications for preventing major depressive disorder and overcoming treatment resistance. Dr. Meyer's keynote presentation at the Psychiatry Research Day is entitled, "**Neuroimaging Biomarkers of Dysphoria: Implications for Prevention and Treatment of Mood Disorders.**"

The remainder of the day will feature talks by faculty, graduate students and departmental collaborators as well as two sessions of poster presentations by our research trainees and collaborators. The top presentations by research trainees will be acknowledged with awards, namely the Geoff Hopkinson Memorial Award, the Gordon King Research Prize, and the Glen Baker Award. We thank Drs. Christian Beaulieu, John Greer, Nicholas Mitchell and Anthony Singhal for agreeing to serve as judges for these awards. We also thank Drs. Tejas Sankar and Andy Greenshaw for their valuable presentations. There will also be a presentation to the winner of a major departmental research prize, the Roger C. Bland award for overall excellence in research. We thank Dr. Esther Fujiwara and the Graduate Program Committee for evaluating the applications for this award.

We are grateful to all our research trainees and their supervisors for their overall contribution to the vital research component of our department, and to Tara Checknita for providing excellent ongoing administrative support for our research program. Special thanks this year go to Yasmeeen Krameddine and Erin Martin (our graduate student representatives), Dr. Esther Fujiwara (our graduate program director) and Tara Checknita (graduate program administrator) for their tireless efforts in organizing this Research Day. We also gratefully acknowledge financial support from several sources for this important venture, as indicated in the book of abstracts.

Thank you for joining us in celebrating our research accomplishments for the past year.

Best wishes,

Glen Baker, Professor  
Interim Chair of the Department of Psychiatry

## ACKNOWLEDGEMENTS

The Department of Psychiatry is grateful to the following for providing financial support\*:

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# 12<sup>TH</sup> ANNUAL PSYCHIATRY RESEARCH DAY ITINERARY

8:45 AM – 9:00 AM	<b>OPENING REMARKS</b>
9:00 AM – 10:00 AM	<b>STUDENT PRESENTATIONS</b>  PARAMJIT BHARDWAJ <i>Glutamate and Depression</i>  JAMES BENOIT <i>Diffusion Tensor Imaging of the Anterior Insula–Anterior Cingulate Salience Network in Adolescent Psychiatric Patients</i>  DMITRIY MATVEYCHUK <i>The Monoamine Oxidase Inhibitor Phenelzine and its Metabolite <math>\beta</math>-Phenylethylidenehydrazine (PEH) Increase Rat Whole Brain Methylamine Levels and Sequester Reactive Aldehydes</i>
10:15 AM – 11:00 AM	<b>STUDENT POSTER SESSION (1)</b>
11:00 AM – 12:00 PM	<b>KEYNOTE ADDRESS</b>  DR. JEFFREY MEYER <i>Neuroimaging Biomarkers of Dysphoria: Implications for Prevention and Treatment of Mood Disorders</i>
12:00 PM – 1:00 PM	<b>BREAK FOR LUNCH</b>
1:00 PM – 2:00 PM	<b>FACULTY PRESENTATIONS</b>  DR. TEJAS SANKAR <i>Neuroanatomical Predictors of Response to Deep Brain Stimulation for Treatment Resistant Depression</i>  DR. ANDREW GREENSHAW <i>Early Childhood Experience and Depression in Relation to Risk and Impulsivity</i>
2:00 PM – 3:30 PM	<b>STUDENT POSTER SESSION (2)</b>
2:00 PM – 4:30 PM	<b>AFTERNOON REFRESHMENTS</b>
<b>BETWEEN</b> 3:30 PM & 4:00 PM	<b>AWARD PRESENTATION</b>

## STUDENT PRESENTATIONS

9:00 AM – 10:00 AM

PRESENTER Supervisor	PROGRAM	TITLE	PAGE
<b>Paramjit Bhardwaj</b> Dr. Nick Coupland & Dr. Jean-Michel Le Melledo	Ph.D.	<i>Glutamate and Depression</i>	10
<b>James Benoit</b> Dr. Andrew Greenshaw	M.Sc.	<i>Diffusion Tensor Imaging of the Anterior Insula-Anterior Cingulate Saliency Network in Adolescent Psychiatric Patients</i>	11
<b>Dmitriy Matveychuk</b> Dr. Glen Baker	Ph.D.	<i>The Monoamine Oxidase Inhibitor Phenelzine and its Metabolite <math>\beta</math>-Phenylethylidenehydrazine (PEH) Increase Rat Whole Brain Methylamine Levels and Sequester Reactive Aldehydes</i>	12

## FACULTY PRESENTATIONS

1:00 PM – 2:00 PM

PRESENTER Department	POSITION	TITLE	PAGE
<b>Dr. Tejas Sankar</b> Department of Surgery	Assistant Professor of Neurosurgery	<i>Neuroanatomical Predictors of Response to Deep Brain Stimulation for Treatment Resistant Depression</i>	13
<b>Dr. Andrew Greenshaw</b> Department of Psychiatry	Professor of Psychiatry	<i>Early Childhood Experience and Depression in Relation to Risk and Impulsivity</i>	14

# \* W.G. DEWHURST MEMORIAL LECTURE \*

11:00 AM – 12:00 PM

## Dr. Jeffrey Meyer

PROFESSOR, DEPARTMENT OF PSYCHIATRY AND CENTRE FOR ADDICTION AND MENTAL HEALTH, UNIVERSITY OF TORONTO

Dr. Jeffrey Meyer is a Canada Research Chair in the neurochemistry of major depressive disorder, a professor at the University of Toronto and the head of the neurochemical imaging in mood disorders at the Toronto PET Centre. Dr. Meyer trained as an undergraduate medical student and resident in psychiatry at University of Toronto. He completed fellowship training at the Hammersmith Hospital at Imperial College in London England, and then returned to Toronto to finish his Ph.D. He has over 65 publications in peer reviewed journals, many of which are in lead psychiatric journals like the Archives of General Psychiatry and the American Journal of Psychiatry.

