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Prognostic indicators of functional outcome in first episode psychosis: Linguistic, Anatomical, and Metabolic Predictors of Early Social and Vocational Outcome

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Abstract

A significant cause of disorder related burden in schizophrenia is due to reductions in social and occupational functioning. Because of the early age of onset and the severity of functional impairments experienced, schizophrenia ranks among the leading global causes of disease burden. While comprehensive early intervention services may play a key role in sustainable and effective care, much of the viability of these programs is contingent upon improved community functioning among patients to reduce the longterm dependency burden. Thus, understanding the variables that are associated with good versus poor functional outcomes (particularly vocational outcomes), are key to actualizing the promise of early intervention. This dissertation assessed the associations between three distinct baseline variables that may predict later occupational and social deficits after 6-12 months of treatment. In chapter 1, we used automated linguistic analysis software programs to determine if elements of speech production were aberrant in patients versus healthy controls, or were associated with worsened clinical symptoms. These features were then entered into a prototypical constraint-based algorithm to identify any dependencies with vocational inactivity (NEET), or scores on the Social and Occupational Functioning Assessment Scale (SOFAS). Only reduced speech (lower total words spoken) explained worsened occupational and community functioning. In chapter 2 we assessed whether baseline cortical thickness or local gyrification index (LGI) at baseline was associated with baseline clinical severity and later social and vocational status. Contrary to the literature in chronic schizophrenia samples, we identified increased gyrification in frontal and parietal regions to be associated with increased symptom burden at baseline, as well as with a higher status of vocational inactivity following treatment. Finally, we assessed whether central anti-oxidant tone measured in-vivo was associated with better social and vocational outcomes. We identified that patients with higher glutathione in the dorsal anterior cingulate cortex at baseline showed improved vocational and community functioning after 6-12 months of treatment.

The social, cognitive and clinical underpinnings of functional outcomes in first episode psychosis remain incredibly complex. However, our findings suggest that several variables, identifiable at baseline, may serve as actionable prognostic indicators of poor outcome. By better elucidating these mechanisms within early psychosis samples, clinicians may be able to augment standard treatment paradigms to improve outcomes among patients at risk of poor treatment response.

Lay Summary

In his Labor Day address in 1907, Theodore Roosevelt proclaimed “Far and away the best prize that life offers is the chance to work hard at work worth doing”. This simple quote captures the value that meaningful work has in one’s life. However, for the roughly 1 in 100 individuals who develop schizophrenia or related psychoses, the ability to find and maintain meaningful employment is critically impacted. Studies suggest that only 10-20 percent of schizophrenia patients are able to obtain and maintain employment throughout their lives. This dissertation aims to identify early predictors of poor vocational outcomes in a sample of drug-naïve first episode psychosis patients, with the hope that at-risk patients can be identified, and provided with early support to improve long term community functioning. To this end, we have recruited a group of patients who were recently diagnosed with their first episode of psychosis and have not yet undergone a course of treatment with antipsychotics. We assessed three classes of variables (speech variables, brain anatomy, and brain metabolite concentrations) to determine if they were linked to poor vocational and community functioning after 6-12 months of treatment.

Our findings indicate that reduced speech production (fewer words spoken during 3 minute interview), increased cortical (brain) folding, and lower levels of glutathione (the brain’s primary antioxidant) at baseline were associated with vocational inactivity and worse social functioning in the first year of treatment in an early intervention program. Among schizophrenia samples, a significant portion of clinical and functional recovery occurs within the first year of treatment, and once a chronic course of illness is established it becomes increasingly difficult to return to a pre-morbid level of functioning. Thus, the identification of these risk factors for poor functional prognosis is critical as this may allow clinicians to provide additional therapies to at risk patients before a debilitating course of illness is established.

Keywords

First Episode Psychosis, Schizophrenia, Drug-naïve psychosis, Functional outcome, Social Functioning, Vocational outcomes, NEET Status, Linguistics, 7T-MRI, Gyrification, 1h-spectroscopy, Glutathione, Oxidative Stress

Co-authorship statements

I conducted the research presented in this thesis in collaboration with my supervisor, Dr. Lena Palaniyappan (the principal investigator and senior responsible author for all works contained here-in). I lead all aspects of each project (obtaining ethics approval, recruitment of patients, data collection, data input/analysis, manuscript writing, manuscript editing). The work presented in the chapters of this thesis have either been published (Chapters 2A, and 4,) or submitted for peer review (chapter 2B) or being prepared for manuscript submission (Chapter 3).

Chapter 2A:

Mackinley M, Chan J, Ke H, Dempster K, Palaniyappan L. Linguistic determinants of formal thought disorder in first episode psychosis. Early Interv Psychiatry. 2021 Apr;15(2):344-351. doi: 10.1111/eip.12948. Epub 2020 Mar 3. PMID: 32129010.

I was the lead of this study and was actively involved in all aspects of the project (data collection, data analysis, and writing). JC, HK assisted with editing the manuscript and transcribing speech data. KD assisted in the recruitment of patients and editing of the manuscript.

Chapter 2B:

MacKinley M, Limongi R, Silva A, Richard J, Subramanian P, Ganjavi H, Palaniyappan L. Assessment of Linguistic Factors during Antipsychotic Naïve first Episode Psychosis with later vocational and social outcomes in the first year of treatment. *Psychiatry Res.* (2022): Manuscript submitted for review.

I was the lead of this study involved in all aspects of data collection, preparation of data, completion of analysis, and writing of the manuscript. RL provided hands on supervision and tutelage on the use of Bayesian statistics, and the application of the constraint based PC algorithm and contributed to the writing and editing of the methods/ results section. AS conducted the analysis of analytic thinking scores.

Chapter 3:

I was the lead of this study and was actively involved in all aspects of the project (data collection, data analysis, and writing). PY assisted in the preprocessing of anatomical data.

