



14th Annual Psychiatry Research Day

Abstract Book

Presented by
The Department of Psychiatry

Friday, May 22nd, 2015

WELCOME TO THE 14TH ANNUAL RESEARCH DAY OF THE DEPARTMENT OF PSYCHIATRY 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. Dr. Dewhurst was a pioneer in the area of "trace amines" and a founding Co-Director of the Neurochemical Research Unit. In recent years, 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 clinical and translational research, 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 and postdoctoral fellows 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.

We will begin our Research Day with talks by graduate students in our department, followed by faculty presentations in the afternoon. We thank graduate students James Benoit, Huining Guo, Erin Martin, Dimitar Ourdev, John Paylor, and David Rossolatos for volunteering to present their research this year, as well as Drs. Lisa Buchy, Dawn Kingston and Cameron Wild for their valuable faculty presentations. We will also feature poster session presentations by our research trainees and collaborators. The top presentations by research trainees will be acknowledged with awards.

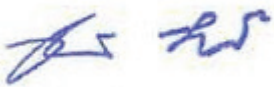
Our keynote lecture is sponsored by the W.G. Dewhurst Memorial Fund. Our keynote speaker for this year's event is Dr. Jaime Hallak, of the Ribeirão Preto Medical School of the University of São Paulo, Brazil. Dr. Hallak is a renowned expert on the neurobiology and treatment of schizophrenia. We are extremely excited to host Dr. Hallak at our event and anticipate that his talk will be substantial, interesting, and informative both for members of our faculty and external attendees. Dr. Hallak's W.G. Dewhurst keynote lecture is entitled, "The role of nitric oxide in pathogenesis and therapies of Schizophrenia." Dr. Hallak's visit to our department was supported by the Faculty of Medicine and Dentistry via the Walter Mackenzie Visiting Speaker Fund, and we are extremely grateful for this generous support.

We are grateful to all our research trainees and their supervisors for their contribution to the vital research component of our department. Special thanks to our organizing commit-

tee for Research Day, consisting of Dimitar Ourdev and Victor Foroutanpay (our graduate student representatives), Dr. Ian Winship and Dr. Andy Greenshaw, for their tireless efforts in organizing this Research Day. Thanks also to Karyn Crawford and Nazleen Madhani for administrative support to ensure this day is a success. We also gratefully acknowledge generous financial support from Mylan Pharmaceuticals, Lundbeck Canada, and Janssen Pharmaceuticals, GenCAN, and Campus Alberta Neuroscience for this important venture.

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

Best wishes,



Xin-Min Li, Professor
Chair, Department of Psychiatry



Andrew Greenshaw, Professor
Associate Chair of Research, Dept. of Psychiatry

ACKNOWLEDGEMENTS

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

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14TH PSYCHIATRY RESEARCH DAY ITINERARY

8:30AM - 8:45AM - OPENING REMARKS

8:45AM - 10:15AM - GRADUATE STUDENT PRESENTATIONS

JAMES BENOIT: *A machine learning approach to classifying depression from DTI data*

HUINING GUO: *Desvenlafaxine attenuated behavioral deficiency and oligodendrocyte damage in a transgenic model of Alzheimer's Disease*

ERIN MARTIN: *Evaluating a child sexual abuse prevention program: a pilot study to determine behavior change in adults*

DIMITAR OURDEV: *An interplay of plaques and quakes: exploring shared mechanisms in Temporal Lobe Epilepsy and Alzheimer's Disease pathogenesis*

JOHN PAYLOR: *Perinuclear net deficits in an Polyl:C model of Schizophrenia*

DAVID ROSSOLATOS: *Exploring the interplay between COMT and cannabis consumption in psychotic disorders*

10:15AM - 10:45AM - CAMPUS ALBERTA NEUROSCIENCE TALK:

DR. LISA BUCHY: *Neural correlates of insight in schizophrenia spectrum disorders*

10:45AM - 1:00PM - POSTER SESSION + LUNCH

1:00PM - 2:00PM - W.G. DEWHURST LECTURE

DR. JAIME HALLAK: *The role of nitric oxide in pathogenesis and therapies of Schizophrenia.*

2:00PM - 3:30PM - FACULTY PRESENTATIONS:

DR. DAWN KINGSTON (FACULTY OF NURSING): *Prenatal and postnatal maternal mental health and school-age child development*

DR. CAMERON WILD (SCHOOL OF PUBLIC HEALTH): *New pathways to addiction services: challenges in implementation and methodology*

3:30PM - 5:00PM - AWARDS PRESENTATION & RECEPTION

W.G. DEWHURST MEMORIAL LECTURE

1:00PM - 2:00PM

Jaime Hallak

MD, PhD, University of Sao Paulo

THE ROLE OF NITRIC OXIDE IN PATHOGENESIS AND THERAPIES FOR SCHIZOPHRENIA

Despite decades of study, the etiology and physiopathology of schizophrenia remain unknown. Recent evidence suggests that nitric oxide (NO) may be implicated in schizophrenia. NO is a gas that mediates the release of neurotransmitters, learning, memory, and neurodevelopment. Studies investigating the role of NO in patients with schizophrenia found evidence that points to a disruption in NO-mediated neurotransmission. Therefore, we investigated the effects of sodium nitroprusside, an NO donor, as an add-on treatment for patients with schizophrenia. Twenty adult schizophrenia patients treated with stable doses of antipsychotics were randomly assigned to two groups that received an infusion of either sodium nitroprusside or placebo for four hours. Psychiatric symptoms were assessed at baseline and every hour during the infusion with the Brief Psychiatric Rating Scale (BPRS) and the negative subscale of the Positive and Negative Syndromes Scale (PANNS-n). Additional assessments were made 12 hours after the infusion, daily for seven days, and weekly for four weeks. Cognitive tests (Stroop Color Word Test, N-back, and FAS) were administered at baseline and 12 hours after the end of the infusion. No side effects were reported by the participants. All the clinical and demographic characteristics of the sample including age, education, duration of disease, gender, diagnostic subtype, and type of antipsychotic in use were matched across groups. Symptom ratings were significantly reduced in the group treated with sodium nitroprusside, but not in the placebo group. Cognitive performance was also significantly improved in the nitroprusside group compared to placebo. There were no significant differences between the two groups regarding the physiological parameters analyzed (systolic and diastolic blood pressure, cardiac rhythm, and oxygen saturation). The strategy of treating schizophrenia patients for four hours with 0,5 mcg/kg/min sodium nitroprusside improved psychopathology and cognitive function. Our findings support the hypothesis that the NMDA-NO-GMPc pathway is affected in schizophrenia and that nitric oxide donors such as sodium nitroprusside could thus be a promising approach in the management of the disorder. Although exciting, these results are preliminary and must be replicated by future studies.

GRADUATE STUDENT PRESENTATIONS

8:45AM - 10:15AM

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A MACHINE LEARNING APPROACH TO CLASSIFYING DEPRESSION FROM DTI DATA.

James R.A. Benoit¹, Matt R.G. Brown¹, Serdar M. Dursun¹, Andy J. Greenshaw¹, Rajamannar Ramasubbu²

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² Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

Accurate and automated classification of mental disorders is one of the holy grails of computational psychiatry. We propose that the field can benefit from adopting a predictive approach from computing science called “machine learning”. Originally developed to make accurate predictions of risk, machine learning is increasingly finding application in health science, especially neurological and mental disorders. In this project, we aim to create a machine learning approach that can accurately classify depression severity from white matter skeletons constructed from their DTI data. We took DTI scans and patient data from a group of 18 healthy controls, and 52 patients diagnosed with varying severities of major depressive disorder (MDD). From these scans, we used FMRIB’s FSL 5.0 TBSS toolkit to create white matter skeletons of participants’ white matter tracts. Patients were then divided into tertiles by HAM-D score. Then, using the Python-based scikit-learn, Nilearn, and Numpy toolkits, we examined whether accurate participant classification of white matter skeletons from each tertile against our control group could be achieved via a machine learning pipeline using five-fold cross-validation.