Dr. Meyer is internationally known for his work in positron emission tomography imaging abnormalities in major depressive disorder and quantitating the effects of antidepressant treatments. This work began with studying monoamine abnormalities in mood disorders and led into mitochondrial markers in mood disorders, with new implications for preventing major depressive disorder and overcoming treatment resistance. He has received several important awards for this work: the AE Bennett Award from the Society of Biological Psychiatry, the John Dewan Award from the Ontario Mental Health Foundation, and the Canadian College of Neuropsychopharmacology Young Investigator Award. Dr. Meyer received the Royal College Medal Award in Medicine for contributions towards understanding the pathophysiology of major depressive disorder and was the first psychiatrist to obtain this award in its 60 year history.

### Neuroimaging Biomarkers of Dysphoria: Implications for Prevention and Treatment of Mood Disorders

**Introduction:** Monoamine oxidase A (MAO-A) is an enzyme found on the outer mitochondrial membrane of neurons, astrocytes and glia that metabolizes monoamines, facilitates apoptosis and creates oxidative stress. In brain, MAO-A density is highly correlated with MAO-A activity and MAO-A  $V_T$ , an index of MAO-A density, may be quantified with [ $^{11}C$ ] harmine positron emission tomography (PET). In a series of studies the relationship of MAO-A  $V_T$  in the prefrontal and anterior cingulate cortex to states of major depressive disorder, states of dysphoria and high risk states for Major Depressive Episode (MDE) was investigated.

**Methods:** [ $^{11}C$ ] harmine PET was applied to measure regional MAO-A  $V_T$ , an index of MAO-A level, during MDE (n=44), recovery from MDE (n=18), alcohol dependence (n=16), acute cigarette withdrawal (n=22), postpartum blues (n=15), and in health (n=35).

**Results:** During MDE and high risk states for MDE, MAO-A  $V_T$  was consistently elevated, particularly in the prefrontal and anterior cingulate cortex as compared to controls (elevation ranged from 25% to 45%, all comparisons to controls highly significant).

**Conclusions:** MAO-A  $V_T$  is elevated in the PFC and ACC during MDE, high risk states for MDE and some pathological dysphoric states. Reversing this marker represents a potential novel strategy for preventing MDE. This also has implications for reducing pathological dysphoria during withdrawal from some types of addiction, which is important since dysphoria during withdrawal predicts recurrence. Monitoring low cost, surrogate measures related to central MAO-A levels has novel potential for improving personalized medicine approaches to MDE.

## STUDENT POSTER SESSIONS (1 & 2)

10:15 AM – 11:00 AM

2:00 PM – 3:30 PM

Poster #	PRESENTER Supervisor or Department	PROGRAM	TITLE	PAGE
1	<b>Jiyun Chung</b> Dr. Satyabrata Kar	M.Sc.	Effect of Cholesterol Accumulation on the Metabolism of Amyloid Precursor Protein in Cultured N2a Cells	15
2	<b>Michal Juhas</b> Dr. Andrew Greenshaw	M.Sc.	Magnetic Resonance Imaging of Altered Brain Connectivity and Regeneration Patterns in Alcohol Use Disorder	16
3	<b>Yasmeen Krameddine</b> Dr. Peter Silverstone	Ph.D.	Homeless Individuals and their Perception of Police: An Outcome Based Analysis	17
4	<b>Marnie MacKay</b> Dr. Serdar Dursun	M.Sc.	Nitric Oxide Neuromodulation in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study	18
5	<b>Erin Martin</b> Dr. Peter Silverstone	Ph.D.	Adult-Targeted Child Sexual Abuse (CSA) Education: The Development of a Canadian Program	19
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9	<b>Anna Sasse</b> Dr. Satyabrata Kar	M.Sc.	Cellular Expression of Amyloid Precursor Protein (APP) and its Processing Enzymes in a new line of Bigenic Mice Overexpressing APP in the Absence of Nieman-Pick Type C Protein	23
10	<b>Yanlin Wang</b> Dr. Satya Kar	Ph.D.	Roles of Insulin-Like Growth Factor-II Receptor in Amyloid Precursor Protein Processing	24
11	<b>Lauren Alston</b> Centre for Neuroscience	M.Sc.	Eye-Tracking and Memory for Threat in Repressive Coping	25
12	<b>Andrea Shafer</b> Centre for Neuroscience	Ph.D.	Effect of Mindfulness Training on Emotional Distraction and Attentional Control in Adolescents with Mental Health Disorders	26
13	<b>Dr. Dharini Sivakumar</b> Adult Psychiatry Program	External	Literature Review of Absconding Patients from Psychiatric Units	27

# DEPARTMENT OF PSYCHIATRY AWARDS FOR RESEARCH TRAINEES

## GENERAL DEPARTMENTAL AWARDS

### **Roger C. Bland Graduate Award in Psychiatric Research**

This award is offered annually to a graduate student who has demonstrated excellence in psychiatric research. This award consists of \$1000 and a certificate bearing the recipient's name.