Chapter 4:

MacKinley M, Ford SD, Jeon P, Théberge J, Palaniyappan L. Central Oxidative Stress and Early Vocational Outcomes in First Episode Psychosis: A 7-Tesla Magnetic Resonance Spectroscopy Study of Glutathione. Schizophr Bull. 2022 Mar 21:sbac012. doi: 10.1093/schbul/sbac012. Epub ahead of print. PMID: 35307736.

I was the lead of this study and was actively involved in all aspects of the project (data collection, data analysis, and writing). SF assisted in the recruitment of patients and editing the manuscript, PJ managed the quantification/fitting of metabolite concentrations & preparation of figures.

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Contents

1.0 Chapter 1: Introduction to Schizophrenia

1.1 Introduction

First described in 1887 by German psychiatrist Emil Kraepelin, schizophrenia (described originally as dementia praecox by Kraepelin) and related psychotic illnesses have captured the attention of psychiatrists, public health officials and the community at large. The cultural and political significance of psychotic illness is largely attributable to the stark nature of symptoms and the illness' deleterious effects on both patients and their broader social units, often resulting in severe impairments and a chronic course. Schizophrenia is characterized by three distinct syndromes: reality distortion (delusions and hallucinations, termed psychotic or '*positive'* symptoms), disorganization (thought disorder, inappropriate affect, bizarre behaviour), and '*negative'* symptoms (blunted affect, poverty of speech, decreased motor activity). Despite impacting less than 1% of the population (Moreno-Küstner et al., 2018), schizophrenia patients typically experience relatively early onset, and in the absence of robust early intervention services are often plagued by a chronic and relapsing course with incomplete remission, near ubiquitous co-morbidity, and major impairments in community and social functioning (Świtaj et al., 2012). Given this degree of morbidity, and the inadequacy of current treatment paradigms (Tandon et al., 2010), schizophrenia consistently ranks among the top causes of disability worldwide (Charlson et al., 2018).

The subsequent sections here-in aim to describe risk factors for psychosis onset, incidence and prevalence rates for schizophrenia, the diagnostic criteria for schizophrenia, and briefly describe the core symptoms of psychosis as well as their neurobiological correlates. Finally, a description of the trajectories for clinical and functional recovery will be laid out alongside the rationale for studying prognostic indicators of early social and vocational outcomes.

1.2 Epidemiology and Public Health Impact

1.2.1 Incidence, Prevalence, and Risk Factors

Whereas numerous studies have assessed incidence and prevalence of schizophrenia, the genetic and environmental factors that predict transition from a pre-morbid state to psychosis vary in individual studies. While individual local studies are particularly useful for regional service planning and resource allocation, these studies may not accurately reflect the overall epidemiologic picture of schizophrenia and non-affective psychoses. Thus, rates of incidence and prevalence reported herein will rely largely on systematic reviews and meta-analyses.

In a systematic review of over 170 discrete core incidence rates from 55 studies across various regions, the median 1-year incidence rate for psychosis was 15.2 individuals per 100,000 population, excluding outliers, a range of 7.7 to 43 per 100,000 was reported (McGrath et al., 2004). The overall prevalence rate for psychosis was 11.1 per 1000 lifetime, consistent with the oft-quoted statistic that schizophrenia impacts “1 in 100 individuals”. However, the median lifetime prevalence rate was slightly lower, at 7.2 per 1000 individuals (McGrath et al., 2008). While the range of incidence and prevalence estimates presented is relatively broad, several geographic and demographic factors likely contribute to rates of schizophrenia diagnosis. For example, demography, urbanity, and migrant status of the catchment area in any particular study is likely to alter observed estimates, with evidence of an up to 8-fold increase in risk in different sites across areas sampled (Jongsma et al., 2018).

Among demographic factors, sex is one of the most commonly postulated risk factors for psychosis. There has been a presumption of schizophrenia disproportionately impacting males dating to the first description of “dementia Praecox” in 1893. However, conclusions regarding sex differences in prevalence are often complicated by sex-related differences in age of onset, symptom expression, illness course, and familial transmission (Goldstein, 1997). Despite these complexities, the putative link between

male sex and higher incidence of schizophrenia is broadly supported. In a systematic review, 84% of findings suggested a higher incidence rate for men than women (McGrath et al., 2004). Although it is possible that systematic error in the production of these studies led to this finding (such as excluding older age of onset where women are likely to be overrepresented), males appear to develop psychosis at a 1.4:1 ratio to their female counterparts. Interestingly, the life time prevalence rates do not show significant sex differences, particularly when broader diagnostic criteria are used (Abel et al., 2010; McGrath et al., 2008; Saha et al., 2005), indicating that differences in help seeking behaviors may contribute.

Of all risk factors, genetics remain far and away the largest known contributor to schizophrenia etiology (Gejman et al., 2010), with meta-analytic data suggesting that as much as 70% of the risk can be accounted for by genetic factors (Moran et al., 2016). While several individual candidate genes have been identified, such as the *Disrupted in Schizophrenia-1* (DISC1) gene (Dahoun et al., 2017), and Neuregulin-1 (Mei & Xiong, 2008), the Psychiatric Genomics Consortium has implicated over 100 genes that are associated with schizophrenia, many of which operate through mechanisms involving neurodevelopment and immune/stress response(Moran et al., 2016). Although polygenetic risk is supported, there is to date no single causative gene for schizophrenia or psychosis. Instead the interaction of genes with environmental factors of early and late development appear to be critical (Moran et al., 2016).

This notion that environmental factors, particularly those of developmental consequence, interact with genetic risk has been the predominant paradigm in schizophrenia for over 30 years since neurodevelopmental theory of schizophrenia pathogenesis first emerged (Lewis & Murray, 1987; Weinberger, 1987). Broadly speaking, neurodevelopmental risk factors can be categorized as risk factors of early development or later development. While a multitude of individual factors of early development are believed to confer later risk, parental age, season of birth, maternal

infection during pregnancy, and obstetric complications have been consistently identified.