DESVENLAFAXINE ATTENUATED BEHAVIORAL DEFICIENCY AND OLIGODENDROCYTE DAMAGE IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

Huining Guo¹, Junhui Wang¹, and Xin-Min Li¹

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Emerging evidence has shown that white matter deficits play an important role in the development of Alzheimer's disease (AD). Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressants that have been clinically used for the treatment of depressive and anxious symptoms associated with AD. However, whether antidepressants affect the pathogenesis of the disease remains to be elucidated. Here, we investigated the role of white matter in AD with APP/PS1 mouse, a well-characterized model of familial AD. Desvenlafaxine (DVS), a relatively new SNRI drug, was used in this study to explore the specific relevance of white matter and AD. We found DVS improved spatial memory, lowered anxiety and hyperactivity of APP/PS1 mice. At the same time, myelin basic protein (MBP), 2,3-cyclic nucleotide 3-phosphodiesterase (CNPase) and platelet-derived growth factor alpha-receptors (PDGFR α), all of which are myelin and oligodendrocyte markers, were significantly reduced in APP/PS1 group, and DVS could attenuate these proteins decrease in mouse brain. These findings suggested that DVS might alleviate the behavioral deficits in APP/PS1 mice by ameliorating myelin damages. While providing evidence for novel mechanism of DVS, our study may also contribute to the understanding of the important role of myelin and oligodendrocytes in the pathogenesis of AD.

EVALUATING A CHILD SEXUAL ABUSE PREVENTION PROGRAM: A PILOT STUDY TO DETERMINE BEHAVIOUR CHANGE IN ADULTS

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¹Department of Psychiatry, University of Alberta, Edmonton, Canada

²Little Warriors, Edmonton, Canada

Child sexual abuse (CSA) is incredibly common, with as many as 1 in 6 girls and 1 in 12 boys experiencing sexual abuse involving bodily contact. Preventing CSA is of utmost importance and experts are calling for prevention approaches that target a range of populations. Relatively few CSA prevention programs have been evaluated to determine effectiveness. Evaluations that have been conducted tend to focus on participant knowledge gain and change in attitude. We know very little about participant's behaviour change in regards to CSA preventative behaviours. Our study aims to determine the effectiveness of the Prevent It! Taking Action to Stop Child Sexual Abuse workshop with a focus on prevention behaviours. We predicted that participants who take this workshop would increase their use of individual and organizational prevention behaviours. Using online questionnaires, we collected baseline data (n=312) prior to an in-person classroom workshop. We then followed up with these individuals at 12-weeks (n=209, 12 week response rate = 67%). Using paired sample t-tests we determined the amount of change that occurred at follow-up. After the classroom workshop use of individual and organizational CSA preventative behaviours was significantly increased. This CSA prevention program increased CSA preventative behaviour in adults who took the classroom workshop. This study provides insight into CSA prevention workshop's ability to change adult participant behaviour. Given the potential cost savings from running online programs compared to in-person programs, further research will evaluate the effectiveness of the online version of this workshop.

THE EFFECT OF A β 42 OLIGOMERS ON APP PROCESSING ENZYMES AND A β 40 EXPRESSION IN CULTURED U373 ASTROCYTES

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³Department of Medicine, University of Alberta, Edmonton, AB, Canada

Amyloid- β (A β) peptides are a family of proteins that are considered to be a principal aspect of Alzheimer's disease (AD), the most common cause of senile dementia. These peptides result from the proteolytic processing of Amyloid Precursor Protein (APP) by the sequential cleavage of enzymes known as secretases. Although much work has been focused on the various interactions between A β and neurons, the relationship between soluble A β peptides and astrocytes has received relatively little attention. To address this issue, we incubated human astrocytes with oligomeric A β 42 and assessed the effect of this treatment on APP processing and A β production. Using the human astrocytoma cell line U373, we investigated the effects induced by A β 42 treatment on the cellular expression of APP and its proteolytically generated products, α CTF, β CTF, and A β 40 via Western Blot and ELISA. In conjunction with these experiments, we examined the relative cellular levels and activity of secretase enzymes, as well as the localization of the various components involved in the cellular processing of APP via immunostaining. Our Western Blot and ELISA data show that A β 42 treatment increased the expression of APP and cleaved products within astrocytes in a time-dependent manner. This treatment additionally increased γ -secretase activity in order to yield greater amounts of A β 40 in both cell lysates and cell media. Our study reveals that exposure to A β 42 potentiates further production of A β peptides in astrocytes. This can potentially form an important positive feedback loop that further exacerbates amyloid pathology observed in diseases such as AD.

PERINEURONAL NET DEFICITS IN THE POLYI:C MODEL OF SCHIZOPHRENIA

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Schizophrenia (SCZ) is a neuropsychiatric disorder that, despite a high prevalence (1% population worldwide) and burden of disease (1% global burden of disease), is still poorly understood in terms of its etiology. While symptoms of SCZ most typically begin to present after adolescence and into early adulthood, there is a substantial body of research linking prenatal events (e.g. early infection) to one's risk for developing SCZ. A number of recent human post-mortem analyses have identified perineuronal nets (PNNs) as a potential biomarker for SCZ as PNNs are deficient in a number of disease-specific regions of SCZ patients. Additionally PNNs, which surround parvalbumin positive (PV) inhibitory interneurons, typically see their maturation occur during late adolescence and early adulthood when SCZ symptoms often first present. As such, we sought to examine whether a similar PNN deficit is present in a maternal immune activation model of SCZ.

For our study, pregnant Long-Evans rat dams were treated at gestational day 15 with polyriboinosinic-polyribocytidilic acid (PolyI:C), a synthetic double-stranded RNA that triggers a strong maternal immune response. The litters were then carried to birth and offspring allowed to develop to 4 months of age. We used immunohistochemistry to assess PNNs, staining with the lectin *Wisteria Floribunda* Agglutinin and examined their integrity using epifluorescent and confocal microscopy across a number of brain regions: frontal association cortex, prelimbic cortex, anterior cingulate cortex, reticular thalamic nucleus, primary auditory cortex, retrosplenial cortex, primary visual cortex, and multiple olfactory regions. Additionally, we used fluorescent immuno-labels for microglia (IBA1) to assess immune activation and for PV interneurons (anti-PV) to assess neuronal integrity.

Our results show that PolyI:C treated offspring have widespread and significant deficits in PNNs in the frontal lobe, temporal lobe, and thalamus. This loss however was not associated with any change in closely-related PV interneurons. Furthermore, we find that in regions deficient in PNNs, there is also a decrease in the number of IBA1+ microglia present.

PNNs are critical structures in the regulation of neuroplasticity and along with PV interneurons are crucial to critical windows of heightened plasticity during development. A deficit in PNNs could lead to permanently pathological upregulation of structural plasticity into adulthood, as well as PV interneuron & cortical inhibitory network dysfunction. Our results not only further validate the PolyI:C model as an effective model of SCZ, but provide platform in which the role of PNNs in SCZ pathology can be further examined.

EXPLORING THE INTERPLAY BETWEEN COMT AND CANNABIS CONSUMPTION IN PSYCHOTIC DISORDERS

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Background: Cannabis use is a known risk factor for the development of psychotic disorders. This is a concern as growing number of adolescents are currently viewing cannabis as safe or even beneficial to one's health. Clinical and preclinical genetic studies provide growing evidence that genes related to dopamine signaling and neuroprotection, like COMT, are implicated in the cannabis-psychosis association.

Methods: In this study, we explore the role of markers in the candidate gene COMT in the development of psychosis after cannabis use in a sample of 244 patients recruited in Edmonton and Halifax, Canada. Data on cannabis use and other relevant variables were collected. Diagnostics were accomplished with the SCID for DSM-IV TR. DNA was extracted from salivary samples using the Oragene kit method. The COMT marker studied, rs4680 (Val158Met), was genotyped using TaqMan and SNaPshot. **Results:** 208 patients had both diagnostic and genetic data, with a mean age of onset for psychosis of 22.5 (sd=0.42) across the following diagnostic categories: schizophrenia (110), substance-induced psychosis (26), psychosis not-otherwise-specified (45), and affective disorder (27). Psychosis was associated with age of regular use of cannabis ≤ 19 years. Linear regression analysis of the patient group of self-reported Caucasian origin showed that COMT genotype predicted age of diagnosis with a p value of 0.038 only in the substance-induced psychosis subgroup.