## RESEARCH DAY AWARDS FOR PRESENTATIONS BY RESEARCH TRAINEES

### **Gordon King Research Prize**

This award is named in honour of Dr. Gordon King, a child psychiatrist with a strong interest in psychopharmacology. Preference will be given to research trainee presentations in child psychiatry or psychopharmacology, but any area of research is eligible. The award will consist of \$500 and a certificate bearing the recipient's name.

### **Geoff Hopkinson Memorial Award**

This award is named in memory of Dr. Geoff Hopkinson, a long-time member of the Department of Psychiatry. Dr. Hopkinson was particularly interested in the training of psychiatry residents and graduate students. Preference for the award will be given to research trainee projects on the neurobiology of psychiatric disorders, but any area of psychiatric research is eligible. The award will consist of \$500 and a certificate bearing the recipient's name.

### **Glen Baker Award**

This award is named after Dr. Glen Baker, a former Chair of Psychiatry and a former Canada Research Chair who is currently a University of Alberta Distinguished University Professor. The award can be given for any area of psychiatric or neurologic research conducted by a research trainee and will consist of \$500 and a certificate bearing the recipient's name.

## JUDGES

DR. CHRISTIAN BEAULIEU

DR. JOHN GREER

DR. NICHOLAS MITCHELL

DR. ANTHONY SINGHAL

# GLUTAMATE AND DEPRESSION

Paramjit Bhardwaj<sup>1</sup>

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Major Depressive Disorder (MDD) is a mood disorder that is characterized by depressed mood, decreased self-esteem, and loss of interest in activities that were previously pleasurable. The lifetime prevalence of MDD is approximately 19%, and it is the leading cause of disability in the 15-44 year old demographic.

Traditionally, pharmacotherapies in the pathophysiology of MDD have targeted monoamine neurotransmission systems. However, animal research and post-mortem clinical data have indicated that glutamate dysregulation also occurs in MDD. More recently, advancements in Proton Magnetic Resonance Spectroscopy (<sup>1</sup>H-MRS) have allowed for researchers to measure glutamate independent from other metabolites. Unlike post-mortem research, <sup>1</sup>H-MRS allows for non-invasive collection of data from the brains of living humans. Thus, assessing glutamate's role in MDD using these recent advancements may contribute to the further development of novel glutamatergic pharmacotherapies.

This talk will review recent findings on the role of glutamate in MDD and its potential treatment.

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# DIFFUSION TENSOR IMAGING OF THE ANTERIOR INSULA-ANTERIOR CINGULATE SALIENCE NETWORK IN ADOLESCENT PSYCHIATRIC PATIENTS

James R. A. Benoit<sup>1</sup>, Andrea T. Shafer<sup>2</sup>, Matthew R. G. Brown<sup>1</sup>, Andrew J. Greenshaw<sup>1</sup>, Serdar M. Dursun<sup>1</sup>, Sunita Vohra<sup>3</sup>, Florin Dolcos<sup>4</sup>, Anthony Singhal<sup>5</sup>

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70% of all mental illnesses begin in childhood and adolescence, with 22.2% of the population severely affected before the age of 19, and 40% of those affected with more than one disorder. Treating mental illness costs almost twice as much per patient as somatic or biomedical disorders, leading to a heavy financial burden for families and the health care system. Diffusion tensor imaging (DTI) is beginning to provide insight into how differences in white matter integrity and connectivity affect mental health, leading to novel treatment targets. Diffusion tensors are measured and fitted to the data, and fractional anisotropy (FA) is computed in each voxel of an image (i.e. the rate and direction of water diffusion in a given volumetric pixel), which allows us to infer white matter connectivity and integrity. Here, we target anterior insula (AI) & anterior cingulate cortex (ACC), two core regions in the salience network (SN) that is responsible for attributing importance to intra- and extra-personal stimuli. Malfunctions of this network have been implicated in several diverse psychiatric disorders, including schizophrenia, autistic disorder, and anxiety disorders. In this study, we used 30-direction DTI to acquire images from 32 adolescents with psychiatric disorders and 11 healthy controls (age 12-17, no neurological disorders or psychotic symptoms). Our goal was to determine the location and magnitude of white matter integrity changes within AI & ACC of patients compared to controls. Results will be presented and combined with existing functional MRI studies of the salience network to suggest novel therapeutic targets.

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# THE MONOAMINE OXIDASE INHIBITOR PHENELZINE AND ITS METABOLITE $\beta$ -PHENYLETHYLIDENEHYDRAZINE (PEH) INCREASE RAT WHOLE BRAIN METHYLAMINE LEVELS AND SEQUESTER REACTIVE ALDEHYDES

Dmitriy Matveychuk<sup>1</sup>, Emerson Nunes<sup>1</sup>, Erin M. MacKenzie<sup>1</sup>, Glen B. Baker<sup>1</sup>

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The MAO inhibitor phenelzine and its metabolite,  $\beta$ -phenylethylidenehydrazine (PEH), have been reported to possess several neuroprotective properties that may be of relevance to Alzheimer's disease (AD). Both drugs increase brain levels of GABA, neutralize toxic formaldehyde and are potent inhibitors of human primary amine oxidase (PrAO) *in vitro*. PrAO was found to be co-localized with cerebrovascular  $\beta$ -amyloid (A $\beta$ ) deposits and have increased activity and expression in AD.