The association between heightened parental age and schizophrenia incidence dates back to the mid-1900s, with parents of schizophrenia patients being 3 years older than average (Messias et al., 2007). Despite being conceptualized as “parental age”, more nuanced analyses reveal that, contrary to speculation, maternal age was not predictive of developing schizophrenia. Instead, the influence of the fathers age on later incidence of schizophrenia seems to be of predominant importance, with fathers over the age of 45 having offspring with a 2.5 times higher relative risk compared to fathers aged 20-24 (Dalman & Allebeck, 2002). While the mechanism for this difference is poorly elucidated in the extant literature, de novo genetic mutations, known to be far more common in older fathers (Francioli et al., 2015) are thought to be a major contributing factor (Malaspina et al., 2001). However, more recent analyses have suggested that in addition to de novo mutations, genetic risk shared by older fathers with their offspring are likely to be the major contributing factors for paternal age as a risk factor (Gratten et al., 2016).

While representing a comparatively small increase in risk, season of birth has consistently been associated with risk of developing schizophrenia(Messias et al., 2007). Regardless of the hemisphere of birth, individuals born in the winter or early spring show a relative risk roughly 10% higher than their same age peers born in the late spring and summer months (Davies et al., 2003; Torrey et al., 1997). While these findings may partially be linked to procreation patterns of parents of patients varying from the general population, it is postulated that this seasonal difference may be the result of patients being born pre-term (arriving earlier than the typical spring glut of births), or heightened exposure to seasonal infectious diseases during the second trimester resulting in a potentially deleterious immune-cascade (Suvisaari et al., 2001). The risk of schizophrenia conferred by gestational insult has been well studied. Links of psychosis

to prenatal infection were initially identified in the 1980s, where birth cohorts exposed to flu epidemics during the second trimester were shown to have higher rates of schizophrenia (Brown & Derkits, 2010). More recent work from both epidemiologic and animal models have supported the theory that exposure to pathogens, and critically maternal immune response during gestation, confers risk both to schizophrenia and disorders of neurodevelopment more broadly (such as autism spectrum disorder and ADHD) (Brown & Derkits, 2010; Fatemi et al., 2008; Meyer et al., 2006). This heightened risk is true of a number of pathogens including influenza, rubella, herpes simplex, and toxoplasmosis Gondii (Messias et al., 2007). However considerably more evidence on the timing and mechanism of action should be produced (Brown & Derkits, 2010). In addition to maternal immune response, broader obstetrical associations with later schizophrenia incidence can largely be classified into three categories, 1. Complications during pregnancy (e.g., preeclampsia, bleeding, gestational diabetes), 2. Fetal growth issues (e.g., low birth weight, lower head circumference), and 3. Complications during delivery (e.g., asphyxia, emergency cesarian section) (Cannon et al., 2002). While much of this data may be impacted by reliability issues, meta analytic data suggests that the increased risk among those with obstetric complications typically is in the range of two- to three-fold (Geddes et al., 1999; Verdoux et al., 1997). However, as with many developmental risk factors, teasing apart external insult and genetic predisposition remains difficult given the retrospective nature of these studies.

In addition to their role in schizophrenia incidence, understanding neurodevelopmental risk factors for schizophrenia is critical to contextualizing outcomes following treatment. Independent of later disease pathology, factors such as obstetric complications likely contribute meaningfully to the reduced pre-morbid functioning seen in patients with schizophrenia (Cannon et al., 1997). Early life developmental anomalies are common in children and adolescents who go on to develop schizophrenia. These insults may preclude patients from returning to a level of functioning that would be expected of their unaffected peers, even if complete

symptom remission is achieved. Thus biomarkers of early life insult are likely prognostic candidates for poor outcome among samples of FEP patients.

Risk factors during later development are similarly strongly associated with heightened incidence of schizophrenia, particularly psychosocial stressors, and use of cannabis. Psycho-social stress in the schizophrenia literature has been broadly defined, capturing a myriad of factors including trauma, discrimination, and negative life events broadly (van Winkel et al., 2008). While nearly all individuals are exposed to some degree of environmental disruption during development, cumulative exposure to multiple (or repeated) psychosocial stressors contribute to the incidence of schizophrenia and psychotic illness (Shevlin et al., 2008). This psycho-social stress hypothesis may be linked to the body of epidemiologic data suggesting that incidence of schizophrenia is highly influenced by geography and migration status. Urban centres have shown a consistent, although modest, increase in psychosis incidence rates (19 vs 13.3 per 100,000)(McGrath et al., 2008). Among both males and females, migrant status showed a consistent increase in incidence rates largely irrespective of the path of migration (McGrath et al., 2004), although this risk was heightened among males (Anderson et al., 2022). Across the analyses, additional risk was conferred to migrants of younger age, of African origin, and among those who lacked proficiency in the national language(s) of the host country (Anderson et al., 2022). Refugee status also appeared to exacerbate this heightened risk when compared to their non-refugee migrant counterparts (Hollander et al., 2016). The data do not suggest a difference between urban and mixed urban/rural regions, however the effects of migrant status remain stark, with a 1.8:1 relative incidence of psychosis among migrant vs. native individuals (McGrath et al., 2008).

One of the most common late-developmental risk factors for schizophrenia incidence is exposure to cannabis products. Prospective studies from several countries have reported a relative risk of schizophrenia to be 2 to 25 times higher among cannabis

users vs non-users (Messias et al., 2007), with the highest risk being reported among individuals with earlier age at initiation (Arseneault et al., 2004; Stefanis et al., 2004). While it is possible that individuals experiencing prodromal psychotic symptoms use cannabis at a higher rate as a form of self-medication, or that the relationship between psychosis and schizophrenia onset is confounded by other substance use, control for these factors only marginally reduces the association between cannabis use and incidence rates for schizophrenia (Arseneault et al., 2004). Systematic reviews have shown this link to be both consistent and dose-dependent based on Δ^9-tetrahydrocannabinol (THC) exposure (Marconi et al., 2016). It is likely that cannabis products interact with several genes through several putative neuro-chemical mechanisms (Luzi et al., 2008). Thus, the preponderance of evidence is suggests that cannabis use, while neither necessary nor sufficient, can play a causative role in schizophrenia etiology (Arseneault et al., 2004; Henquet et al., 2008).

