Principal Applicant: Vincenzo De Luca

Interaction between early life adversities and schizophrenia vulnerability genes in conferring risk for suicide in young people

The proposed grant aims at identifying the genetic risk for suicide attempt (SA) in young schizophrenics and testing whether the interaction between genes and childhood trauma is modulating this risk. Being diagnosed with schizophrenia (SCZ) significantly increases the risk for suicide. Furthermore, having a history of childhood trauma is a risk factor for SA. In 2014, a large successful genome-wide association study was published highlighting 108 genes that may increase the risk for SCZ. Our hypothesis is that the genetic risk for SCZ interacting with a history of childhood trauma may lead an individual with SCZ to attempt suicide. We plan to study a sample of 754 young patients with SCZ, recruited from two hospitals in Toronto. A diagnosis of SCZ will be ascertained and the lifetime history of SA and childhood trauma will be collected using standardized tools. DNA will be extracted from the blood of study subjects and the 108 identified risk variants for SCZ will be genotyped in our sample. This study will allow the systematic evaluation of validated SCZ genetic risk variants and childhood trauma in conferring risk for SA in young schizophrenics. We will evaluate the interaction between childhood trauma and the 108 recently discovered SCZ susceptibility genetic variants combined as an individual risk score. These genetic changes in combination with early life adversities may lead to a better prediction of SA in SCZ. The genetic risk for SCZ in combination with a history of childhood trauma may allow us to predict those who are at risk for suicide in SCZ. The early identification of persons at risk will facilitate suicide prevention through counseling and early intervention. Finally, identifying genetic and gene-environment mechanisms that modulate SA in SCZ may enhance our understanding of the pathways resulting in suicide, facilitating the development of novel treatments.

Principal Applicants: Joanna Henderson & Aristotle Voineskos

Early Identification of Psychosis Spectrum Symptoms: A Novel Ascertainment Approach Through Tertiary Care Child & Youth Clinics

We aim to identify early evidence of psychosis spectrum symptoms (PSS) in individuals already enriched for psychopathology by accessing youth presenting to tertiary care child and youth psychiatric clinics. To
our knowledge, ours will be the first study to quantify and establish the prevalence and predictors of dimensional PSS in a tertiary care youth psychiatric cohort.

Recent findings from the (n~10,000) Philadelphia Neurodevelopmental Cohort (PNC) study suggest that PSS are prevalent (approximately 15-20% of all youth). This designation was validated by greater suicidal ideation, poorer neurocognitive performance, and functioning. Notably, the presence of a psychiatric disorder, and in particular disruptive behavior disorders, doubled the likelihood of PSS designation. While autistic symptoms were not assessed in the PNC, a recent Scandinavian registry study highlighted autism as a major risk factor for psychosis onset. Similarly, the combination of adverse life events and cannabis use is emerging as a potential risk factor. Therefore, we hypothesize that a) tertiary-care presenting youth will demonstrate elevated PSS symptoms in relation to community-based samples, b) youth with PSS will have poorer functioning than their non-PSS counterparts controlling for comorbid psychopathology, and c) autistic and disruptive behaviour antecedent symptoms, as well as will demonstrate greater predictive significance for PSS relative to those from other disorders.

We will recruit a consecutive series of referrals (14-24 years) from CAMH’s child and youth mental health clinics (concurrent disorder, disruptive behaviour, autism, and mood/anxiety disorder clinics). We plan to recruit and follow 200 individuals for one year. Across this time, PSS prevalence and severity will be quantified. Demographic and clinical confounding and predictor variables will be identified. A pilot algorithm will be developed to forecast a worsening developmental course of PSS over time.

Identification of the prevalence and predictors of PSS in a youth tertiary-care service, has immediate potential to a) increase rates of early identification of PSS, b) shorten time to early intervention, and c) change clinical practice through shared care between child/youth services and early psychosis services. Findings will also inform the development of predictive biomarker and treatment studies as immediate next steps.
Miner’s Lamp Innovation Fund in the Prevention and Early Detection of Severe Mental Illness: 2017 Awards

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Principal Applicant: Benjamin Goldstein

Early Detection of Anomalous Microvasculature to Inform Novel Treatment and Prevention Targets in Early-Onset Bipolar Disorder

Bipolar disorder (BD), the 4th most disabling condition among adolescents worldwide, is prevalent among 2-5% of adolescents. Adolescent-onset BD is considered an especially severe form of the illness, with substantial mood symptom burden, psychiatric comorbidities, and neurocognitive impairment. BD predisposes adolescents to early cardiovascular disease, independent of lifestyle factors and traditional risk factors such as high blood pressure and obesity. The question therefore arises, are microvascular abnormalities part of the underlying cause of BD? Adolescents can inform our understanding of the role of microvascular abnormalities in the genesis of early-onset BD, offering the advantage that adolescents have not been exposed to decades of BD symptoms and treatments.

