Discovery Fund Talent Competition 2023-24

Awardee: Heather Brooks

Supervisor: Tarek Rajji

Title: Optimizing Theta-Burst Stimulation to Enhance Plasticity in the Dorsolateral Prefrontal Cortex

Lay Abstract: Depression is a leading cause of disability worldwide, and is a major contributor to the overall global burden of disease. Current treatments for depression have modest efficacy. Theta-burst stimulation (TBS) is a form of brain stimulation that changes the plasticity of the brain, leading to antidepressant effects. Similar to medications, TBS has limited efficacy, although is usually better tolerated than antidepressant medications. Recent work in rodents demonstrates that we could improve the antidepressant effects of TBS by modifying some of its parameters, namely the time between episodes (the inter-episode interval, or IEI). The goal of the project is to test a newly developed TBS protocol, with longer IEI, compared to the traditional TBS protocol currently used in individuals with depression. We will recruit 40 individuals with depression and randomly assign them to receive one session of (1) the current TBS protocol, or (2) the newly developed TBS protocol with a longer IEI. We will determine if the new TBS protocol is better at inducing plasticity in the brain as compared to the current protocol. We will also explore the differences in antidepressant effects between the two protocols by measuring depressive symptoms before and after the TBS session. If successful, the project would lead to a TBS protocol that can better change the brain's plasticity, and could lead to greater antidepressant effects.

Awardee: Jesse Lacasse

Supervisor: Liisa Galea

Title: Identifying age-specific biomarkers underlying the link between major depressive disorder and hormonal contraceptive use.

Lay Abstract: Currently, over 300 million women worldwide use hormonal contraceptives (HC). In Canada, 16% of women between the ages of 15 and 49 use them. Despite the fact that they are one of the mostly widely prescribed drugs and that a significant number of women+ will use HC at some point during their lives, we understand very little about how HC affect the brain. In certain cases, women who use HC have an elevated risk of developing major depressive disorder (MDD) or being prescribed antidepressants. Research has shown that this is more often the case for young adolescent women. This link with MDD is not related to other factors like socioeconomic status or ethnicity which points to the role of a biological factor. Therefore, we aim to uncover brain-based changes related to use of HC by examining their effects both during adolescence and adulthood in female rats. We will target brain based biological markers that are associated with MDD to see how they might differ between life stages and HC exposure.
Biomarkers that are generally associated with MDD are the dysregulation of the stress response, reduced formation of new neurons in the brain, and heightened immune signaling throughout the brain. We will therefore examine these three endpoints in both adolescent and adult female rats. Given what is known about the risk of MDD with use of HC during

adolescence, we predict that adolescent rats will be more susceptible than adult rats to having dysregulated biomarkers related to MDD. This project stands to uncover how the adolescent brain might be at an elevated risk for MDD after exposure to HC. By knowing how biomarkers may become dysregulated at different life stages, we can begin to target future treatments and adopt a more precision-medicine approach to prescribing HC. With the pervasive and growing use of HC, it is essential to increase our understanding of their brain-based consequences.

Awardee: Davide Momi

Supervisor: John Griffiths

Title: Computational modelling of TMS-EEG brain network dynamics in depression

Lay Abstract: Transcranial magnetic stimulation (TMS), is a non-invasive brain stimulation technique, extensively employed for the treatment of major depressive disorder (MDD). Despite its widespread use, how TMS acts on the brain to achieve positive therapeutic outcomes remains largely unclear. Advancing our understanding of TMS neurobiology has the potential to considerably improve its clinical utility, through more effective and personalized technology and therapy designs. Combining TMS with electroencephalography (EEG) offers a compelling way to achieve this, by measuring the changes in neural excitability and brain network activity believed to underlie its therapeutic benefits. Multiple studies have demonstrated the potential utility of TMS-EEG as a prognostic biomarker for MDD, but this is complicated by high levels of both intra- and inter-individual variability, which likely contributes also to the large heterogeneity in clinical outcomes. To overcome these limitations, our project will draw on recent advances in computational neuroscience and machine learning to build personalized, whole-brain mathematical models of EEG-measured responses to TMS stimulation in the dorsolateral prefrontal cortex. The project will launch an exciting new initiative bringing together partners at the Stanford University Psychiatry Department and the CAMH Krembil and Temerty Centres. This collaboration will allow the unique opportunity to combine analyses of TMS-EEG data from large multisite clinical trials in depressed populations with rare, high-quality intracranial electrophysiology recordings in brain surgery patients. Building on and integrating these complementary data types, our novel ‘in silico’ approach will allow us to investigate the brain mechanisms of TMS responses, and offer potential explanations for - and solutions to - the problem of high TMS-EEG measurement variation. Our aim is for this tool to directly contribute to the development of improved TMS therapies and outcomes.

Awardee: Ju-Chi Yu

Supervisor: Stephanie Ameis

Title: Developing and applying new multivariate methods to compare dimensional and categorical subtypes of Schizophrenia and Autism Spectrum Disorders using structural and functional brain connectivity

Lay Abstract: Individuals with Autism Spectrum Disorder (ASD) and Schizophrenia Spectrum Disorder (SSD) both independently experience difficulties in social cognitive abilities (e.g.,

reading emotions and perspective taking). Unfortunately, these deficits are rarely targeted for treatment, and their underlying neurobiology is not understood. Research suggests that individuals with the same clinical diagnoses can show different relationships between brain activation and social cognitive behaviours, implying a need for individualized treatment plans. To further investigate these individual differences, we will use neuroimaging techniques and develop advanced statistical methods to understand how brain connectivity (i.e., how different brain regions work together) is associated with social cognitive performance in ASD and SSD. Specifically, we examine whether the individual differences in this association are better described by continuous rather than discrete subtypes (such as clinical diagnoses). From the results, we will determine the best characterization of individual differences in SSD and ASD with the long-term goal of deriving the best strategy to develop personalized treatment plans.