Similar to early-developmental insult, psycho-social stress (Beilharz et al., 2020) and cannabis use (Fergusson & Boden, 2008) during late adolescence have been linked to poor outcome, even among non-clinical community samples. Among schizophrenia patients, it is likely that exposure to these risk factors would reduce premorbid functioning prior to any deficits accumulated during psychotic illness. Therefore, recovery from psychosis is unlikely to be complete even with total symptom remission, suggesting the need to expand the conceptualization of recovery beyond symptom severity. These developmental factors, once again, may predict poor vocational and community functioning and could be clinically relevant in the planning of individualized treatment plans.

1.2.2 Mortality

In addition to significant morbidity from illness symptoms, schizophrenia is linked to a 2 to 3 fold increase in mortality compared to their non-affected peers (Auquier et al., 2007), resulting in a 15-20 year reduction in life expectancy (Ringen et al., 2014). While a major contributor to mortality and years of life lost relates to a

heightened rate of suicide, particularly among recently diagnosed male patients, two-thirds of the excess mortality is associated with several physical health problems resulting in a premature death.

The contribution of suicide as a cause of death in schizophrenia, while rare, is substantially higher than the general population – with reported lifetime risk of around 5% for patients (Hor & Taylor, 2010). The risk of suicide is not, however, equally distributed amongst the patient population. A number of risk factors are positively associated with death by suicide, including comorbid depression and substance abuse, more recent diagnosis, male sex, higher education, being single, and persistent unemployment(Hor & Taylor, 2010). While still accounting for a minority of deaths among schizophrenia patients, suicide is the leading cause of death among the youngest patients, suggesting it represents a substantial public health impact in terms of years of life lost. These numbers are likely underreported as the next largest cause of death (Accidents – including falls and motor vehicle collisions) may include misclassified suicide (Lin et al., 2018). As is consistently found in non-psychotic samples, suicide is strongly associated with markers of poor community and social functioning, once again suggesting that a focus on functional response during early treatment may be a clinically relevant pursuit to reduce mortality among an at-risk population.

Despite suicide rates being highly elevated among schizophrenia patients, once patients are through the first episode and acute phase of illness, medical causes account for the vast majority of excess mortality among individuals with schizophrenia. In particular, cardiovascular disease and cancer remains disproportionately high. Mortality rates from cardiovascular disease in particular has been found to be threefold in schizophrenia patients versus healthy controls in the 19-49 year old age group, and twofold in the 50-75 year age group (Ringen et al., 2014). While the focus of schizophrenia management is primarily on the alleviation of psychotic symptoms and their proximal consequences, the significant mortality & morbidity burden from physical

health concerns suggests a substantial deficit in improving general physical well-being (Auquier et al., 2007). The underlying risk factors for physical health concerns in this patient population are fairly well understood, largely linking back to the substantially increased risk of metabolic syndrome/obesity, substantially higher rates of tobacco use, physical inactivity, poor diet, and the use of antipsychotics (although much of this risk from antipsychotic use and premature death is mediated by aforementioned metabolic factors) (Newcomer, 2007). Once again, these factors are likely contributors to worsening functional response as physical health concerns reduce social and occupational opportunities for patients, and may partially explain the association between chronicity of illness and worsening community functioning.

1.2.2 Early Intervention Programs for Psychoses

While the morbidity, mortality and disability caused by schizophrenia paints a bleak picture, a poor outcome is far from certain. There remains significant opportunity for complete functional and clinical recovery, particularly if intervention is achieved at the earliest stages of the illness, ideally at the onset of the first psychotic symptoms (Addington, 2007; Dama et al., 2019; Henry et al., 2010). Over the past several decades, a strong case has been made for the proliferation of early intervention programs targeting first episode psychosis (FEP) patients. By intervening as early as possible in the course of illness, with robust psycho-social and medical care, EIPs are able to reduce the duration of untreated psychosis (DUP) (Killackey & Yung, 2007), a critical metric in producing desirable outcomes (Marshall et al., 2005). This reduction in untreated psychosis both improves the rates of clinical remission, and reduces the compounding psychosocial and behavioral issues stemming from acute illness (O'Connell et al., 2022). More recent emphasis has been focused on attempting to identify patients at high risk for psychosis and either prevent transition to a full psychotic episode, or at a minimum ensure the DUP is shortened drastically (Erzın & Gülöksüz, 2021; Killackey & Yung, 2007).

While the operational approach of each EIP may vary (due to differences in staffing and resource allocation by region), fidelity scales have typically identified several features that EIPs should strive to attain. These include 1. Focus on early detection, 2. Small patient-to-staff ratios, 3. Antipsychotic prescription and monitoring, 4. Provision of psychosocial and behavioral treatments, 4. One to three years program duration, 5. Explicit admission criteria and 6. Defined missions to serve specific geographic populations (O'Connell et al., 2022). While these programs have flourished in Canada, the United Kingdom, Scandinavia, and Australia, the rate of expansion in other jurisdictions has been slow. The major barriers to their broader uptake have been insufficient funding. Underresourced EIP clinics result in understaffing, insufficient training, poor community outreach, and fewer resources focused on psychosocial (rather than strictly medical) care (O'Connell et al., 2022). Despite these challenges, when implemented, EIPs are consistently found to be cost-effective despite their higher upfront costs (Aceituno et al., 2019), a benefit largely obtained through their effectiveness in reducing co-morbidity and improving clinical response and consolidating recovery (McGorry, 2015). Critically, early intervention programs that can emphasize improvements in functional recovery may see more pronounced benefits to their application in the community (Killackey & Yung, 2007).