We have investigated rat whole brain levels of methylamine, a physiological substrate for PrAO, after injection of phenelzine or PEH using gas chromatography with mass spectrometry (GC-MS). Administration of PEH caused a significant accumulation of methylamine starting at 3 hours and reaching the highest levels at 12 hours. Phenelzine also increased methylamine levels at 6 and 12 hours, but to a much lesser extent than PEH.

In addition, we have investigated the ability of phenelzine and PEH to sequester the reactive/neurotoxic aldehydes acrolein, malondialdehyde (MDA) and methylglyoxal using a GC-MS assay. These aldehydes are increased in the AD brain, and have been reported to contribute to tau hyperphosphorylation and A $\beta$  oligomerization/fibrillogenesis. When incubated at equimolar concentrations with the aldehydes, phenelzine and PEH sequestered acrolein by 80-90%; MDA by 30%; and methylglyoxal by 10%. With the exception of phenelzine with MDA, sequestration was observed in a dose-dependent manner for both drugs with the aldehydes tested.

These results suggest that phenelzine and PEH may be potentially useful adjunctive treatments in AD where there is increased PrAO activity and excess acrolein, MDA and methylglyoxal.

Funding: CIHR (GB) and QE II Scholarship (DM).

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## NEUROANATOMICAL PREDICTORS OF RESPONSE TO DEEP BRAIN STIMULATION FOR TREATMENT RESISTANT DEPRESSION

Tejas Sankar<sup>1,2</sup>, M. Mallar Chakravarty<sup>3</sup>, Natasha Jawa<sup>2</sup>, Peter Giacobbe<sup>4</sup>, Sidney H. Kennedy<sup>4</sup>, Sakina J. Rizvi<sup>4</sup>, Clement Hamani<sup>2,3</sup>, Andres M. Lozano<sup>2</sup>

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**Introduction:** Deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG) is an exciting and novel therapeutic approach to treatment-resistant depression. However, SCG DBS improves the symptoms of refractory depression in only some patients but not others. Identifying those patients who are likely to respond is therefore an important ongoing aim. We propose that there are pre-existing structural differences between the brains of responders and non-responders to SCG DBS, detectable prior to surgery using conventional, pre-operative structural magnetic resonance imaging (MRI) scans.

**Methods:** We studied pre-operative, T1-weighted MRI scans of twenty-five patients treated with SCG DBS within the last eight years at the Toronto Western Hospital. Responders (n=14) were patients whose 12-month Hamilton Rating Scale for Depression (HAM-D-17) score improved by >50% from baseline prior to DBS. A trained observer blinded to patient identity measured the pre-operative volume of the SCG region in each patient. Automated measurements of hippocampal, thalamic, whole-brain, total grey matter, and total white matter volume were obtained. Automated whole-brain cortical thickness analysis was also performed.

**Results:** Baseline SCG and thalamic volumes were significantly larger in patients who responded to DBS surgery. Hippocampal volume did not differ between groups. Interestingly, grey matter volume across the entire brain was significantly higher in non-responders, and the ratio of pre-DBS grey:white matter volume distinguished between eventual responders and non-responders with high sensitivity and specificity.

**Discussion:** Greater structural integrity of the target SCG region may correlate with response to DBS, while non-response may be related to a developmental phenotype in which the structure of the whole brain is affected.

**Conclusions:** There are indeed structural differences between the brains of depressed patients who respond to SCG DBS and those who do not. These structural differences may point to a subset of patients with treatment resistant depression characterized by a unique neurodevelopmental trajectory.

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## EARLY CHILDHOOD EXPERIENCE AND DEPRESSION IN RELATION TO RISK AND IMPULSIVITY

Andrew J. Greenshaw<sup>1</sup>

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Childhood and adolescence can be a tough time, ‘accidents and unintentional injuries’ and suicide, respectively, are consistently the two leading causes of death in persons aged 15-21 in Canada. Risky behaviour in childhood and adolescence is associated with increased psychopathology later in life. Brain imaging and behavioural studies indicate that differential maturation of limbic neural pathways related to emotion, and prefrontal cortical pathways associated with response inhibition give rise to relatively high expression of risky behaviours in adolescence. Early experience influences patterns of human brain maturation and there is compelling evidence for adverse childhood experience as a significant determinant of psychopathology. Consequent alterations in the relative function of limbic and prefrontal cortical circuits during childhood and adolescence may give rise to increased risk and impulsivity. Such effects may have relevance for understanding the course and outcomes of depression and other mental disorders in childhood and adolescence. Recent research indicates that ‘risk’ and ‘impulsivity’ may be dissociable. We tend to think of risk and impulsivity as tightly related concepts – but risk is not always associated with impulsivity. It is important for us to understand the relationship of risk and impulsivity in terms of brain function. Our work in the CARPI research group at the University of Alberta, analysing functional magnetic resonance imaging (fMRI) measurements during a response inhibition task (Go/Nogo) with emotional visual distractors has revealed evidence for possible dissociation of ‘risk’ and ‘impulsivity’. These and other results will be discussed in the context of implications for child and adolescent depression.