Current approaches rely on challenging operator-dependent methods, with limited reliability, that focus on larger macrovessels. Examining tiny microvessels may provide a more sensitive measure of early cardiovascular risk. We will use multiple innovative microvascular measures, including magnetic resonance imaging of the brain and heart, retinal photography, and peripheral arterial tonometry. We believe that a multi-systemic microvascular phenotype, derived from measures of cerebral, retinal, cardiac, and peripheral microvascular structure and function, will optimize discovery. This will be the first study of a multi-systemic microvascular phenotype in BD.

This project will enroll 140 adolescents including 70 with BD, 35 offspring of parents with BD, and 35 without personal or family history of major psychiatric disorders. BD is about 10 times as prevalent among offspring of parents with BD vs. the general population; these offspring can therefore provide insights regarding early identification. This study comprises a substantial step forward, as it integrates multiple convergent themes that have not previously been examined concurrently in relation to BD. This project will yield important advances regarding microvascular pathology as an underlying biological contributor to BD, and may provide a new approach to early treatment and prevention in BD.

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Principal Applicant: Michael Kiang

Using Electrophysiological Indices of Auditory Processing to Estimate Psychosis Risk in Clinical High Risk Youth

Efforts to identify individuals with symptoms placing them at “clinical high risk” (CHR) for schizophrenia, and to prevent them from developing this chronic debilitating illness, are crucial. However, because a majority of CHR patients will not develop schizophrenia or a related psychotic disorder, it is important to seek additional predictors of their psychosis risk. Algorithms combining symptom measures and
cognitive tests have shown good accuracy for predicting development of a psychotic disorder in CHR patients. Such measures, however, are relatively lengthy and require specialized training to acquire. Neurophysiological measures, such as scalp-recorded event-related brain potentials (ERPs) or “brainwaves,” are another potential tool for predicting psychosis which are objective and can be rapidly acquired. ERP measures that are reduced in schizophrenia, and have been found to predict development of psychosis in CHR patients, include the mismatch negativity (MMN) and P300 waveforms, which reflect pre-conscious and attentive detection of salient sounds, respectively. Another ERP measure that is reduced in schizophrenia, but whose predictive value in CHR patients has not been examined, is the auditory steady-state response (ASR), reflecting earlier, basic sensory processing of sounds. We hypothesize that ASR abnormalities in this population also predict risk of developing a psychotic disorder. Moreover, because different ERP measures show low correlation with one another, we hypothesize that a combination of these measures will better predict psychosis than any of them alone. We hypothesize that, in CHR patients, reduced ASR will predict development of schizophrenia or a related psychotic disorder over 2 years; and that a combination of MMN amplitude, P300 amplitude, and/or ASR will predict this more strongly than any of these measures alone. The results of this study could yield an objective, rapidly administered prognostic test for psychosis risk in CHR patients, and thus help target treatment trials to those most at risk.

Principal Applicant: Nathan Kolla

Early Detection of Aggression in First Episode Psychosis: A Structural and Functional Magnetic Resonance Imaging Study

Schizophrenia (SCZ) is a serious psychiatric illness that typically onsets in adolescence or young adulthood when individuals experience their initial symptoms of first episode of psychosis. While most persons with SCZ are non-violent, individuals with SCZ are still at increased risk for violence and aggression. Two distinct types of violence in first episode psychosis have been identified: 1) individuals with prior conduct disorder (CD) who exhibit violence before and during first episode psychosis (SCZ+CD); and 2) individuals with no history of CD or violence who then display aggression during first episode psychosis (SCZ-CD). CD refers to a persistent pattern of breaking rules and violating the rights of others. Cognitive or brain impairments in SCZ have been linked to violence, perhaps because they pose too great a challenge for some individuals to learn to inhibit aggressive behavior. Investigating the neural basis of cognitive processes in first episode psychosis could provide much needed information for enhanced treatment and/or earlier identification of individuals with SCZ at increased risk for violence. In this study, we propose using structural and functional magnetic resonance imaging (sMRI; fMRI) to study cognitive processes related to aggressive behavior when impairment is present. sMRI and fMRI are brain imaging techniques that delineate the structure and function of brain regions. We will recruit 20 SCZ+CD participants, 20 individuals with SCZ-CD, 20 subjects with SCZ who do not have a history of violence, and 20 healthy controls. All individuals with SCZ will be within one year of their first episode of psychosis. Subjects will complete cognitive tasks or brain games while in the scanner. They will also undergo a magnetization transfer scan (sMRI) to measure myelin (white matter)
level in the medial prefrontal cortex, a brain region important in making decisions. This investigation of first episode psychosis participants would be the first multi-biomarker imaging study of cognitive processes associated with violence. Positive study results could provide an incentive to determine whether the anticipated findings are able to prospectively identify young individuals who are at ultra-high risk for SCZ and violence. Findings of key biomarkers would also help reduce the stigmatization of all patients with SCZ as habitually violent.
Principal Applicants: Albert Wong and Fang Liu

The DISC1-D2 protein complex as a biomarker for early detection of schizophrenia.