1.2.3 Burden of Schizophrenia in Canada

Despite several regional differences in schizophrenia epidemiology across the world, the incidence and mortality rates in Canada are consistent with international data. Roughly 1 in 100 Canadians were living with a diagnosis of schizophrenia, with men slightly over represented in this group (56% of cases)(Stats Canada, 2020). Similar to the broadly reported statistics, the all-cause mortality rate among patients was 2.8 times higher than the general population. Despite incidence of schizophrenia seeing a small decline in the preceding 20 years, the number of individuals living with schizophrenia has risen (Stats Canada, 2020). While this is a testament to improvements

in early intervention and medical management of patients over the intervening years, it speaks to a growing economic/dependency burden that is worth noting.

While the data is out of date, in 2004 the direct economic burden of schizophrenia was estimated at roughly CAN$2.02 billion (Goeree et al., 2005). These costs were primarily driven by CAN$474 million and CAN$761 million in acute and non-acute hospital care, respectively, with CAN$142 million spent on community psychiatric and mental health clinics. An additional CAN$340 million was spent on residential care facilities for patients, and a further CAN$150 million on antipsychotic medications (Goeree et al., 2005). In the past 30 years, Canada has undergone significant transition to incorporating early intervention programs (EIPs) as a care model for psychosis. While EIPs are considered to be cost effective (A. Malla & Pelosi, 2010; Rosenheck et al., 2016), the economic viability of EIPs is contingent on curbing the largest indirect costs of schizophrenia: loss of economic productivity. Loss of productivity due to morbidity and early mortality is believed to cost between CAN$ 4.83 billion dollars (if 50% employment is reached), to as high as 7.14 billion (if only 10% of patients are employed) (Goeree et al., 2005). More recent studies assessing the true employment rates among patients with schizophrenia have suggested employment figures in the ranges of 10-20% (Evensen et al., 2016; Holm et al., 2021), suggesting that costs to the system are likely on the higher end and continuing to grow.

Unfortunately, despite improvements to models of care with early intervention programs proliferating, the costs of schizophrenia in Canada remain staggeringly high, while simultaneously failing to ascribe a dollar value to the pain, suffering, and reductions in life quality to persons with schizophrenia and their social networks. These data suggest the heightened need for research focused on understanding and treating the factors that influence functional outcomes, particularly employment and physical health, both from an economic and humanitarian standpoint.

1.3 Clinical Presentation

1.3.1 Diagnostic Criteria

The diagnostic criteria are based on clinical symptoms ascertained through interviews, rather than through physiologic diagnostic testing. The diagnostic criteria for schizophrenia, according to the Diagnostic and Statistical Manual for Mental Disorders Fifth edition (DSM-5), requires the presence of at least two of the following: Hallucinations, delusions, disorganized speech, catatonic behavior, or negative symptoms with a duration of at least one month (American Psychiatric Association & American Psychiatric Association, 2013). It warrants noting, at the present time, there is no genetic, blood, or imaging technique that is used in the diagnosis of schizophrenia (or major psychiatric illnesses broadly), thus diagnoses are largely made based on how symptoms manifest through behavior and self-report of patients in clinical settings. How symptoms manifest is largely unique between patients, with each individual experiencing a unique clinical course. What ties these diagnostic criteria together is the requirement of a 6 month period of general social/functional decline to be diagnosed (American Psychiatric Association & American Psychiatric Association, 2013).

While the diagnostic criteria do not formally mention the development of cognitive dysfunction, a decline in multiple cognitive domains is nearly ubiquitous in schizophrenia samples (Mihaljevi & Janovi, 2019), with many of these deficits appearing during the prodromal period prior to the onset of psychosis and are linked to reductions in functioning throughout the treatment course (Sheffield et al., 2018). The subsequent sections will address the key elements of positive symptomology, negative symptomology, cognitive deficits, and their neurobiological correlates, with clinical and functional remission discussed in section 1.4.

1.3.2 Positive Symptoms

1.3.2.1 Clinical Presentation

The positive syndrome in schizophrenia captures a number of clinical symptoms thought to be the “hallmark signs” of psychosis, including hallucinations and delusions.

Hallucinations, perceptual experiences that are not grounded in the physical environment, are the most common single symptom in schizophrenia with estimates that 70% of patients experience hallucinations throughout their illness (Sartorius et al., 1986), with auditory hallucinations being the most common type, followed by visual hallucinations (Chaudhury, 2010). Tactile, olfactory, and gustatory hallucinations while less common, are also regularly reported. Interestingly, hallucinations are commonly reported in other psychiatric and neurologic disorders such as bipolar disorder, autism spectrum disorder, PTSD, a number of dementias, and occasionally among healthy populations (Tang & Tang, 2020). The clinical relevance of hallucinations is largely dependent upon the level of distress and interference in functioning posed by the presence of hallucinations, and the exclusion of other explanatory factors such as tumors, recreational or prescription drug use (Tang & Tang, 2020).

Delusions, another hallmark sign of psychotic illness, are beliefs that are not grounded in reality and indicate an underlying abnormality in a patient's thought content, not explained by other cultural factors (such as widely held religious beliefs) (Kiran & Chaudhury, 2009). The content of delusions is broad, with paranoid or persecutory delusions, delusions of grandeur, and somatic delusions – among others- commonly reported. The content of delusions is well understood to be impacted by a variety of sociocultural factors (Butler & Braff, 1991). Similar to hallucinations, delusions are a trans-diagnostic construct that have been observed in other psychiatric and neurodegenerative illnesses, and while delusions are not typically observed outside of clinical samples, delusion-like or over-valued ideas are often observed in the general population (Kiran & Chaudhury, 2009). The certainty with which a delusion is held underlies it's clinical relevance (Schultz et al., 2007), with relapse and re-hospitalization more likely among patients with the most fixed delusions (Harrow et al., 2004).