Conclusions: We found an association between the COMT rs4680 SNP and log age of diagnosis of psychotic disorder in the Caucasians with substance-induced psychosis. The next step in our study is determine genetic admixture in our population. Ancestry informative markers have been genotyped and the data are being analysed, in order to factor in any hidden genetic substructure into the analysis. In addition, we are conducting time-to-event analysis covarying for gender, diagnosis and age of regular cannabis use.

NEURAL CORRELATES OF INSIGHT IN SCHIZOPHRENIA SPECTRUM DISORDERS

Dr. Lisa Buchy¹

¹ Campus Alberta Neuroscience Invited Speaker, University of Calgary, Calgary, AB, Canada

Cognitive insight is measured through one's "Self-Reflectiveness", the willingness to acknowledge fallibility, consider alternate explanations and recognize dysfunctional reasoning, and "Self-Certainty", an assessment of overconfidence. Early works established that people with psychotic disorders endorse lower Self-Reflectiveness and higher Self-Certainty than controls, and this is interpreted as poorer cognitive insight. Through a series of research reports our research group and others have modelled the psychopathological, neurocognitive and structural and functional neural correlates of cognitive insight in people with psychotic disorders. It is now established that cognitive insight is sensitive to patients' clinical characteristics including positive symptom severity and current level of functioning. Associations between cognitive insight and neurocognition in psychosis have also been documented, most notably with verbal memory and executive cognitive functions. Neuroimaging data have provided complementary results, linking cognitive insight to hippocampal volume, fractional anisotropy of the fornix, and more recently with gray matter volume and functional activation in ventrolateral prefrontal cortex. The current talk will present an overview of these findings. In addition, a cognitive neuropsychiatric model of cognitive insight is introduced in which we model how cognitive insight operates in non-clinical samples to better understand how these processes may become dysfunctional in psychosis.

NO HEALTH WITHOUT PERINATAL MENTAL HEALTH

Dr. Dawn Kingston¹

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In March, 2015 the Lancet published a bold editorial (No Health Without Perinatal Mental Health) that highlighted the findings of the UK's Royal College of General Practitioners report, *Falling through the gaps: Perinatal mental health and general practice*. The report described the UK's perinatal mental health system as "...a predominantly rushed, reactive and unreliable system of identification and support which often led [women] to fall through the gaps in this system of care" and followed with a recommendation to improve availability of specialist perinatal mental health services.

While on one hand the Lancet editorial captured the limitations of the perinatal mental healthcare system in the UK, it also highlights the stark contrasts between the Canadian and UK systems. In reality, Canada has no functional 'system' of perinatal mental healthcare. The purpose of the presentation is to examine the state of perinatal mental healthcare in Canada, to propose 'what is keeping us back', and to describe potential approaches for moving forward in building a system that detects perinatal mental health problems early and responds in a timely manner with appropriate, evidence-based mental healthcare.

NEW PATHWAYS TO ADDICTION SERVICES: METHODOLOGICAL AND IMPLEMENTATION CHALLENGES

Dr. Cameron Wild¹

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International and Alberta-based research consistently shows that the reach of treatment and other interventions for problematic addictive behaviours is less than population need for those services. Many people are reluctant to seek services for such a highly stigmatized health issue. Policy makers and service system managers recognize that creative approaches are needed to address unmet needs for care. One approach to this issue includes programs to enhance access to internet-based and other brief intervention strategies. Another approach includes policies to enhance access to specialty addiction treatment by using a variety of social control tactics. Unfortunately, no consensus has yet emerged on best practices for either of these pathways, and each brings with it a host of challenges that are seldom appreciated by policy makers and the public. This presentation presents two recent Canadian studies that highlight methodological and implementation challenges associated with these service models.

THE TRAUMA AND ATTACHMENT GROUP (TAG) PROGRAM: A NOVEL DYAD-BASED GROUP INTERVENTION FOR CHILDREN WHO HAVE ATTACHMENT ISSUES FOLLOWING EARLY DEVELOPMENTAL TRAUMA

Chandra Kirn Ashton¹, Peter H. Silverstone¹

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As part of a healthy childhood, children will experience a variety of stressors, but when the people who are supposed to care for the child's health and well-being are the cause of that stress, the effects on the developing child can include, among other sequelae, significant long-term issues with attachment and interpersonal relationships.

This study seeks to examine a latency-aged intervention program offered at CASA Child, Adolescent, and Family Mental Health, in Edmonton, AB. This intervention, the Trauma and Attachment Group (TAG) Program, is a novel, dyad-based, group-therapy program aimed at addressing the impact of significant relational and developmental trauma. Fifty-three child/caregiver dyads have attended the TAG program since 2011. Preliminary data demonstrates that there were significant improvements in attachment, communication, discipline practices, involvement, relational frustration, and reflective functioning in the caregiver, as well as a decrease of PTSD symptomology in the children. This intensive program shows promise as a way to improve trauma and attachment related outcomes, even past the proposed "critical period" for attachment. This study seeks to contribute to this growing body of research by learning more about what makes relational intervention effective with this vulnerable population.

DETERMINATION OF PV+ NEURONAL ACTIVITY USING MULTIPLE AAVs AND IMAGED IN VIVO WITH TWO-PHOTON CALCIUM IMAGING IN THE MOUSE SOMATOSENSORY CORTEX

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To distinguish between varying somatosensory stimuli, the somatosensory cortex should process dissimilar stimuli with different patterns of neuronal activation. Intrinsic optical signal (IOS) imaging reveals activation in the mouse somatosensory cortex in response to limb stimulation and allows functional segregation of cortical regions activated by the contralateral hindlimb (cHL) and contralateral forelimb (cFL). IOS imaging and electrophysiological recordings of small numbers of single cells have been used in the past to demonstrate “tuning” of cortical regions and of individual cells within the somatosensory cortex of monkeys to different modalities of cutaneous stimulation. However, a large scale population based examination of somatosensory tuning to complex somatosensory stimuli has never been reported within the limb associated somatosensory cortex of rodents. Further, the differential role of excitatory and inhibitory neuronal responses to the processing of somatosensory information has never been elucidated.

Here we used in vivo two-photon Ca²⁺ imaging after IOS to measure HL and FL somatosensory neuron responsiveness and response dynamics of populations as large as 250 neurons per optical section. We show that individual neurons within the somatosensory cortex can be precisely tuned to particular frequencies of vibrotactile limb fluctuation or broadly tuned to multiple frequencies of fluctuation, thereby forming a population code for sensory processing. We further demonstrate that higher frequency vibrotactile fluctuation of the limbs results in a larger percentage of neuron populations responding and with greater neuronal response strength. These population codes may result from preferential activation of different subsets of cutaneous and musculoskeletal receptors that respond to particular stimuli features and encode a sensory percept of somatosensory information needed for fine adjustment of motor control during limb movement.

Here we also demonstrate a new technique being employed in our lab where we expressed an AAV for GcAMP6S under a neuron specific promoter and an AAV for tdTomato selectively in parvalbumin positive (PV+) inhibitory interneurons under CRE dependent control in PV-CRE mice. As PV+ cell dysfunction is thought to be a contributor to sensory abnormalities in disorders such as schizophrenia and stroke, future studies using this technique will be highly useful for determining cell population specific changes in activity in these disorders.