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# 1. EFFECT OF CHOLESTEROL ACCUMULATION ON THE METABOLISM OF AMYLOID PRECURSOR PROTEIN IN CULTURED N2A CELLS

Jiyun Chung<sup>1</sup>, Mahua Maulik<sup>2</sup>, Satyabrata Kar<sup>1,2</sup>

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Alzheimer's disease (AD) is a progressive, multifactorial neurodegenerative disease thought to be initiated by abnormal aggregation of  $\beta$ -amyloid ( $A\beta$ )-related peptides. Over the last decade, there has been a wealth of evidence suggesting a connection between cholesterol and components of  $A\beta$  synthesis. Many of these studies have found that a rise in cholesterol level and/or its redistribution may influence AD pathology by increasing the production of  $A\beta$ -related peptides from the  $\beta$ - and  $\gamma$ -secretase-mediated processing of Amyloid Precursor Protein (APP).

The present study aims to examine the role of cholesterol in APP processing using cultured N2a cells treated with U18666A, a class II amphiphile which triggers redistribution of cholesterol to the endosomal-lysosomal system. Three variations of N2a cell lines – wild type (N2awt) and N2a cells transfected with wild type human APP (APPwt) or human APP containing Swedish mutation (APPsw) – were treated with U18666A in 0%, 5%, and 10% fetal bovine serum. Our results obtained so far indicate that U18666A treatment differentially increases the levels of APP, APP-CTFs, and  $\beta$ -secretase in the three cell lines. Detection of  $\alpha$ -secretase,  $\gamma$ -secretase, and extracellular  $A\beta$  levels are currently under investigation. These results suggest that cholesterol accumulation within cells can increase APP metabolism via amyloidogenic pathway, which may have a role in AD pathology.

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## 2. MAGNETIC RESONANCE IMAGING OF ALTERED BRAIN CONNECTIVITY AND REGENERATION PATTERNS IN ALCOHOL USE DISORDER

Michal Juhas<sup>1</sup>, Tiffanie Tse<sup>1</sup>, James R. A. Benoit<sup>1</sup>, Marnie MacKay<sup>1</sup>, Matthew R.G. Brown<sup>1</sup>, J. Tim Gillese<sup>2</sup>, Andrew J. Greenshaw<sup>1</sup>, Serdar M. Dursun<sup>1</sup>

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As reported recently in The Lancet, alcohol use disorder is the biggest addiction problem facing Western civilization. Alcohol dependence affects up to 4.1% of Canadians and alcohol abuse was in 2002 responsible for direct health care costs of over 3.3 billion dollars. Treatment strategies for alcohol dependence have traditionally relied primarily on psychosocial therapies without pharmacological intervention. The psychosocial therapies, however, result in very high relapse rates exceeding 50%. Currently available pharmacotherapeutic options offer a moderate improvement of the clinical outcome but yield mixed results, often without significant improvement from placebo. This study aims to use magnetic resonance imaging to examine neural patterns of regeneration in recovering alcohol dependent patients undergoing psychosocial therapy with or without pharmacological intervention with a clinically effective opioid receptor antagonist naltrexone. We hope that our findings will help us better understand altered connectivity in alcoholic brain and effects of naltrexone on regeneration in the recovering brain. Our hypothesis is that naltrexone will result in a clinical improvement that will correlate with decreased differences in functional and structural connectivity between normal and alcoholic brains. Our regions of interest include anterior cingulate cortex, insula, nucleus accumbens, and pre-frontal cortex. Although naltrexone primarily acts on the opioid receptors, it is also known to affect mesolimbic dopaminergic pathways and might have yet unknown effects on other addiction circuitry. The results of this study will eventually be combined with related animal studies to identify possible novel therapeutic targets and help bridge the gap between experimental and clinical studies of alcohol dependence.

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### 3. HOMELESS INDIVIDUALS AND THEIR PERCEPTION OF POLICE: AN OUTCOME BASED ANALYSIS

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Police officers constantly interact with individuals exhibiting varying forms of mental illness. Although research has been conducted concerning the perceptions that police officers have towards those with mental illness, there is limited research regarding how vulnerable and homeless individuals view the police. This is of interest as the large majority of these also have a mental illness and/or addiction. To examine this issue, 127 homeless individuals (male = 72%, female = 28%, mean age = 41, SD = 12.1), were interviewed regarding their attitudes towards police, and the outcome of their last interaction with the police service. The survey was intended to gauge attitudes concerning empathy and communication abilities displayed by officers, level of trust and confidence these individuals had in police, perceptions on how police interactions have impacted their life over all and how individuals felt after the interaction. Overall, level of satisfaction after police interactions was positive in 29%, neutral in 8%, and negative in 63%. Of the total, 37 (29%) had been arrested or handcuffed during their last interaction with police. This group that was arrested or handcuffed viewed their interactions with police significantly more negatively, and this also correlated with them being strongly dissatisfied with the outcome of their most recent police interaction ( $p=0.007$ ). Those who were arrested or handcuffed also have much less positive views of the police, and see the police as not being empathetic ( $p=0.015$ ), having a negative impact on their lives ( $p=0.003$ ), causing escalation of their anger ( $p=0.016$ ), and having low overall confidence in the police ( $p=0.048$ ). It should be noted that these impacts are long-lasting, and these findings suggest that even a single negative interaction with the police can have impacts that last at least 12 months. Those who have not been arrested, handcuffed, ticketed, or taken anywhere have much more positive views of the police in all instances, with statistical significance in viewing police as having positively impacted their life ( $p=0.008$ ), and leaving them in a happier mood ( $p=0.024$ ). Continued data collection will occur over the next few months to allow further analysis of this relationship.