1.3.2.2 Neurobiological Correlates

Many early hypotheses explaining neurobiology of psychotic illness were based on findings from pharmacology. Specifically, the dopamine hypothesis of positive symptomology was based on the serendipitous discovery of dopamine (D2) agonists as an effective method of managing delusions and hallucinations (Ross et al., 2006). This finding was further supported by observations that stimulants acting on dopamine receptors can exacerbate psychosis among patients with schizophrenia, and even cause temporary psychotic like states among healthy individuals(Ellison, 1994; Henning et al., n.d.; Ujike, 2002). While the original hypothesis of hyperdopaminergic transmission has been refined over the intervening decades, with most work focusing on striatal/ mesolimbic dopaminergic transmission (Brunelin et al., 2013) – the dopamine hypothesis alone cannot effectively explained the complete syndrome of positive symptoms. Thus, research has since expanded to other brain systems that may underlie the development, and persistence of, psychotic states.

The glutamatergic hypothesis suggests that N-methyl-d-aspartate (NMDA) receptor hypoactivity on GABA interneurons in the prefrontal cortex leads to overactive downstream glutamate signaling. This overactive glutamate introduced by excessively stimulating the mesolimbic dopamine pathway in the ventral tegmental area (VTA) may underlie the production of auditory hallucinations and paranoid delusions (Stahl, 2018). This proposed mechanism is linked to neurodevelopmental insult with anomalies in glutamate levels present prior to the onset of symptoms (Egerton et al., 2020), suggesting that risk factors from early life function through glutamatergic signaling to impact the dopamine hyperactivity observed among actively psychotic patients.

Similarly, pharmacologic findings from patients with other neurologic illnesses with psychotic features (specifically Parkinson's disease and dementia) have shown that antagonism of serotonin 5HT2A receptors resulted in reduced psychotic features in patients despite no activity at the D2 receptor sites (Stahl, 2016). The mechanism is

thought to involve increase in the expression of 5-HT2A receptors can result in downstream release of glutamate, with some of these glutamate neurons projecting to the ventral tegmental area and activate it prompting further activation of the mesolimbic dopamine pathway as part of a chain reaction leading to psychosis. Ultimately, this cascade leads to typical auditory hallucinations and delusions (Stahl, 2018).

While the effectiveness of D2 receptor antagonism in reducing psychotic symptoms suggests that mesolimbic dopamine hyperactivity is the proximal cause of positive symptoms, the growing literature suggesting other receptor sites as potential upstream causes warrants continued investigation. For example, the effectiveness of Clozapine at treating persistent positive symptoms is thought to be related to its activity at receptor sites beyond striatal D2 receptors (Wahlbeck et al., 1999). Clozapine is shown to be active at both NMDA and 5HT2A receptors (Seeman, 2013). While the complete picture of the neurobiological underpinnings of positive symptomology is still being developed, an understanding of these complex mechanisms is necessary to improve available treatments for positive symptomology.

1.3.3 Negative Symptoms

1.3.3.1 Clinical Presentation

The negative Syndrome in schizophrenia represents a broad spectrum of potential symptoms relating to the overall weakening or paucity of normal thoughts, emotions or behaviour (Andreasen, 1986; Mäkinen et al., 2008). Negative symptoms are composed of five constructs which are broadly categorized into two domains: expressive deficits, and avolition/apathy (Correll & Schooler, 2020).

Expressive deficits capture the negative symptomology defined by reductions in the normal breadth or degree of communicative or expressive gestures. These features of the illness are typically easily clinically identifiable at presentation. Affective flattening refers to a patient's unidimensional emotional expressivity, manifested by

diminished facial and vocal expression, as well as minimal use of gestures (Kring & Moran, 2008). Flat affect is understood to be a distinct factor from true emotional withdrawal, as many patients report similar internal emotional experiences to healthy controls despite their lack of external cues (Burbridge & Barch, 2007; Herbener & Harrow, 2001). This disconnect between subjective and expressed emotional states may relate to underlying neural abnormalities present in schizophrenia (Anticevic et al., 2012; Stolar et al., 1994). An additional expressive deficit present in schizophrenia is alogia, or the marked reduction in speech quantity (Andreasen, 1986). Alogia is identifiable by the use of short or monosyllabic answers to questions, and avoidance of meaningful communication (Correll & Schooler, 2020). Expressive deficits are likely to result in poor outcomes for patients through several mechanisms. Affective flattening is highly likely to result in poor responses from social partners (Krause et al., 1992), and thus will substantially reduce social functioning In both professional and personal settings. Similarly, the presence of alogia is likely to hamper the ability to navigate complex social and occupational settings(Correll & Schooler, 2020). Thus, alogia is a likely prognostic candidate for functional deficits that warrants additional clinical attention early in the treatment course.

The avolition/apathy factor captures three primary symptoms: avolition, asociality, and anhedonia (Galderisi et al., 2018). Unlike expressive deficits, these symptoms require probing questions relating to features of the patient's life beyond the clinical setting, as they are more experiential and are typically contextualized as reductions in occupational, social, and recreational pursuits from premorbid levels (Correll & Schooler, 2020). Avolition reflects deficits in self-motivation to engage in meaningful activity, such as gaining employment. Asociality is the reduction in the number or quality of social relationships, and a lack of motivation to acquire and maintain such relations. Finally, anhedonia refers to the inability to anticipate future pleasure, the reduction in leisure activities, and a reduced interest in sexual activity (Correll & Schooler, 2020). Whereas expressive deficits may hinder occupational and

social functioning through indirect means, avolition/apathy are by their nature likely to directly result in worsened functioning.

While less common than positive symptoms at first episode, the prevalence of negative symptomology is staggering. At first presentation to clinical settings, between 50-90% of patients experience some degree of identifiable negative symptomology, with these numbers only falling to between 35-70% after 1-2 years of treatment (Bottlender et al., 2003; Husted et al., 1992; A. K. Malla et al., 2004). Broadly speaking, negative symptoms may represent idiopathic primary negative symptomology, which comprises symptoms directly relating to psychotic illness, and secondary negative symptoms which comprise non-idiopathic symptoms typically linked either to preoccupation with positive symptomology (such as suspicious withdrawal, or distraction), and negative symptoms as a consequence of comorbid depression (Mäkinen et al., 2008).

