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2020/2021 Seed Funding
Projects:

Awardee: Mahavir Agarwal
Project title: Does abnormal insulin action in the brain underlie cognitive and metabolic dysfunction in schizophrenia?

Total Awarded: $200,000
Abstract: Background: Schizophrenia is associated with poor cognitive and metabolic outcomes that are not addressed adequately by currently available treatments leading to higher illness burden and lower quality of life. Brain insulin resistance has emerged as a potential mechanism underlying cognitive and metabolic disorders; preliminary evidence suggests that it might be a feature of schizophrenia as well. Direct markers of brain insulin action are not currently available. However, uptake of 18F-labelled fluorodeoxyglucose ([18F]-FDG) during a positron emission tomography (PET) scan following an intranasal insulin challenge can provide a surrogate marker.

Aim: To examine if antipsychotic-naïve/free schizophrenia patients have greater brain insulin resistance compared to matched healthy controls.

Hypotheses: Schizophrenia patients will have abnormal brain insulin action, evidenced by less [18F]-FDG uptake in response to intranasal insulin challenge, compared to healthy controls.
Moreover, change in [18F]-FDG uptake will be negatively correlated with the severity of cognitive and metabolic dysfunction in patients with schizophrenia.

Methods: Ten antipsychotic-naïve/free schizophrenia patients and ten matched healthy controls will participate in a single-blind crossover design, wherein all participants will undergo an overnight fast and two [18F]-FDG PET scans one week apart, one following intranasal placebo administration, and second with intranasal insulin challenge (160 IU) in a randomized order while receiving a somatostatin infusion. A cognitive battery and standardized symptom severity rating scale will also be administered. Significance: This pilot study can uncover aspects of schizophrenia disease process that are amenable to intervention using novel therapeutic strategies so as to target cognitive and metabolic abnormalities.

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Awardee: Vanessa Gonçalves
Project title: Mitochondria, Inflammation and Genetics: A new approach for psychosis early detection and intervention

Total Awarded: $198,022.23
Abstract: Schizophrenia is a complex disorder with both clinical and biological complexity (heterogeneity), and to-date, effective diagnosis, treatment and prevention strategies are largely absent, in-spite of the recent success in identifying contributing genetic variants from the nuclear genome. Mitochondrial DNA (mtDNA) plays a crucial role in the brain suggesting that genetic variants in this system may contribute to the etiology of mental illnesses; previous studies of primary mitochondrial diseases have observed impairment in brain function and high prevalence of psychosis among cases. Here, we propose four interconnected studies that aim to reduce biological complexity in early detection and prevention of schizophrenia, by considering the mitochondrial DNA in addition to the chromosomal DNA. These include:

1. conducting a largest to-date association analysis between mtDNA variants and schizophrenia using the worldwide Psychiatric Genomics Consortium (PGC) data with over 50,000 cases,
2. investigating mitochondria and chromosome gene-gene interactions, including those involving the X-chromosome,
3. evaluating one risk score made up of many genes to predict schizophrenia when incorporating mtDNA variants and their interactions, and
4. exploring the use of circulating cell free mtDNA in the blood as a marker for the presence of mitochondrial abnormalities and inflammation in schizophrenia.

Access to mtDNA data from PGC, the largest schizophrenia dataset, allows us to perform the analyses with strong statistical power. The results from our studies will likely identify new mtDNA variants from the previously over-looked mitochondrial system, which could lead to increased accuracy in disease prediction and personalized treatment of schizophrenia and other psychosis-related disorders.

Awardee: Ishrat Husain
Project title: Astrocytes as targets of lithium treatment in bipolar disorder: a [11C]SL2511.88 positron emission tomography study

Total Awarded: $199,991
Abstract: Up to 50% of patients with bipolar disorder (BD) experience recurrent mood episodes on currently available treatments. Thus, the development of new treatment approaches is a major health priority. A growing number of studies demonstrate that:

1. BD is associated with abnormal inflammatory and oxidative processes linked to astrocyte dysfunction;
2. immunomodulatory agents may improve mood symptoms. However, results of randomized controlled trials (RCTs) of these agents in BD have been mixed and none have incorporated brain imaging to understand their putative mechanism of action. Lithium has been widely used in the treatment of BD for more than 50 years; it remains a first-line treatment for both manic and depressive episodes. However, its specific mode of action is still unclear. Some evidence indicates that lithium has both immunomodulatory and anti-oxidative actions and regulates astrocytes. We propose to investigate the effect of lithium on astrocytes in BD using positron emission tomography (PET). We are completing pilot [11C]SL2511.88 scanning in 20 adults with BD to assess brain MAO-B volume distribution (VT) as an index of the baseline measure of astrocytes. With the support of seed funding from the Discovery Fund, we propose to rescan 20 participants with BD after 6 months of lithium treatment to determine whether clinical outcomes are associated with a change in astrocytes as quantified by MAO-B VT. This study has the potential to elucidate the impact of lithium on pathophysiological mechanisms in BD. If it establishes that astrocytes can be used as biomarkers and are potential therapeutic targets in BD, it will be a foundation for a precision medicine approach in the treatment of BD.

Awardee: James Kennedy
Project title: Identifying suicidality subtypes using machine learning and genomic data

Total Awarded: $200,000
Abstract: There are over 800,000 suicide deaths worldwide each year. With over 3,500 suicides and 70,000 suicide attempts each year, it is the ninth leading cause of mortality in Canada. Suicidal thinking (ideation) and behaviour (SIB) is very complex and is likely affected by many variables, including genetic factors. Finding genetic factors for SIB may require separating SIB into subtypes to reduce complexity.

Objectives: We aim to collect data from 550 participants and evaluate them on their SIB and a number of endophenotypes. We aim to uncover SIB subgroups based on these endophenotype measures. Then, we aim to find genes relating to each of the SIB subgroups.

Hypotheses:

1. Patients cluster into SIB subtypes based on the endophenotypes.
2. Genetic variants, in the form of genes, gene-sets, and risk scores calculated from thousands of genes, each with small effect, are associated with SIB subtypes.

Methods: Participants will be assessed through a series of questionnaires about their history of SIB (Columbia Suicide Severity Rating Scale (CSSRS)), stressful life events, personality, as well as through several neurocognitive tasks. A number of machine learning algorithms will be used to cluster participants based on these clinical assessments. A preliminary genetic analysis (gene-based, gene-set, and multigene-risk score) will be conducted across these SIB subtypes.

Significance: Findings from this study will provide for a better understanding of the biology of one or more SIB subtypes, which will inform the design of future suicide studies and the development of subtype-specific drug therapies and prevention.

Awardee: Yuliya Knyahnytska
Project title: Neural Correlates of anti-suicidal response to ketamine in treatment resistant bipolar depression

Total Awarded: $168,821.60
Abstract: The overall aim of this proposal is to investigate ketamine for the treatment of suicidality in bipolar depression and to use neurophysiological measures of NMDA neurotransmission to identify key biological targets of ketamine treatment response. Suicide is one of the top ten leading causes of death with rates progressively increasing making suicide a critical public health issue. Suicidality refers to a combination of suicidal thoughts, intent, and plan, and is the most lethal symptom affecting patients with depression. Bipolar disorder is one of the most incapacitating psychiatric conditions and one of the most costly to society. Researchers estimate between 25-60% of those with bipolar depression will attempt suicide at least once in their lifetime, and about 10-15% will die by suicide. Several interventions, such as lithium, clozapine, electroconvulsive therapy, and cognitive behavioral therapy demonstrated anti-suicidal properties; however, these treatments are often ineffective, difficult to tolerate or take months to have a full effect. Therefore, newer and more effective treatments for suicidality in bipolar disorder are needed. Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, which has shown rapid antidepressant and anti-suicidal effects. The development of an effective intervention for suicidality in BD remains a major therapeutic challenge and opportunity. Ketamine represents a promising treatment due to its rapid effect and for targeting underlying NMDA neurophysiological mechanisms. Establishing biological markers of treatment response is essential to enhance our understanding of both illness and treatment mechanisms.