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#### 4. NITRIC OXIDE NEUROMODULATION IN SCHIZOPHRENIA: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Schizophrenia is a complex neuroprogressive illness that often requires combined treatments to control its symptoms. Despite the availability of several neuroleptic medications on the market, many patients remain symptomatic. The opportunity exists to identify safe and well-tolerated treatments that can be used in conjunction with antipsychotic medications that will improve efficacy with minimum side-effects. Glutamate/nitric oxide (NO)-based therapies may offer an alternative approach as a therapeutic target for drug development. In this study, our goal was to determine whether the augmentation of antipsychotic medication with L-arginine in schizophrenia could further improve and enhance the therapeutic efficacy and effectiveness of antipsychotic treatment. In a blinded cross-over design, 13 subjects with a DSM IV TR diagnosis of schizophrenia were administered L-arginine or placebo for 21 days at a dosage of 6 g per day (3g twice a day), with a wash-out period of 5 days; then re-commenced on the alternative arm of the randomization. Pre- and post- treatment scores were obtained from the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions Scale (CGI), and the Calgary Depression Scale for Schizophrenia (CDSS) to evaluate the positive, negative, cognitive, and depressive symptoms of schizophrenia. Significant improvement in anxiety and cognitive symptoms were found in patients while they were receiving L-arginine treatment relative to placebo. There were no clinical side-effects observed by the structured Udvalg for Kliniske Undersogelser (UKU) rating scale or the Abnormal Involuntary Movement Scale (AIMS). Improvement in anxiety and cognitive symptoms with L-arginine augmentation may indicate that NO production in the brain can modulate neurotransmission and improve treatment-resistant symptoms in schizophrenia with no additional side-effects. Nitric oxide donors may be a safe and effective augmenting strategy and a novel approach to the advancement of future pharmacological treatments in the illness. Additional investigations of the NPAS3 gene, a potential susceptibility gene in schizophrenia, as well as plasma amino acid and neuroactive steroid measurements were also conducted to determine their possible role in glutamate neurotransmission.

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## 5. ADULT-TARGETED CHILD SEXUAL ABUSE (CSA) EDUCATION: THE DEVELOPMENT OF A CANADIAN PROGRAM

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Child sexual abuse (CSA) is a common problem with serious consequences. Retrospective prevalence studies estimate around 30% of girls and 10% of boys experience sexual abuse. Because the problem is so wide reaching, CSA education efforts have become increasingly common. Most programs evaluated in research literature target children and demonstrate varying rates of effectiveness. Far fewer evaluated education programs target adults. Moreover, few published evaluations outline the program development process making it difficult to assess content or the development process. Currently, a national Canadian program aimed to educate adults about CSA does not exist. It is critical, given the seriousness of the issue that adults receive accurate and effective training about CSA including how to respond to suspicions of CSA. One way to achieve this goal is to develop program content after thorough review of literature. Another approach is to learn from those people who have the lived experience of CSA: adult survivors of CSA themselves.

The program we are developing targets non-offending adults who have interactions with children. We aim to increase accurate knowledge about CSA, to decrease negative attitudes about CSA, and to increase positive CSA related conversations with children (i.e. responding positively to disclosures of CSA). First, comprehensive literature review and consultation with experts are utilized to develop an education program with accurate information that is grounded in adult teaching and learning theory. Second, once the program is developed it will be run and evaluated to assess effectiveness using questionnaire and focus group methods.

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## 6. A PILOT STUDY: OXYTOCIN AS AN INTERVENING FACTOR IN THE RELATIONSHIP AMONG DOMAINS OF TRUST AND VIOLENCE

Michael Mazo<sup>1</sup>, Kaitlin A. Chivers-Wilson<sup>2</sup>, Colleen Norris<sup>3</sup>, Gerri Lasiuk<sup>3</sup>, Anthony S. Joyce<sup>1</sup>, Nicole Pitre<sup>3</sup>, Glenda MacQueen<sup>4</sup>, Kathleen M. Hegadoren<sup>3</sup>

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Oxytocin (OT), the putative biological correlate of trust, has been suggested as a physiologic mechanism that underlies women's responses to serious stressors and a unifying mechanism underlying the psychological and physical manifestations of distrust. To date, pre-clinical trials as well as experimental paradigms using mixed gender populations have overlooked the role of sex and gender differences in the relationships between OT, trust and stress. **Methods:** 45 pre-menopausal women were enrolled in this pilot study. A clinical interview and standardized psychometric tools assessed psychological and physical health dimensions such as self-reported measures of trust and perceived stress. Plasma and saliva samples were collected and analyzed for levels of oxytocin, cortisol, progesterone, estradiol, and corticotropin releasing factor. **Results:** Descriptive data and correlational analyses were completed to look at OT levels, three domains of trust scores and the impact of interpersonal violence experiences. No significant differences were found between OT levels and the three domains of trust however on subgroup analysis, the relationship between OT and trust scores differed depending on stage of life and type of violence, suggesting interactions not previously reported. **Conclusions:** Preliminary data from the pilot study suggests that the trust inventory can delineate different aspects of trust, and that the direction of trust scores is related to the type of violence and life stage where violence was experienced. Controlling for OT levels change some of the directions observed in the relationship between domains of trust and violence, suggesting imbedded interactions requiring further study with a larger cohort of women.