While secondary negative symptoms are to some extent attenuated through controlling positive symptoms with antipsychotic medication, primary negative symptoms represent a significant burden of illness and are resistant to treatment effects leading to chronic illness and poor outcomes (A. K. Malla et al., 2004). While the severity of negative symptomology is unstable for much of the first year of treatment (Chang et al., 2011), between 20-40% of first episode patients will go on to experience persistent negative symptomology (Buchanan, 2007; Herbener & Harrow, 2001). Unfortunately, Compared to positive symptoms, the use of antipsychotic medications have not been shown to effectively treat negative symptoms. While some studies have shown atypical antipsychotics to show marginal benefits in treating negative symptoms vs placebo, the effects are often not clinically meaningful (Fusar-Poli et al., 2015). Because of their resistance to treatment, negative symptoms are responsible for significant burden of illness among patients with psychosis/schizophrenia(Galderisi et al., 2018). Negative symptoms are consistently linked to poor functioning in clinical, economic, and social

domains(Bottlender et al., 2003; Galderisi et al., 2018; Hwu et al., 2002; Mueser et al., 1991; Rabinowitz et al., 2012). Interestingly, patients with substantial negative symptoms, appear to be unaware or indifferent to the effects these symptoms have on their quality of life, suggesting that insight into the severity of illness is impaired. As the ability to overcome established, chronic, negative symptomology is limited, a concerted effort to maximize and maintain functioning as early as possible in the course of illness may prove beneficial, although this likely requires continued assertive treatment to sustain beneficial effects (Secher et al., 2015).

1.3.3.2 Neurobiological Correlates

Overall, the identified neurobiological correlates of negative symptomology have been largely ambiguous with several mixed findings. This inconsistency in the literature is likely due to the heterogeneity of negative symptoms both in clinical presentation and in putative etiology. Studies on the neurobiological underpinnings of negative symptoms are strongly influenced by how the symptoms are classified (a unitary construct, or particular factors), resulting in discrepant findings. It is likely that even among narrowly defined symptom categories, a breadth of potential neural substrates may be implicated (Galderisi et al., 2015). This neural complexity underlying negative symptomology likely underlies the difficulties in treating this syndrome. Despite these limitations, a number of neurobiological correlates of negative symptomology have been established.

Rather than stemming from issues relating to specific neural regions, negative symptoms are thought to be linked to irregularities in neural networks. Functional magnetic resonance imaging (fMRI) studies have linked functional deficits in frontal and prefrontal networks to negative symptoms (Gruber et al., 2014). This hypofrontality is also present at both first episode (Molina et al., 2005), and drug-naïve disease states (Andreasen et al., 1997), and are thought to be related to hypo-dopaminergic signaling in frontal-mesolimbic networks (Correll & Schooler, 2020). Because dopamine D_3 receptors are localized in mesolimbic brain regions that control reward and motivation

receptors, down regulation in these areas may underlie negative symptoms (Correll & Schooler, 2020).

An alternative to the dopaminergic hypothesis is that glutamate dysregulation may underlie negative symptom pathology (Coyle, 2012). This hypothesis is linked to observations that N-methyl-D-aspartate (NMDA) receptors mimics the clinical presentation of negative symptomology and cognitive dysfunction seen among patients(Correll & Schooler, 2020) and that glutamate deficiency is associated with treatment non-response (Coyle, 2006). While studies have reported that treatment at the NMDA receptors may reduce negative symptoms over twenty years (Goff & Coyle, 2001; Heresco-Levy & Javitt, 2004), these findings have been inconsistent (Goff, 2014; Weiser et al., 2012). Glutamate levels are likely dynamic over the course of illness, with low levels in established schizophrenia samples (Théberge et al., 2003), but higher levels in the acute (Théberge et al., 2002) and prodromal (James, 2009) phases of illness, and thus elucidating the relationship between glutamatergic function and negative symptomology remains a relevant avenue for the investigation of new potential treatment paradigms.

One of the most established anatomical correlates of negative symptomology is evidence of tissue loss (Galderisi et al., 2015). Reductions in both grey and white matter have been identified in patients with persistent negative symptoms in several samples (Hazlett et al., 2008; Koutsouleris et al., 2008; Sigmundsson et al., 2001). While there have been some findings showing no association (Keilp et al., 1988; Luchins et al., 1984), in general, enlargement of the lateral ventricles has also been identified among patients with negative symptoms. Further, tissue loss has been reported in the temporal cortex, caudate, parietal cortex, left fusiform gyrus, and corpus callosum in various studies (Galderisi et al., 2015). While many of these changes are identifiable at first episode, they did not appear to associated with negative symptomology scores at baseline (Cahn et al., 2002).

Additionally, aberrations in gyrification, the process by which the originally lissencephalic fetal brain takes on its characteristic folding, are linked to negative symptoms. However, this relationship is likely dependent on disease chronicity with psychosis patients early in the course of illness (late adolescence and early adulthood) tend to show increased gyrification, however with more chronic illness, a disease state where negative symptoms tend to be more readily identifiable, schizophrenia patients show reduced gyrification compared to healthy controls (Sasabayashi et al., 2021). While there is a promising signal that gyrification may be meaningfully linked to negative symptomology, considerably more clarification of the literature is required as the later reductions in gyrification may be linked to cortical atrophy influencing measurement of gyrification.

1.3.4 Cognitive impairment

1.3.4.1 Clinical Presentation

Largely due to the dramatic presentations of positive and negative symptoms, cognitive impairments in schizophrenia are relatively unrecognized and under-investigated. However, nearly 98% of patients with schizophrenia will experience some degree of cognitive impairment (Mihaljevi & Janovi, 2019). Dysfunctions in working memory, attention, processing speed, visual and verbal learning with substantial deficit in reasoning, planning, abstract thinking and problem solving have been extensively documented in established schizophrenia samples for several decades (Heinrichs & Zakzanis, 1998). In analyses restricted to early psychosis, it is clear that these deficits are present (Aas et al., 2014) and likely develop very early during the psychosis prodrome (Harvey, 2009). However, the value of cognitive deficits in predicting transition from ultra-high risk to first episode schizophrenia remains mixed (Carrión et al., 2018).