The goal of this project is to evaluate a potential serum biomarker to predict who will develop schizophrenia. We previously showed that a protein complex composed of DISC1 (Disrupted-in-schizophrenia 1) and the dopamine D2 receptor (D2R) is elevated in post-mortem brain tissue from schizophrenia patients. We then developed a peptide that disrupts the Disc1-D2R protein complex, and normalizes behaviours related to schizophrenia in animal models. Thus, this protein complex could be both a biomarker and a novel target for drug development.

We propose to investigate the Disc1-D2R protein complex as an early diagnostic marker for schizophrenia. We propose to recruit 50 patients presenting with their first episode of psychosis, or with non-specific prodromal signs and symptoms that often precede a psychotic break and a later diagnosis of schizophrenia. Age and sex-matched control subjects will also be recruited. Each subject will undergo standard diagnostic and schizophrenia symptom ratings and levels of the Disc1-D2R protein complex will be measured from blood samples. All subjects will be reassessed one and two-years later, and the eventual diagnosis determined with contributing information from the chart and treatment team.

We have two hypotheses. (1) The Disc1-D2R complex will be elevated in blood samples from schizophreniform disorder patients compared to unaffected controls (our earlier finding was with schizophrenia post-mortem brain tissue). (2) The Disc1-D2R complex will be higher in prodromal subjects who later develop schizophrenia vs. unaffected controls or other psychiatric diagnoses (e.g. depression or drug-induced psychosis). Thus, the Disc1-D2R complex could predict which prodromal or early psychosis patient will develop schizophrenia vs. mood disorders or drug-induced psychosis. At present, there is no biochemical or other clinical test that can help to distinguish between these common disorders, and the correct diagnosis is important in selecting the best treatment plan and having an accurate prognosis.

Principal Applicant: Philip Gerretsen

The effects of adjunctive transcranial direct current stimulation on medication adherence in first-episode schizophrenia spectrum disorder.

Schizophrenia is a psychiatric illness that affects approximately 1% of the world’s population. Medication adherence is critically important to the treatment of schizophrenia. Studies suggest 33–44% of patients with first-episode schizophrenia spectrum disorder (FES) become nonadherent within 6-months of treatment initiation with more than 60% of nonadherent patients discontinuing their medication. Although high, the rates of nonadherence reported in the literature are based primarily on
self-reports and may be an underestimate of the actual level of nonadherence in this population. Medication nonadherence in FES is associated with more frequent readmissions to hospital and is the principal factor associated with relapse.

One of the main drivers of medication nonadherence is impaired insight, described as having partial or lack of conscious awareness of one’s illness, its symptoms, and the need for treatment. Currently, there are no established treatment strategies to improve insight and medication adherence in patients with schizophrenia. An increasing number of studies suggest transcranial direct-current stimulation (tDCS), a form of non-invasive neurostimulation, is an efficacious treatment for schizophrenia, including a recent RCT that showed tDCS improves insight.

The proposed study will employ a novel approach to examine the effects of adjunctive tDCS on insight and antipsychotic medication adherence in FES. Participants stabilized on an antipsychotic medication will receive twice-daily tDCS for 10 days. Brain scans will be performed pre- and post-tDCS. Medication adherence will be assessed monthly based primarily on pill-count, and secondarily, plasma level concentrations and clinician judgement. Positive results will provide support for the use of tDCS in outpatient and ambulatory settings as an adjunctive treatment to antipsychotic medication. If proven effective, this intervention would have the potential to improve individual’s capacity for illness recognition and early treatment engagement, undoubtedly having a significant impact on the well-being of patients with FES and their families.

Principal Applicant: Vanessa Goncalves

The Use of Mitochondrial DNA as Marker of Clinical Subtypes of Youth Psychosis Patients: Potential Tool for Precision Medicine.

Mitochondria play crucial roles in the brain suggesting that genetic variants in this system may lead or contribute to the etiology of mental illnesses. Primary mitochondrial diseases show impairment in brain function and frequently have psychosis. There is compelling evidence for mitochondrial genes to play a role in both schizophrenia and bipolar disorder. The research on mitochondrial DNA in psychiatric disorders is not progressing as well as research for chromosomal DNA due to unique features of mitochondria including presence of many copies (and not always identical) per cell. In this study, we will examine the association between mitochondrial DNA variants and severity of clinical outcomes, and medication response in youth diagnosed with major psychoses. Data include brain imaging measures such as fractional anisotropy and cortical thickness; cognitive scores for speed of processing and attention; and response to medication. We will perform mitochondrial DNA next generation sequencing of 550 individuals for which clinical data were already collected. We expect to find a subset of mitochondrial variants associated with one or more of these traits. These variants can be used (with replication of results) in future tests for screening of patients at risk for more severe course of psychosis or better response to drug treatment. This is a pilot study to be used for future CIHR and NIH grant applications for a large scale test of our hypotheses.