SOCIAL ANHEDONIA AND CATECHOL-O-METHYLTRANSFERASE (COMT) IN HEALTHY YOUNG ADULTS

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The multi-faceted phenomenology of an episode of psychosis has impeded delineation of a measurable syndromatic phenotype that might provide a clinical reference to a relevant genotype. Although there is as yet no confirmed clinical endophenotype for psychotic disorders, there is an accumulation of indirect evidence that social anhedonia may be a good candidate for at least one type of psychotic disorder, schizophrenia, as well as more direct evidence from a recently demonstrated association between scores on the Social Anhedonia Scale – Revised (SAS-R) and a functional polymorphism of the catechol-O-methyltransferase (COMT) gene within family members of individuals with schizophrenia. The current study assessed further the potential value of the SAS-R as an endophenotype marker for psychosis by attempting to generalize the reported association between SAS-R scores and COMT genotype to a sample of 87 healthy high school students, approximately 17 years of age. The group homozygous for A/A at codon 108/158 of rs4680 had higher SAS-R scores than the group with the A/G genotype, and the group homozygous for the G/G codon exhibited a trend towards higher SAS-R scores than the A/G group. The homozygous A/A group has two methionine substitutions (met/met) resulting in a less efficient COMT enzyme and more available dopamine than the A/G genotype which has only one methionine substitution for valine (val/met). The homozygous G/G genotype has no substitutions and this val/val variant is associated with the most efficient COMT and the least amount of available dopamine. Our results are consistent with previous work supporting a measure of social anhedonia as a potential endophenotype marker for psychosis. The results are also consistent with prior suggestions that very low or very high dopamine metabolism may be linked with personality characteristics relevant to psychosis.

CYP2D6: DETECTING NEW STRUCTURES FOR CLINICAL PRACTICE

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Background

A gene that has been the focus of extensive pharmacogenomic research is the cytochrome P450 enzyme 2D6 (CYP2D6), which is highly polymorphic. Identifying how different alleles impact phenotype in terms of metabolism is desirable because CYP2D6 is involved in the metabolic pathway of up to 50 different drugs currently used in medicine. This project continues work that identified individuals with anomalous copy number calls¹, that might indicate combinations of CYP2D6 with its adjacent gene (CYP2D7), known as hybrid alleles. Our objective is to identify precisely which such hybrid variants are present. In this manner, the improvement in technology gained will enable correct identification of a wider range of variants of this enzyme than was previously possible, for translation into clinical practice in the form of more accurate pharmacogenetics testing.

Methods

The methodology applied was a long-PCR approach to identify hybrid alleles of CYP2D6 using the technique described by Kramer et al. (2009)² and Black et al. (2012)³, with fragment delineation by both agarose gel and Agilent 2100 Bioanalyzer (Agilent Technologies, Canada) electrophoresis.

Results

Results showed some successful amplification (generating products of the expected length, e.g., approximately 8 kb) for the conditions established. Comparison made between different runs point to effective changes to the initial method. The technique employed is a modified version of that described by Kramer et al., using a buffer that is specific for GC-rich regions.

Conclusions

Using a buffer specific for GC-rich regions facilitates this long-PCR analysis, which will be taken forward in other samples with anomalous copy number calls.

EFFECTS OF U18666A ON APP METABOLISM IN CULTURED N2a CELLS

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Amyloid β ($A\beta$) peptides originating from β -amyloid precursor protein (APP) are considered to play a critical role in the development of Alzheimer's disease (AD). Multiple lines of evidence suggest that elevated levels of cholesterol can influence amyloidogenic processing of APP, leading to increased production of $A\beta$ peptides. However, it remains unclear how sequestration of cholesterol within endosomal-lysosomal (EL) system, the major site of $A\beta$ production, can regulate APP metabolism. In this study we investigate how alteration in cholesterol level/distribution following treatment with U18666A, a class II amphiphile that triggers redistribution of cholesterol to the EL system, can influence the levels/processing of APP in cultured N2a cells grown in media containing 0%, 5% or 10% fetal bovine serum (FBS). The N2a cells used in the study includes wild type N2a cells (N2awt), N2a cells transfected with either wild type human APP (N2aAPPwt) or human APP containing Swedish mutation (N2aAPPsw). Our results indicate that U18666A treatment in 0% FBS, but not in 5% or 10% FBS, decreases the levels of total and free cholesterol in all categories of N2a cells. Changes in SREBP2 activation reflect this decrease in cholesterol. The levels of APP, APP-CTFs and intracellular $A\beta$ 1-40/42 are not markedly altered in N2awt cells but are differentially increased in N2aAPPwt and N2aAPPsw cells. However, levels of α -secretase ADAM10, β -secretase BACE1 and components of γ -secretase (PS1, Nicastrin, PEN2 and APH1) remain unaltered in all three types of N2a cells following U18666A treatment. We are currently evaluating levels of secreted $A\beta$ and activities of APP processing enzymes in U18666A treated N2a cells. Our results, obtained so far, suggest that redistribution of cholesterol into the EL system differentially alters the levels/processing of APP depending on the cultured conditions and endogenous levels of APP.

THEORY OF SELF ASSESSMENT

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We propose that cartoons could be used for accessing concepts related to the 'theory of self'. It consists of four basic concepts namely: (1) Self-awareness is the individual's ability to recognize independent thoughts or to attribute a mental state. (2) Self-others distinction is a basic set of cognitive and emotional processes that differentiates between own status and others status. (3) Self-reference is the ability to apply first-person (i.e. I, me & myself) to perceive, compare and respond to the state of the others. (4) Alter-self is the ability to use a second-person (i.e. you & yourself) to perceive, compare and respond to the state of the other.

Cartoons will be used in tasks for (1) Evaluation of self-awareness: Subjects will be directed to infer the status of the characters in three perspectives like physiologically, psychologically and spiritually contexts. It will assess the number of choices for the same status. It is believed that subjects will project their own status while choosing same interpretations regularly. (2) Evaluation of self-others distinction and self-reference: Subjects will be asked to make choice between characters with different facial characteristics and their preferences will be recorded. It assesses the number of chosen same facial characteristics repeatedly. It is believed that subjects will choose same facial characteristics repeatedly because of their own representation. (3) Evaluation of alter-self: Subjects will choose among characters one who would react or not to be a substitution to the main character. We will count the number of choices made by subjects on behalf of the main character.

We hope this project will provide valuable insights for assessment of mental disorders.

EFFECTS OF A β 1-42 ON APP PROCESSING IN CULTURED N2A CELLS

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Alzheimer's disease (AD), the most common cause of senile dementia and a growing global medical concern, is characterized by neuronal loss, tau-positive neurofibrillary tangles and amyloid- β (A β) containing neuritic plaques in selected brain regions. A β peptides are a family of proteins that are considered to contribute to AD pathogenesis. These peptides are derived from Amyloid Precursor Protein (APP) via sequential processing by β - and γ -secretases. Although much work has been focused on the interactions between A β peptide and neurons, the potential role of A β in APP processing is relatively unclear. Here we aimed to elucidate the effects of A β peptide on APP processing using cultured neuronal N2a cells. Through use of RT-PCR, we have shown that APP transcription is increased after A β treatment. Further analysis indicates an increase in APP and APP-CTFs levels in a time- and dose-dependent manner; however, the levels of secretases do not appear to alter following A β treatment. Similarly, our ELISA results have shown an increase in A β levels both in cell lysates and conditioned media. As a follow up, we will examine activity of β - and γ -secretases, as well as the subcellular localization of the various components involved in the cellular processing of APP and clearance of A β . These experiments will provide an insight into the molecular mechanisms by which A β can regulate the proteolytic processing of APP that can influence the loss of neurons and subsequent development of AD pathology.

SUBSTANCE USE AND CRAFFT SCORES IN YOUTH AGED 11-18: BASELINE FINDINGS FROM EMPATHY (EMPOWERING A MULTIMODAL PATHWAY TOWARD HEALTHY YOUTH) WHICH INCLUDES AN SBIRT INTERVENTION IN SCHOOLS.

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Background: Adolescent substance misuse continues to be a growing concern. Screening, brief intervention, and referral to treatment (SBIRT) may help reduce this in youth. While well studied in adults, it has been much less commonly studied in youth. Here we describe baseline findings in a large school-based SBIRT.

