Discovery Fund Talent Competition – 2022-2023

Awardee: Anna Pees

Supervisor: Neil Vasdev

Title: Development of PET radiopharmaceuticals for imaging cannabinoid receptors

Lay Abstract:
Cannabis and cannabis-derived products have recently been legalized in Canada for medicinal and recreational purposes and are the second most used substances in Canada, after alcohol. However, the benefits and harms are still uncertain. The part of the brain that is targeted by cannabis is known as the endocannabinoid system (ECS) and is implicated in several psychiatric and neurological disorders, e.g. addiction and Alzheimer's disease (AD). The ECS has been explored as target for drugs and biomarkers with little success since the knowledge about the underlying processes is rather limited. The general aim of this research proposal is to increase our knowledge and understanding of the ECS and its involvement in psychiatric and neurological disorders by medical imaging using a technique called positron emission tomography (PET). PET employs radioactive drug molecules (radiotracers) which are injected in the body and a PET scanner (camera) takes a picture of the living human brain. This work aims to develop a radiotracer targeting the CB1 receptor, which is the most abundant cannabinoid receptor in the ECS. A PET tracer lead targeting this receptor has recently been discovered; however, the tracer and its synthetic method need to be further developed to be able to translate it to widespread human applications. We will therefore establish new derivatives and radiochemical synthesis strategies for this PET tracer, test them in rodent models of brain disease, and use them to study human brain tissues. The most successful radiotracer will be prepared for human PET imaging studies to study several brain health illnesses for the first time in Canada.

Awardee: Jennifer Lepock

Supervisor: Michael Kiang

Title: Effects of N-acetylcysteine on cognitive event-related potential biomarkers of the clinical high risk state for schizophrenia

Lay Abstract: Clinical high risk (CHR) patients have milder forms of schizophrenia (SCZ) symptoms, and only a minority of CHR individuals will go on to develop SCZ. Efforts to refine our ability to identify those at highest risk are critical. To target treatment to those most in need, tests are needed to predict which CHR patients are most likely to develop psychosis. Measures such as event-related potentials (ERPs) offer objective reliable tools for predicting psychosis in CHR patients. N-acetylcysteine (NAC) is a natural health product shown to reduce SCZ symptoms such as hallucinations and delusions, and improve certain ERP deficits in SCZ. We are using the N400 ERP, which is seen as a reflection of how different concepts are related in the brain. The N400 ERP has been found to be deficient in CHR patients. We hypothesize that CHR patients taking NAC in a clinical trial over 8 weeks will have more normal N400 effects than those taking a placebo. In addition, we will examine the ERPs P3b and gamma auditory steady state response, which have been found to be abnormal in SCZ and CHR patients. We will measure gamma, P3b and N400 ERPs in CHR patients at baseline and again at 8 weeks of

NAC or placebo treatment. We will examine whether NAC treatment has a beneficial effect in patients on the N400, gamma and/or P3b. The results may identify ERP abnormalities associated with the effectiveness of NAC as a pharmacological treatment for reducing psychotic symptoms in high risk individuals.

Awardee: Shohreh Kariminezhad

Supervisor: Pushpal Desarkar

Title: Does hyperplasticity at the primary somatosensory cortex underlie atypical tactile reactivity in autism spectrum disorder?

Lay Abstract: More than 90% of individuals diagnosed with autism spectrum disorder (ASD) have atypical sensory processing manifested as either too much or too little reactivity to sensory stimuli. In the sensory domain, atypical tactile reactivity (TR) is very common and negatively affects social interaction and daily functioning. Many adults with ASD and the sensory reactivities disabling, therefore, TR has been identified as a key target for treatment. The exact brain mechanism underlying atypical TR that might inform treatment is not known. Animal experiments of ASD have shown that the brain in ASD can be abnormally responsive to modifying stimuli, i.e., has excessive plasticity and such excessive plasticity was noted to underlie atypical sensory reactivities in ASD. However, whether this is true for humans with ASD is not known. In this proposal, we will study plasticity in the sensory cortex in the brain to check the evidence for excessive plasticity. We will also test if such excessive plasticity is associated with atypical TR in ASD. We will recruit 20 adults with ASD and 20 age, sex, and IQ-matched matched controls. We will use an innovative combination of brain stimulation and electroencephalography to assess plasticity in the sensory cortex. If successful, this study will be a leap towards our understanding of the mechanisms underlying atypical TR, with the ultimate goal of offering the brain stimulation interventions required to improve TR and outcomes in ASD.

Awardee: Samar Salah Mohamedahmed Elsheikh

Supervisor: Daniel Mueller

Title: Integrative and Multifactorial Prediction of Antidepressant Remission in Late-Life Depression Using Structural Equation Modelling

Lay Abstract: Late-life depression (LLD; defined as age ≥50) affects 5.7% of people older than 60 years in Canada and this number is expected to double by 2041. However, treatment of LLD is particularly challenging due to a high prevalence of comorbid neurodegenerative and cerebrovascular diseases which also affect treatment outcomes. Notably, our recent study has shown that a higher polygenic risk score (PRS) for cardioembolic stroke was the second strongest predictor of non-remission (Marshe et. al 2021). Structural equation modelling (SEM) is a comprehensive framework that offers a unique opportunity as compared to other methods of inference (eg. genome-wide association studies (GWAS)). SEM provides flexibility in selecting a wide-range of predictors; accounting for their inter-correlation and mediated effects as well as analyzing the hidden heterogeneity and causal relationship while simultaneously

correcting for measurement errors. The overarching goal of this proposal is to develop SEM to understand the complex interplay between, and contribution of, various risk factors (i.e. socio-demographic, PRS) in the variability of depressive symptoms and the prediction of antidepressant remission in LLD. In addition to our unique samples available at CAMH, we will also utilize large and well-powered, publicly available GWAS summary statistics (e.g. UK Biobank) and seven well-characterized clinical cohorts of LLD patients treated with antidepressants (N~2733) to construct PRS and develop and validate our SEM. These findings will provide a platform to predict antidepressant remission, help develop a genetic test to personalize treatment leading to faster remission, and reduce disability in patients with LLD.