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## 7. DECISION MAKING IS IMPAIRED IN MORE ADVANCED MULTIPLE SCLEROSIS AND RELATED TO BRAIN ATROPHY

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Cognitive deficits affect approximately 50% of multiple sclerosis (MS) patients. Cognitive deficits are usually more strongly related to measures of brain atrophic changes than MS lesion load. We examined MS patients using the Game of Dice Task (GDT), a task that measures decision making with explicit rules and has not been used in this population. Although prior studies found decision making deficits in MS patients using different tasks, these were usually uncorrelated to cognitive or executive functions. Brain atrophy was never assessed together with decision making in MS. The GDT and a standard neuropsychological battery were administered to healthy controls (n=20) and MS patients with varying levels of neurological impairment: 1) “RR-1”: 13 relapsing-remitting (RR) MS patients with mild disability, 2) “RR-2”: 9 RR-MS patients with moderate disability, 3) “SP”: 10 patients with secondary progressive MS. Compared to controls, decision making deficits in the GDT were confined to the two more disabled patient subgroups RR-2 and SP, while the RR-1 subgroup was unimpaired. Only RR-2 patients showed a trend correlation between decision making and executive functions, while decision making in the entire patient group correlated with processing speed. Patients’ brain atrophy was studied with linear measurements on clinical MRI images. Among several parameters, third ventricular width (TVW) showed strongest correlations with cognition, especially processing speed, as well as to decision making. In summary, decision making with explicit rules in MS is impaired, but only in more disabled patients. In these patients, deficits are related to cognitive impairment and to ventricular enlargement.

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## 8. ADVERSE CHILDHOOD EXPERIENCES AND PSYCHOTIC SYMPTOMATOLOGY; PRELIMINARY INVESTIGATIONS

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Adverse Childhood Experiences (ACEs) have been shown to increase the risk for social and health problems later in life (Felitti et al. 1998). In addition, for many health outcomes, there is a linear relationship between number of ACEs experienced and severity of health outcome (Anda et al. 2006). Onset of psychosis appears to be related to ACEs (Varese et al. 2012). There has also been early research that suggests the type of ACE may affect the symptomatology of psychosis. In particular, having experienced childhood adversity results in an increase in positive symptoms (Hainsworth et al. 2011).

In a preliminary analysis of data collected on a subset of the NPAS3 study, a small sample of psychotic participants (n=27) completed a 10-item ACE questionnaire (Felitti et al. 1998) and the frequency counts were analyzed. 18.5% reported no ACEs, 14.8% reported one ACE only, with 66.6% reporting two or more ACEs. Additionally, we found a statistically significant association on an ANOVA between ACEs and positive symptoms using self-reported measures of abnormal perceptions on the Cardiff Abnormal Perception Inventory (F=3.516, p=0.034) controlling for diagnosis and sex, and delusional ideation on the Peters' Delusions Inventory (F=6.129, p=0.007) controlling for age.

Future directions will be to increase the sample size of this study to increase the power, as well as to further delineate how specific ACEs may relate to particular psychotic symptoms in order to aid psychiatric and psychological interventions.

### Acknowledgements

The NPAS3 study is funded by the Canadian Institute of Health Research.

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## 9. CELLULAR EXPRESSION OF AMYLOID PRECURSOR PROTEIN (APP) AND ITS PROCESSING ENZYMES IN A NEW LINE OF BIGENIC MICE OVEREXPRESSING APP IN THE ABSENCE OF NIEMAN-PICK TYPE C PROTEIN

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Alzheimer's disease (AD) is a progressive neurodegenerative disease and is considered to be the leading cause for dementia affecting the elderly population in our society. The pathological hallmarks of the disease are neuritic plaques and neurofibrillary tangles located principally in medial temporal lobe, association cortex and to some extent in subcortical nuclei of AD brains. The neuritic plaques comprise of a dense core of amyloid  $\beta$  peptides ( $A\beta$ ) surrounded by activated microglia and astrocytes, as well as dystrophic neuritis. The  $A\beta$  peptides are derived from its precursor APP by successive cleavages of  $\beta$ - and  $\gamma$ -secretases. Glial cells are increasingly recognised as partners in cerebral neuronal system function and recent data from our lab has implicated that a subset of reactive astrocytes but not the microglia express APP and its processing enzymes. In the present study, we are using a new line of bigenic mice overexpressing mutant APP in the absence of NPC1 protein. We showed that APP and its processing enzymes such as  $\alpha$ -secretase,  $\beta$ -secretase and components of  $\gamma$ -secretase are expressed in a subset of reactive astrocytes but not in microglia, compared to the wild-type mice. These results suggest that astrocytes may have an important role in the generation of  $A\beta$ -peptides in AD pathology.