Methods: This study was part of a larger school-based intervention program (Empowering a multimodal pathway toward healthy youth, EMPATHY), whose primary goal is to reduce depression and suicidal thinking. As part of this screening occurs for drug, alcohol, and tobacco (DAT) use, there is a brief school-based intervention (guided internet-based cognitive behavioural therapy), and referral for treatment (both to primary care and specialist services). We screened over 80% of all students in Grades 6 – 12 (ages 11-18) within a single school system. We collected data on drug, alcohol, and tobacco use with a self-report measure administered electronically, which included the 6-items of the CRAFFT, a scale designed to measure the substance abuse in youth. A CRAFFT score of 2 or more may indicate elevated risk of subsequent abuse.

Results: A total of 3,244 students completed baseline measures, and 14% of students in Grades 6 to 12 scored at least 2 on the CRAFFT. There was a marked increase in students scoring at least 2 on the CRAFFT between Grades 8 (3.4%, mean age 13.3 years) and Grade 9 (18.3%, mean age 14.3 years), corresponding to the first year of High School. Approximately 10% of students had a score of at least 2 on the CRAFFT as well as significant symptoms of either depression or anxiety.

Conclusions: These baseline findings are in keeping with those previously described by others. Subsequent follow-up will determine if the form of SBIRT intervention contained within the EMPATHY program has a meaningful impact on drug, alcohol, and tobacco use in youth.

A CROSS-SECTIONAL STUDY TO EXAMINE RATES OF MENTAL HEALTH PROBLEMS AMONG WOMEN WITH HIGH RISK PREGNANCIES AND THEIR MENTAL HEALTHCARE NEEDS

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Up to one in four women experience mental wellness challenges, such as depression, anxiety, or stress during pregnancy. As such, rates of mental health morbidity are similar to the most prevalent medical complications in pregnancy, including gestational diabetes and hypertension. Without early intervention, up to 70% of women with prenatal depression or anxiety experience chronic symptoms that extend through the postnatal and early childhood periods. Indeed, systematic reviews of pregnancy cohort studies examining early life determinants of adverse child outcomes suggest that prenatal mental illness is one of the main predictors of sub-optimal mother-infant interactions, ultimately impeding child mental wellness and development. Few studies have explored mental health rates and needs in women with high-risk pregnancies. Available research suggests that these women represent a vulnerable group with rates of anxiety and depression up to 50%, and is consistent in showing that rates are over three times greater than those reported in pregnant women without medical complications.

The first step to helping women with pregnancy complications is to understand how many women are affected by mental illness, who is most at risk for mental illness, what help these women are currently accessing, and what help they need. We invited pregnant women admitted to 3W at the Lois Hole Hospital for Women for medical complications between October, 2014 and April, 2015 to participate in Part I of the study. Women were assigned to complete a baseline questionnaire, which was then entered into a database stored securely in the Health Research Data Repository housed in the Faculty of Nursing.

Our findings indicate rates of anxiety (49%) were greater than those for depression (8-36%). Among women with anxiety or depression, the majority had mild-moderate severity; thus, over 75% of women on the unit who screen positive for anxiety or depression would benefit from web-based therapy and would not require referral to specialty mental health services. If (based on the MINI diagnostic interview) 15% of women had severe symptoms of anxiety or depression in this cohort of 75 women, findings suggest that 5 women would be referred for anxiety and 1-4 for depression. While 15% of women on the unit were diagnosed with depression or anxiety, 5% of women reported receiving a referral to specialty mental health services. 33% of women had high psychosocial risk, and would benefit from ongoing/regular mental health assessment. While over 50% of women will not raise concerns about their mental health with a nurse, 97% will respond favorably to nurse-initiated screening. At present, the majority of women are not assessed for mental health while on the unit.

ASSESSING THE NEED FOR SUPERVISED INJECTION SERVICES AMONGST A POPULATION OF SOCIALLY MARGINALIZED PEOPLE WHO INJECT DRUGS IN EDMONTON

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Supervised injection services (SIS) are an important means for preventing HIV-related risk behaviours and overdose mortality amongst people who inject drugs (PWID). However, in Canada scale-up of this public health intervention has been slow due to consistent political opposition at the federal level. The Respect for Communities Act (recently passed by the House of Commons and expected to become law in 2015), outlines 26 onerous requirements SIS applicants must satisfy prior to receiving a federal exemption. In particular, the Act requires extensive epidemiological data on illicit drug use in a prospective jurisdiction. In Edmonton (as well as many other mid-sized Canadian cities) these data are not available. The present study was designed to address this gap, inform local SIS discussion and planning, and develop the scientific basis for a potential federal exemption application.

Adopting a community-based research approach, we conducted the largest-to-date survey of people who use illicit drugs in Edmonton. A group of 324 study participants were convenience-sampled from two community agencies with embedded needle exchange sites. Interviewers administered a structured questionnaire measuring illicit substance use, HIV-related risk behaviours and willingness to attend SIS. Descriptive and inferential statistics were used to describe characteristics of the sample.

A total of 279 participants reported recent injection drug use. Of these PWID, approximately 80% reported recent public injection; 47% reported difficulty accessing sterile syringes; 29% reported improper syringe disposal; 18% reported syringe sharing; and 22% reported experiencing a nonfatal overdose in the past 6 months. 90% of PWID were willing to attend SIS, if made available in Edmonton.

Relative to other Canadian jurisdictions, PWID in Edmonton engage in high rates of HIV-related risk behaviours and are at considerable risk for overdose-related morbidity and mortality. Supervised injection services should be made available in Edmonton in an effort to improve health and safety for PWID.

INFLAMMATORY PROFILE OF MICROGLIA VARIES BETWEEN MICROGLIA DERIVED FROM DIFFERENT REGIONS OF THE CENTRAL NERVOUS SYSTEM

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Microglia are the innate immune cells of the CNS and are important for maintenance of homeostasis in the central nervous system (CNS) as well as the inflammatory response to brain insult. 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. Notably, release of inflammatory cytokines tumor necrosis factor alpha (TNF α) and interleukin-1beta (IL-1 β) 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 a shaking technique to isolate microglia from the spinal cord of microglia. 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 TNF α and IL-1 β (reduced in spinal microglia relative to brain) after LPS activation. Microglial activation has been implicated in neurodegenerative diseases such as Alzheimer'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.

CHANGES IN RESTING STATE FUNCTIONAL BRAIN ACTIVITY IN EARLY ABSTINENCE FROM ALCOHOL USE DISORDER

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Alcohol use disorder (AUD) is a persistent health problem affecting approximately 5.43% of males and 1.92% of females over the age of 15 in Canada (WHO, 2012). Dynamic brain changes associated with alcohol dependence, recovery, and different treatments are only partially understood. We compared changes in the resting state networks in patients undergoing treatment for AUD. Our objective was to identify changes in the resting state networks specifically during early abstinence.

23 male patients (age 24-64) with AUD (DSM-IV TR) were recruited 5-10 days after detoxification and scanned (4.7 Tesla Varian system) before and after a 21-day residential treatment. 16 healthy volunteers matched for age, handedness, and education level were scanned for comparison. Both scanning sessions included an anatomical scan, a resting-state functional magnetic resonance scan, and a diffusion tensor scan. The functional data was analyzed using an independent component and region of interest analyses with FMRIB Software Library.

Our analyses revealed changes in several resting state networks including the default mode, the frontal, and other networks. In comparison to controls, patients had significant differences in functional connectivity between anterior cingulate cortex and an array of somatosensory, motor, visual, and association regions.

These findings suggest changes in functional connections of anterior cingulate cortex in AUD patients during early abstinence. Due to the role of anterior cingulate cortex in modulating execution of appropriate and suppression of inappropriate responses during reward anticipation and impulse control, these results could help us better understand dynamic changes in functional connectivity which are closely associated with addiction.

CHANGES IN BONE TURNOVER MARKERS IN AN ARIPIPRAZOLE ADD-ON OR SWITCHING STUDY

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Background:

Osteoporosis is two and a half times more common in patients with schizophrenia than matched controls[1]. The risk of having fractures is higher in schizophrenia than controls[2]. It is therefore important to investigate any role of antipsychotic use on bone health in patients with mental illness.

