Schizophrenia is a neuropsychiatric disorder affecting about one percent of the population worldwide. It is characterized by a combination of positive (e.g. hallucination, grandiosity, delusion), negative (e.g. apathetic social withdrawal, blunted affect), and cognitive (e.g. attention and memory problems) symptoms. The cause of schizophrenia is still unknown, but it is believed to involve both genetic and environmental factors (Picchioni and Murray 2007).

Earlier disease models attempting to map a pathophysiological explanation for schizophrenia symptoms have been based on excessive dopamine release in the basal ganglia. As such, dopamine-based treatments are used, to this day, as first-line treatment for schizophrenia. Although positive symptoms seem to be alleviated by dopamine-based treatments, negative symptoms still persist (Insel 2010). Therefore, another explanation was necessary to account for the full spectrum of schizophrenia symptoms.

Recently, the “N-methyl-D-Aspartate (NMDA) hypofunction hypothesis” has shown promising explanations of the mechanisms behind schizophrenia symptoms. This theory has been largely supported by the fact that glutamate NMDA receptor antagonists are able to replicate the full range of positive, negative and cognitive symptoms of schizophrenia (Javitt and Zukin 1991, Krystal et al. 1994). Since abnormal resting glutamate levels have been linked to poor outcome in first-line treatments (Egerton 2012), dynamic glutamate measurements (Taylor 2015) may be a more sensitive early marker in schizophrenia treatment outcome.

This study aims to show abnormal glutamate dynamics in individuals with schizophrenia compared to healthy controls. More specifically, building on the protocol of Taylor et al. (2015), which showed an attenuated and delayed glutamate response in patients with first episode schizophrenia, I will explore the link between these abnormal glutamate responses and measures of functional outcome at 6, 18 and 30 months after the scan as well as measures of treatment resistance. I hypothesize that patients with greater glutamate abnormalities early in the disease will show a poorer outcome and be more likely to become treatment-resistant.

Measurements will be acquired on a Siemens MAGNETOM 7-Tesla MRI scanner, the human scanner with the highest field strength in Canada, using an 8-channel transmit/ 32-channel receive, whole-head, radiofrequency coil at the Centre for Functional and Metabolic Mapping at the University of Western Ontario. Brain glutamate dynamics will be measured using a proton functional magnetic resonance spectroscopy (1H-fMRS) pulse sequence (semi-LASER) with a 20 x 20 x 20 mm MRS voxel placed in the dorsal anterior cingulate cortex. This study will consist of 32 participants (16 schizophrenia, 16 healthy controls). The cognitive Stroop task performed during the fMRS data acquisition will consist of four periods of four minutes (rest, active, rest, rest). Differences in glutamate levels between Stroop task periods will be explored with repeated measures ANOVA and correlation of glutamate levels with measures of functional outcome and treatment resistance will be explored through logistic regression.

Results from this work will help develop approaches to identify patients who will experience poor outcome and/or treatment resistance early in the course of their illness so that alternative to standard treatment algorithms can be considered, thereby reducing the expenses of failed treatments and associated human suffering. Stratification of patients entering a drug trial is another foreseeable application.