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## 10. ROLES OF INSULIN-LIKE GROWTH FACTOR-II RECEPTOR IN AMYLOID PRECURSOR PROTEIN PROCESSING

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The insulin-like growth factor-II (IGF-II) receptor involves in the transport of newly synthesized lysosomal enzymes from the trans-Golgi network to endosomes. The endosomal-lysosomal system, the major site of IGF-II receptor expression, plays a critical role in the processing of amyloid precursor protein (APP) leading to the generation of  $\beta$ -amyloid ( $A\beta$ ) peptide - a key player in the development of Alzheimer's disease pathology. However, the role of IGF-II receptor in APP processing remains unclear. To address this issue we used IGF-II receptor overexpressing and deficient fibroblast cell lines to study the influence of the receptor on APP processing and  $A\beta$  metabolism. A variety of biochemical assays were used to measure mRNA or protein levels of APP, its processing enzymes and  $A\beta$  in these cells. Confocal microscopy and lipid raft isolation were used to detect the distribution of the IGF-II receptor, APP and its processing enzymes. Our data revealed higher mRNA levels of APP as well as  $\beta$ - and  $\gamma$ -secretases in IGF-II receptor overexpressing cells. Accordingly, we observed increased levels of APP, immediate precursors of  $A\beta$  and activities of  $\beta$ - and  $\gamma$ -secretases in these cells. Secreted APP fragments and  $A\beta_{1-40}/A\beta_{1-42}$  were also higher in their conditioned media. These changes were reversed by knocking down IGF-II receptor levels. Additionally, higher levels of APP and its processing enzymes were localized with IGF-II receptors on lipid raft, an active APP processing site. In summary, our results suggest that higher levels of IGF-II receptors can increase APP level/processing leading to enhanced production of  $A\beta$  peptides.

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## 11. EYE TRACKING AND MEMORY FOR THREAT IN REPRESSIVE COPING

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People with a repressive coping style under-report physiological stress and display early vigilance followed by attentional avoidance of threat. Repressors also show reduced memory for threat. Unclear is how their attention patterns relate to later memory. To test how early threat vigilance changes into avoidance and if both translate into later memory, participants were monitored with eye-tracking during incidental encoding of neutral and negative pictures. Coping styles were determined according to a continuous scale of repressiveness: the Index of Self-Regulation of Emotion (ISE), with high ISE scores indicating greater repressive coping (REP). To provide opportunity for attentional avoidance, pictures were either presented alone or alongside scrambled pictures. Memory was tested thereafter. Electrodermal responses to an acute stress induction were acquired before the experiment, along with subjective reports, to validate questionnaire-based coping styles. Higher ISE scores correlated with reduced reported stress, frustration, and embarrassment after stress task, but not with physiological stress response. Overall viewing durations were similar across groups: we found no evidence for threat vigilance with higher ISE. While longer time spent fixating on negative pictures increased recognition memory in low ISE groups, this was not the case for high ISE (REP) participants. Since viewing time predicted later memory for negative pictures in NREPs but not REPs, it is possible that reductions in negative memories in REP are not only mediated by early vigilance and avoidance in visual attention, but also retrieval-based strategies.

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## 12. EFFECT OF MINDFULNESS TRAINING ON EMOTIONAL DISTRACTION AND ATTENTIONAL CONTROL IN ADOLESCENTS WITH MENTAL HEALTH DISORDERS

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In the past decade Mindfulness-based-stress-reduction therapy (MBSR) has become a growing topic of interest as it has been shown to be an effective non-pharmacological approach to decreasing symptoms of anxiety, depression, and stress in adult and adolescent patient populations. MBSR is a therapeutic technique designed to enhance one's ability to remain non-judgmentally focused in the present moment. This intervention is thought to specifically act on attention regulation mechanisms and research examining the neural correlates of meditation in experienced practitioners shows a strengthening of executive processes when engaged in meditation, presumably due to the focusing of attention required to perform meditation. However, the neural mechanisms underlying improvements in the symptoms associated with affective mental health disorders remains unknown. To investigate this issue, twenty adolescents with affective mental health disorders (10 with MBSR, 10 without) performed an emotional-oddball task pre- and post-treatment while brain imaging data were recorded. The emotional-oddball task was designed to allow for the assessment of emotion and executive processes, and the interactions between them. Preliminary analyses of behavioral and brain imaging data show MBSR to have a greater impact on emotion compared to executive processing. Moreover, the effect of MBSR was modulated by the type of emotion (fearful images showing the greatest effect, sad the smallest effect). Typical treatment (without MBSR) was found to have no effect on behavioral performance to the emotional images. Although analysis is ongoing, results-to-date provide novel findings concerning the effects of MBSR on emotion regulation processes in adolescents with affective mental health disorders.

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### 13. LITERATURE REVIEW OF ABSCONDING PATIENTS FROM PSYCHIATRIC UNITS

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**Background:** Psychiatric wards are at significant risk of patients absconding. This can be associated with serious risk of patient harm to self and the community. Moreover, although patients with serious mental illness are rarely prone to injuring others, the occasional act of violence by patients that have discharged themselves prematurely without medical approval tends to receive inordinate media attention further stigmatizing patients and their families. Premature discharge from the hospital is also associated with additional economic, social, and emotional costs.

**Aims and Objectives:** The current review will summarize the most outstanding burdens associated with absconding patient events, as well as the most salient factors contributing to these events.

**Method:** The method entails a qualitative literature review with emphasis on discrete factors that may be pursued within a later quantitative meta-analysis.

**Relevance to Clinical Practice:** A better understanding of the precipitating factors and associated costs is hoped to provide an empirical basis for guidelines towards best practices to reduce the frequency of occurrence and the costs associated with the events.

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12<sup>TH</sup> ANNUAL RESEARCH DAY*

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