Method:

We conducted a one-year prospective study in which patients with psychosis were either switched to aripiprazole or aripiprazole was added on to their existing antipsychotic. We then conducted specific analysis of markers of bone resorption (NTXC) and bone formation (BSAP). In addition, levels of hormones prolactin, oestrogen and testosterone were measured. All these measurements were done at baseline (week 0) and then at weeks 1, 2, 6, 12, 26 and 52. Data analysis was done using generalized estimating equations in SPSS V22.

Results:

We found that NTXC levels reduced over time and approached significance in the whole group ($\beta = -0.20$, $p = 0.070$). The addition of or replacement with aripiprazole resulted in a significant reduction in BSAP ($\beta = -0.118$, $p = 0.008$). In the hormones, only prolactin showed a significant reduction ($\beta = -3.624$, $p = 0.002$), while oestrogen and testosterone did not change significantly. On sensitivity analysis, switching to aripiprazole was the main factor affecting a reduction in NTXC compared to the addition of aripiprazole.

Conclusions:

This is the first such study to show a change in markers of bone turnover. Switching to aripiprazole was important in effecting a reduction in bone resorption. Considerations pertinent to long term bone health and hence fracture risk should play a part in antipsychotic prescribing.

TRANSLATIONAL ANALYSIS OF L-ARGININE METABOLISM IN SCHIZOPHRENIA AND A PHENCYCLIDINE MODEL OF PSYCHOSIS

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Glutamate/nitric oxide (NO)-based therapies may offer an alternative approach for drug development in schizophrenia since a recent clinical study indicated that the NO-donor sodium nitroprusside was able to induce rapid improvement of symptoms in patients with the illness taking antipsychotic medication. The amino acid L-arginine, the substrate for the NO-producing enzyme neuronal nitric oxide synthase (nNOS) in the brain, may also be of interest as an augmenting treatment in schizophrenia. In addition to its role as a NO precursor, L-arginine also plays an important role in the urea cycle, mediated by the enzyme arginase. We investigated the effects of oral L-arginine and related amino acids in human plasma and the dose- and time-response effects of a single injection of L-arginine, the antipsychotic medications clozapine and risperidone, alone and in combination in whole brain samples in a PCP animal model of psychosis. Results indicate that in the post-absorptive state, human plasma levels of L-arginine are maintained at physiological levels within 12 hours of oral dosing. Whole brain samples indicate that L-arginine crosses the blood-brain barrier (BBB) within 15 minutes of administration. Significant dose-related increases in ornithine levels mediated by the enzyme arginase were also found in the brain, while potentiation of citrulline levels were only significant within 15 minutes of L-arginine administration, an indicator of early NO biosynthesis. The addition of antipsychotic medications did show a trend for increasing brain L-arginine and ornithine levels further. The competing actions of nNOS and arginase for L-arginine binding will be discussed in relationship to these findings.

ANTEMORTEM NEUROIMAGING MARKERS OF ALZHEIMER'S DISEASE: A META-ANALYSIS

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Alzheimer's disease (AD) is the world's most common form of dementia, which mostly affects older people. AD has a precursor step known as Mild Cognitive Impairment (MCI). However, According to the world Alzheimer's report, it is estimated that more than 135 million people worldwide will suffer from dementia by 2050. Like heart disease and cancer, AD imposes a severe financial and caregiving burden on health care system.

Although research has explained great deal about AD, there is much yet to be uncovered. At present, the diagnosis of AD is based on clinical observations and cognitive testing but the absolute diagnosis can only be confirmed by a postmortem study. Most of the neuroimaging techniques are non-invasive in nature and are used in in-vivo the detection of brain changes. A literature survey of neuroimaging studies particularly on magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) will be carried out to try to answer several ongoing questions about AD. These questions are: (1) Are there any in-vivo neuroanatomic structures that could be used for early absolute diagnosis of Alzheimer's disease? (2) Why does not all mild cognitive impairment (MCI) lead to full AD? (3) What is the rate of magnitude of medial temporal lobe atrophy during the course of disease progression?

I am planning to conduct a meta-analysis of all published neuroimaging studies and will use advanced neuroimaging datasets to find advanced antemortem markers for early diagnosis of AD. I am hoping this project would help one day clinicians with diagnosis of AD by providing them with a set of antemortem neuroimaging markers for AD.

SEQUESTRATION OF TOXIC REACTIVE ALDEHYDES BY THE MONOAMINE OXIDASE INHIBITOR PHENELZINE AND ITS METABOLITE β -PHENYLETHYLIDENE-HYDRAZINE (PEH)

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The antidepressant/anxiolytic drug phenelzine has been shown to possess neuroprotective properties in animal models of cerebral ischemia, multiple sclerosis and traumatic brain injury. It appears that a metabolite of phenelzine, β -phenylethylenedihydrazine (PEH), shares some of its neuroprotective mechanisms. Due to the presence of a hydrazine moiety, phenelzine and PEH may be able to directly sequester aldehydes. Levels of acrolein and malondialdehyde, toxic reactive aldehydes generated by lipid peroxidation, are increased in the brains of Alzheimer's disease (AD) patients and implicated in AD pathogenesis via several pathways, including potentiation of amyloid- β oligomerization/fibrillogenesis and tau hyperphosphorylation. We investigated the ability of phenelzine and PEH to sequester acrolein and malondialdehyde *in vitro*, attenuate acrolein toxicity in mouse cortical neurons and reduce rat whole brain levels of extractable acrolein and malondialdehyde *ex vivo*.

We employed GC-MS for quantitation of acrolein and malondialdehyde sequestration *in vitro* and in rat whole brain following administration of both drugs. Mouse cortical neurons were co-treated with acrolein and phenelzine or PEH, followed by assessment of cell viability with the MTT assay.

Phenelzine and PEH dose-dependently sequestered acrolein and malondialdehyde *in vitro*. In mouse cortical neurons, cell viability was increased when acrolein was co-treated with phenelzine or PEH. Neither phenelzine nor PEH treatment had a significant effect on rat whole brain acrolein levels. Phenelzine, but not PEH, reduced rat whole brain malondialdehyde levels. These results suggest that further investigation is warranted on aldehyde sequestration by phenelzine and PEH, as both drugs have the potential to be protective against aldehyde toxicity and may be useful as adjunctive treatments in AD.

PILOT RANDOMIZED CONTROLLED TRIAL OF INTERNET-BASED CBT FOR ADOLESCENT ANXIETY

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Introduction: There is a demand to make first-line treatments, including cognitive behavioural therapy (CBT) for adolescent anxiety disorders, more widely available [e.g.,1]. Internet-based CBT is proposed to circumvent access and availability barriers and reduce healthcare system costs [2, 3]. Recent reviews suggest further study is needed to establish the treatment effects of Internet-based CBT in children and adolescents and determine economic impacts [4,5].

Methods: We are conducting a multi-centre, 2-arm parallel-group, pilot randomized controlled trial (RCT) (NCT02059226). Outcomes will inform the planning of a full-scale RCT aimed to test the effectiveness of Internet-based CBT with a population of adolescents with moderate-to-mild anxiety. Adolescents aged 13-17 years seeking care for an anxiety-based concern at a participating emergency department, primary care setting or community-based clinic are being screened for interest and eligibility. Enrolled adolescents are randomly allocated to 8 weeks of Internet-based CBT with limited telephone and email support, or a control group with access to a webpage listing anxiety resources. Data on recruitment and retention, self-assessed anxiety, intervention use and acceptance, co-interventions, and healthcare resource use/costs are being collected at baseline, post-intervention, and 3-month follow-up.

Results: We aim to enrol 80 adolescents. To date, 87 adolescents have been screened for eligibility and 11 have been enrolled in the trial. We will present data on the trial's recruitment rate and interim results for participant demographics and outcomes of interest.

Conclusions: This pilot RCT is an essential step to designing a robust RCT for evaluating the effectiveness of Internet-based CBT for adolescents with moderate-to-mild anxiety problems.