Awardee: Matthew Sloan
Project title: Evaluating Cannabidiol as a Novel Anticraving Medication for Alcohol Use Disorder: A Human Laboratory Study

Total Awarded: $199,470
Abstract: Alcohol use is one of the leading causes of death and disability worldwide. Despite this, only three medications are approved to treat alcohol use disorder (AUD) in Canada and these medications are only effective in a subset of individuals. Developing new and effective pharmacotherapies is essential to reduce the rate of disability associated with AUD. Cannabidiol, a non-psychoactive component of the Cannabis Sativa plant, shows potential promise. Studies have demonstrated that cannabidiol decreases alcohol preference, self-administration, and relapse-like behaviours in rodents. However, despite these exciting findings, the effects of cannabidiol have not been studied in humans with AUD. The purpose of this pilot study is to determine the effects of cannabidiol on craving and alcohol self-administration in this population. We hypothesize, based on the preclinical findings, that cannabidiol will reduce craving and alcohol self-administration. We propose to recruit 28 non-treatment seeking subjects with AUD for a within-subject trial. Participants will be randomized to cannabidiol or placebo in a counterbalanced order for two 7-day treatment periods. On day 7 of each treatment period, subjects will complete an alcohol self-administration task that has been shown to identify effective pharmacotherapies for AUD. Craving, subjective response to alcohol, and alcohol consumption will be measured. If cannabidiol effectively reduces craving and alcohol self-administration, it could potentially be used either alone or in combination with approved pharmacotherapies for AUD. The addition of another effective anticraving medication would be a major clinical advance that could substantially reduce the rate of disability associated with AUD.

Awardee: Gillian Strudwick
Project title: Co-producing interventions to improve the adoption of OpenNotes in Ontario mental health contexts

Total Awarded: $199,120
Abstract: The purpose of the study is to co-produce and contextualize interventions that improve the adoption of OpenNotes by providers and patients. Our pilot research at the Centre for Addiction and Mental Health (CAMH) has identified from patients and providers the specific interventions that may be useful, and that should be developed for the Ontario context. Therefore, the aims of our study are to:

1. Identify the needs of mental health providers and patients in their use of OpenNotes at three distinct stages of adoption (before, during, and after implementation) building on our pilot data from CAMH;
2. Categorize the needs from the first objective to identify agreements and differences in the requirements for OpenNotes use from providers and patients. The differences will then be mapped to the interventions;
3. Contextualize the interventions from the second objectives through co-production with user groups. We will then apply for funding to evaluate the implementation of the interventions at the various study sites. The study will be conducted at four large organizations in Ontario that serve people with mental illness (two urban, one semi-urban, one rural) over a period of 2 years. The interventions to be co-produced consist of an electronic toolkit, short videos and podcasts. The present study will act as a catalyst for future digital mental health initiatives, where Ontario organizations can work together to support people with mental illness.

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Awardee: John Vincent
Project title: Identification and assessment of therapeutic potential of small molecules as allosteric modulators or chaperones for the Rett syndrome protein MECP2

Total Awarded: $200,000
Abstract: Rett syndrome (RTT) is the second most common genetic cause of intellectual disability in girls, and is caused by mutations in the X-linked gene MECP2. ~40% of RTT is caused by nonsense mutations which truncate the protein, and ~40% are caused by missense mutations (substitution of one amino acid for another). MECP2 is a transcriptional regulator, and current therapeutics research is mainly focussed on the downstream effects of the resulting dysregulation.

Objectives: This proposal aims to develop compound to reverse MECP2 protein degradation, and/or restore its function.

Hypothesis: small molecules or peptides with ability to bind to MECP2 can restore its activity and/or stabilize the protein.

Methods: We aim to utilize, in parallel, a. computational screening for small molecules, and b. screening for short peptides, targeting wild-type MECP2, and the most common missense and nonsense mutations. We will assay selected molecules for ability:

1. to recover DNA-binding and/or chromatin-clustering and gene regulation abilities of MECP2;
2. to stabilize MECP2 protein;
3. to recover normal neuronal morphology. For this purpose we have established a series of DNA binding and chromatin assays. We will also generate brain cells with the relevant MECP2 mutations using CRISPR/cas9 editing, so we can measure MECP2 mRNA and protein levels, before and upon addition of our selected compounds.

Significance: This project outlines the first steps to develop precision therapeutic compounds to treat RTT. This approach will spearhead a move towards precision therapeutics for other autism or intellectual disability genes.