REALIST REVIEW OF INTERNET-BASED INTERVENTIONS FOR ADOLESCENT ANXIETY

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Introduction

Internet-based cognitive-behavioural therapy (CBT) and interpersonal therapy (IPT) aim to provide timely, accessible, cost-effective intervention alternatives. Recent reviews indicate encouraging evidence for the effectiveness of Internet-based interventions for treating adolescent anxiety (1-4). However, since therapeutic, technology and interaction features differ between interventions, understanding the factors that maximize treatment effectiveness for adolescent anxiety is important. This realist review objective is to develop an explanatory treatment model of how and for who internet-based CBT and IPT have been effective, ineffective or inconclusive in effect.

Methods

Diverse evidence from clinical trials, descriptive articles and theoretical and research literature on CBT and IPT interventions for adolescent anxiety and internet-based intervention/eHealth processes will be included. Analysis will be structured according to Pawson's (5) review techniques and meta-ethnography. During analysis, context-mechanism-outcome (C-M-O) hypotheses, based on eHealth program and persuasive system design, will be used to explain how and why internet-based CBT and IPT are effective or ineffective, pinpoint which components have the greatest impact, and identify for whom different content, interaction and technology features may yield the best outcomes.

Results

Ten C-M-O hypotheses have been developed to guide analysis (e.g., "Intervention contexts with real-time dialogue support elicit behaviour changes", "Intervention contexts that incorporate user-centred design elements increase user satisfaction"). Screening of 11,474 articles for review inclusion is underway. Development of the explanatory treatment model will follow.

Conclusions

This realist review will provide an understanding of how internet-based interventions for adolescent anxiety are differentially effective across various CBT or IPT principles, techniques, types of interactions between users, and technology features.

VULNERABILITIES TO PSYCHOSIS IN YOUNG PEOPLE.

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The etiology of psychosis has been difficult to ascertain owing to the complex nature of the illness. Many vulnerabilities to psychosis have been identified including genetic predisposition, social disadvantage, substance use, prenatal influences and life adversities. While no single vulnerability is enough to cause a psychosis, a combination of predisposing factors working synergistically appears to be of importance. We sought to evaluate several vulnerabilities to psychosis in a group of 229 local adolescents to see if these might predict their scores on scales of psychosis proneness. To measure vulnerabilities, we asked about psychological risk for mood (Mood and Feelings Questionnaire, MFQ) and psychosis proneness (Magical Ideation Scale, MIS, and Social Anhedonia Scale, SAS), as well as about Adverse life Events (AEs) and their substance abuse history. Additionally, we were given permission to contact 81 of their mothers for information regarding obstetric complications (OCs) and prenatal maternal stressors (PNMS). 80% of our population endorsed at least one AE and 70% endorsed having experienced two or more. AEs were correlated with scores on the MIS ($r=0.312$, $p<0.001$) and the MFQ ($r=0.338$, $p<0.001$), but not with the SAS. 55% of respondent mothers endorsed at least one OC in their pregnancy and 66% endorsed one or more PNMS. PNMS were correlated with MFQ ($r=0.230$, $p=0.039$), however there was no association with the proneness scales. Cannabis use at least once in lifetime was associated with MIS ($r=0.202$, $p=0.002$) and MFQ ($r=0.249$, $p<0.001$), but was not related to SAS. Now we must attempt to combine vulnerabilities to see if we can better predict vulnerability to psychosis scores. It is promising that several of our vulnerabilities are resulting in elevated psychological risk, however we must further investigate why the SAS has shown no associations and whether gender may play a role in the analyses.

EXPRESSION OF APP AND ITS PROCESSING ENZYMES IN GLIAL CELLS OF APP-Tg MICE IN THE PRESENCE OR ABSENCE OF NPC1 PROTEIN

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Evidence suggests that increased levels of amyloid beta ($A\beta$) peptides derived from amyloid precursor protein (APP) contribute to the development of Alzheimer's disease (AD). The regions primarily affected in AD brains are hippocampus and cortex, whereas striatum and cerebellum are relatively spared. Although neurons are considered to be the major source of $A\beta$ in the brain, the activated astrocytes associated with neuritic plaques have been shown to accumulate $A\beta$ which correlates positively with the severity of AD-associated tissue damage. Since cholesterol has been shown to influence $A\beta$ production, it is of interest to determine whether accumulation of cholesterol within endosomal-lysosomal system, the major site of $A\beta$ production, can influence levels and/or processing of APP. To address this issue we used mutant APP transgenic mice, mice lacking Neimann Pick Type C1 (NPC1) protein required for intracellular cholesterol transport and ANPC mice that overexpress mutant APP in the absence of NPC1 protein. The results obtained so far indicate that APP and its processing enzymes involved in $A\beta$ production such as β -secretase BACE1 and four components of γ -secretase complex (PS1, nicastrin, Pen2 and APh1) are expressed in a subset of reactive astrocytes in ANPC, APP-Tg and NPC1 knockout mice but not in wild-type control mice. The relative number of astrocytes expressing APP and its processing enzymes appear to more in ANPC>APP>NPC1 knockout mice. These results indicates that reactive astrocytes may have an important role in the generation of $A\beta$ -peptides in AD-related pathology. Additionally, accumulation of cholesterol within endosomal-lysosomal system may influence APP levels/processing in the activated astrocytes.

A COMPARATIVE ANALYSIS OF PROVINCIAL/TERRITORIAL HARM REDUCTION POLICY MAKING: AN INNOVATIVE METHODOLOGICAL APPROACH

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Scientific evidence indicates that harm reduction services prevent the spread of HIV/AIDS and other diseases, reduce the risk of overdose death, and connect people who use illicit drugs to addiction treatment and other health and social services. Under an instrumental-rational view of health policy making, a large evidence base supporting the cost-effectiveness of harm reduction interventions should translate into unproblematic policy support for the uptake of this approach as a routine component of health services. However, Canadian provinces and territories exhibit wide variability with respect to implementation of these services, and the approach remains highly contentious. Unfortunately, little research to date has explored factors that underlie the diversity of these services across Canada.

To address this gap we have assembled a team of academics and national and provincial-level knowledge users to implement a mixed-method, multiple case, policy analysis study. Drawing on four data sources: policy documents, media articles, key informant interviews, and a national public opinion survey we will 1) systematically document and compare the strength of each province and territory's harm reduction policy framework (including funding commitments, governance structures, etc.) and 2) explore relationships between the comprehensiveness of these policy frameworks and the way media, stakeholders, and the public frame these services.

Funding for this project has been secured and preliminary planning is underway. This poster describes our novel methodology and introduces the project to potential key informants and additional interested knowledge users. Findings are expected to contribute to academic scholarship on contentious health interventions for socially marginalized target populations, and will generate timely data to assist knowledge users in their efforts to advocate for equitable evidence-based policy supporting the expansion of harm reduction services across Canada.

DOMAIN-SPECIFIC MCCB-ASSESSED COGNITIVE ASSOCIATIONS TO SYMPTOMS OF METABOLIC SYNDROME IN PATIENTS REFERRED TO AN EARLY PSYCHOSIS INTERVENTION CLINIC.

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The metabolic syndrome (MetS) is a cluster of symptoms that have been identified as significant risk factors in the development of cardiovascular disease. The relevance of MetS to the psychiatric population has been demonstrated with independent connections to both the taking of medications and having a severe mental illness (SMI). Furthermore, a number of studies have investigated the link between cognitive dysfunction and MetS; however, most studies focus on older members of the general population.

An initial review of the literature focusing on studies involving non-geriatric general populations revealed that memory, executive functioning, processing speed, and general intellect were affected by having MetS, with specific MetS symptoms appearing to correlate with domain-specific cognitive changes. However, the data remain limited with respect to children and adolescents.

As well, several studies have explored the role of cognitive dysfunction and MetS specifically occurring in the context of severe mental illness, with studies involving a younger population also being limited.

Individuals presenting with early psychosis (having less than one year of treatment) to the Edmonton Early Psychosis Intervention Clinic, in Edmonton, Alberta were assessed with the MATRICS Consensus Cognitive Battery (MCCB) and evaluated on the components of MetS as defined by the NCEP ATP-III criteria. This preliminary analysis appears to show that higher triglyceride levels may have a detrimental influence in the specific cognitive domain of verbal learning. We also found that increased fasting blood glucose values within normal ranges may actually improve performance in other domains. Sample size was an obvious limitation; it is hoped that this will be extended. Should the findings continue to be upheld, further investigation and replication in larger independent datasets would be warranted.

PSYCHOBOTICS IN CLINICAL TRIALS: A SHORT REVIEW

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Objectives: Probiotics and prebiotic that may benefit to psychiatric illnesses are named as psychobiotics. The studies on gut-brain axis reveal the connection between gut microbiota and brain activity and behaviour. Certain probiotic strains can alternate GABA receptors expression, corticosterone and BDNF level on mice. Probiotics/prebiotics may become a new medicine for psychiatry diseases. With the intention we do a briefly review about the effect of current probiotic/prebiotic clinical trials on human.

Data Sources: Searchers were conducted in Medline databases in English and Chinese CNKI database with key words" probiotic, prebiotic, lactobacillus, bifidobacterium, yogurt, oligosaccharide, cheese, diet", combining with words linked with psychiatry such as "mood, depressive, anxiety, stress, cognitive, brain, behavior".

Review Methods: We pick up the studies on probiotics/prebiotics that reported the psychiatric effect in human participants. Including intervention studies and Retrospective studies. Patients with Gastrointestinal Diseases or other chronic disease diagnosis are excluded.

Results: These studies shows probiotics/prebiotics to some extent, can improve mood such as depressive, anxiety. The intake of Bimuno-galacto-oligosacchrides may smooth emotional response. Low fat cheese product may have some effect on elderly people's cognition function. The changes in cortisol and blood oxygenation level-dependent activity give us further clues on the mechanism. There is no positive result shows probiotics/prebiotics can ease psychotic symptoms, however, it reduces the side effect of antipsychotic. And there is no reports about severe adverse reaction to probiotics/prebiotics in these trails. That confirms the safety of microbiota treatment. As we still need further study to assess the probiotic's benefit to mentally illnesses. The use psychobiotic in mood disorder and schizophrenia is considerable.

COMPARING ADME-RELATED GENES WITH VARIOUS TECHNOLOGIES

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Introduction

ADME-related genes are involved in drug Absorption, Distribution, Metabolism and Excretion. The CYP450 family of enzymes plays a key role in the metabolism of most drugs, especially CYP2D6 and CYP2C19. We have also compared data across platforms on the gene encoding a protein highly important for the distribution of many drugs, the multidrug resistance transporter (ABCB1).

Methods

We have data available on a large sample genotyped using the Roche AmpliChip CYP450 Test® (covering variants in CYP2D6 and CYP2C19), with which we can cross-validate output from the Affymetrix DMETPlus Array.™ In addition, we have prior data on ABCB1 via candidate marker genotyping (including via TaqMan). Although the Roche test has the ability to identify individuals heterozygous for gene amplification alleles, the DMETPlus array includes many more ADME variants. In addition, the Roche test varies in terms of sensitivity by allele, with the CYP2D6*2XN having only 85.7% sensitivity, while the DMETPlus array is able to estimate only loss of gene copy number, not gain in gene copy number.

Results

This preliminary analysis shows some discrepancies in the data between the AmpliChip and DMETPlus arrays. For example, sample GDP0101 was called CYP2D6*1/*1 by DMETPlus, while the AmpliChip CYP450 Test® data was CYP2D6*1/*5. In addition, GDP0106 was called *2XN/*2XN by DMETPlus, while the AmpliChip CYP450 Test® results was *2XN/*41. For SNP rs2235015 in ABCB1, the apparent discrepancy in fact simply results from forward vs. complementary strand usage by different technologies (TaqMan, HapMap, A>C; Affymetrix, G>T). Finally, it appears that the latest version of the DMETPlus software is able to call rs28381915 with a higher call rate than previously.

Conclusions

There are some contrasts between two platforms; moreover, supplementary assays need to be conducted for specific markers.

CYTOSOLIC RELEASE OF CATHEPSIN D TRIGGERS NEURONAL DEATH

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Up-regulation of certain lysosomal enzymes within lysosomes can prevent sub-lethal damage, whereas sustained release of the enzymes into cytosol can induce cell death via cytochrome c release from mitochondria. However, very little is known about the subcellular distribution of lysosomal enzymes and their significance in Alzheimer's disease (AD). Since endosomal-lysosomal system is critical in the generation of β -amyloid ($A\beta$) peptides, which play important roles in the degeneration of neurons and development of AD pathology, we hypothesize that release/activation of lysosomal enzymes may participate in $A\beta$ -mediated toxicity and development of AD pathology.

We have used oligomeric human $A\beta$ 1-42-induced primary mouse cortical neuronal death model to evaluate the levels, activities and subcellular distribution of the lysosomal enzyme cathepsin D – an aspartic protease known to be involved in cell death mechanisms in a variety of conditions. Experiments are also carried out in the cortex of TgCRND8 mouse model of AD. We have observed that cathepsin D cellular/cytosolic levels increase with time during the oligomeric human $A\beta$ 1-42-induced neuronal death. Enhanced cytosolic levels of cathepsins D are associated with increased expression of pro-apoptotic molecular markers. By treating neurons with pepstatin A, an inhibitor of cathepsin D, we are able to protect them from $A\beta$ 1-42-induced toxicity. In parallel, cellular and cytosolic levels as well as activities of cathepsin D are found to be increased in the cortex of TgCRND8 mice compared to age-matched control mice. These changes appear to be correlated with increased neurodegenerative events associated with the cortex. Collectively, these results show that levels and activities of cathepsin D are increased in $A\beta$ 1-42-mediated toxicity in cultured neurons as well as in the cortex of mice exhibiting AD-related pathology. Enhanced cytosolic levels of cathepsin D may have a role in determining the selective vulnerability of neurons in AD pathology.

REOPENING THE WINDOW OF PLASTICITY: SOMATOSENSORY RECOVERY AFTER STROKE WITH DELAYED SPINAL CHONDROITINASE ABC TREATMENT

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Traditional therapies for stroke commonly focus on reducing damage in the brain soon after ischemic onset, leaving pathophysiological and adaptive processes in regions distal to the infarct, such as the spinal cord largely overlooked as therapeutic targets. Thus we directed therapeutic targets at the spinal cord during the chronic phase of stroke when spontaneous recovery had finished. We injected ChABC at the level of the spinal cord one month after a photothombotic stroke, long after stroke-induced axonal sprouting and recovery had plateaued.

Adult male Sprague-Dawley rats were given a unilateral focal ischemic stroke using the photothombotic model to target forelimb sensorimotor cortex. This stroke model was chosen for its ability to induce highly reproducible ischemic lesion in a selected area of the cortex with clearly defined infarct boundaries.

To determine functional recovery, rats were trained and tested on the single pellet reaching task, a task commonly used to assess forelimb function. Rats were tested before stroke and again at 7, 14, 21 and 28 days post-stroke. Based on persistent reaching deficits, rats were assigned to treatment groups. Intraspinous injections (into the spinal grey matter receiving corticospinal input from the stroke affected cortex) of ChABC or penicillinase (the control injection for ChABC) were given in the cervical vertebrae under isoflurane anaesthesia. Rats were again tested on the reaching task at 7, 14, 21 and 28 days after injection.

Comparing reaching scores from the various time points and treatment groups we were able to establish a trend which shows that ChABC injection improves functional forelimb recovery after delayed intraspinal administration relative to control.

Following final behavioural testing (56 days post-stroke) anterograde neuronal tract tracers were injected near the site of ischemic injury to assess changes in spinal cord connectivity. We found ChABC spinal injection facilitated sprouting and structural changes in spared fibres.

We evaluate the functional benefits of ChABC spinal administration and ability it to induce axonal sprouting at a delayed time point after stroke.