Increasingly, cognition literature in schizophrenia has begun to extend beyond traditional neurocognitive deficits and into social cognition. Social cognition is defined as one's ability to create mental representations of themselves and their relationships that

helps to facilitates skillful social interactions (Sergi et al., 2007). Unfortunately, patients with psychosis are often impaired in emotional processing, social perception/knowledge, and theory of mind (Green et al., 2015). While on their face, these elements appear to be largely dependent on negative symptomology, social cognition is independent of other clinical symptoms and neurocognitive deficits, and persists across all stages of illness (Bertrand et al., 2007).

Cognitive deficits among schizophrenia patients represent one of the most consistent and substantial predictors of poor functional outcomes (Green et al., 2004; McCleery & Nuechterlein, 2019), however treatment of cognitive impairments associated with psychosis and schizophrenia has proven to be difficult. While some modest improvements in cognition have been found among individuals on atypical vs typical antipsychotics (Harvey et al., 2004; Keefe et al., 2004), the impacts of these differences on community functioning are not well known. Over the past 2 decades, optimism has abound relating to behavioral cognitive remediation strategies, with some studies showing promising results in specific domains, particularly when combined with adjunct rehabilitation methodologies (Wykes et al., 2011). However, these strategies are expensive and labor intensive both for patients and clinical teams – and tend not to be generalizable across cognitive domains. Thus efforts to identify patients who are most likely to benefit from these specific interventions will help to maximize their utility in clinical care.

1.3.4.2 Neurobiological correlates

Although negative and cognitive symptoms are considered separate domains of psychopathology in schizophrenia, shared features suggest that symptoms from one domain may reinforce the other or that they may originate in similar neurobiological structures. Several interacting factors are likely to induce the underlying cognitive issues in schizophrenia, including genetic, epigenetic, developmental and environmental factors(Mihaljevi & Janovi, 2019). While much of our understanding of cognition in

schizophrenia is derived from imprecise animal models (Tamminga, 2006), we do understand that cognition can best be understood to relate to complex networks (Millan et al., 2012). While some insights can be gleaned from the study of other diseases of cognitive dysfunction (such as Alzheimer's Disease), cognition in schizophrenia appears to be predominantly a problem of neuronal, glial, and neuronal network dysfunction rather than a process of neurodegeneration (Millan et al., 2012; Tamminga, 2006).

Originally the neurobiological underpinning of cognitive deficits was believed to be primarily a matter of hypo-activity, particularly in the prefrontal cortex (Pratt et al, 2008; Roesch-Ely et al., 2009) and parietal regions (Chieffi et al., 2018), however subcortical structures are increasingly viewed as critical mediators of cognitive disruptions in schizophrenia. The anterior cingulate cortex (ACC), hippocampus, and basal ganglia, have a substantiated role in cognitive disruption associated with schizophrenia (Tamminga, 2006). Rather than simply hypo-activity, cognitive impairments are linked to a series of network level disturbances constituting both hypo- and hyperactivity. However, it remains to be seen if these areas of hyperactivity (specifically in the prefrontal cortex as well as temporal and parietal areas), are primary deficits, or compensatory cognitive responses to characteristic changes other than from cognition (e.g., differing emotional experiences among patients) (Thorsen et al., 2014). Understanding the nuance in the neurobiology of cognitive deficits remains in its infancy with substantially more research required.

1.4 Recovery

1.4.1 Clinical remission

Recovery from schizophrenia and psychosis varies greatly, and how recovery is conceptualized matters greatly to how rates of recovery are determined. The most commonly considered domain in early psychosis treatment tends to be clinical recovery or clinical remission, most often defined using criteria derived from Andreason et al (2005). This criteria is based on the Positive and Negative Syndrome Scale (PANSS) with

remission defined as no relevant item (delusions, hallucinations, conceptual disorganization, blunted affect, social withdrawal, alogia, mannerisms/posturing, and unusual thought content) rated as greater than a 2, or "mild" (Andreasen et al., 2005). This area of clinical response tends to occur relatively rapidly after the onset of antipsychotic medication, with much of the clinical improvement apparent within the first month of treatment. In fact, patients who do not show at least minimal (>20 %) improvement after 2 weeks of antipsychotic treatment are highly likely to be non-responsive to treatment after a longer course, and thus discussions around medication changes are warranted (Samara et al., 2015).

With improved antipsychotic treatment paradigms and the proliferation of non-pharmacologic treatment modalities, data from meta-analyses suggests that rates of symptom remission have improved over time, with some studies suggesting as high as 58% of first episode patients achieving clinical remission (Lally et al., 2017). However, while remission from clinical symptoms is a laudable goal, particularly in early treatment, full recovery from psychosis (which includes elements of social, occupational, educational, and community functioning over a sustained period) remains considerably lower with only 13-40% of patients with first episode psychosis managing to achieve this higher threshold for recovery (Lally et al., 2017). Because treatment goals of patients typically address features beyond the management of symptoms, with emphasis often placed on educational and vocational supports, and a focus on independent living (Ramsay et al., 2011), framing treatment around recovery rather than simply the absence of symptoms is increasingly becoming the primary metric for treatment success in clinical and research settings alike.

1.4.2 Functional Outcomes

Functioning in schizophrenia is defined as social functioning/adaptation in a community, including independent living, financial management, employment, and leisure/social activities (Green et al., 2000). While a laudable goal from a humanitarian

perspective, focus on functional improvement takes on particular relevance when attempting to address the underlying medical and social services costs of schizophrenia treatment. Rates of functional recovery vary considerably, based on how recovery is defined. On the high end, studies have suggested that recovery rates to be as high as 40% (Hegarty et al, 2014) to 50% in short term outcome studies (Menezes et al., 2009). However, studies using more stringent criteria have suggested that rates of functional recovery are considerably lower at only 1-2% per year reaching a peak rate of recovery of only 13-14%, with this figure appearing to be stable regardless of whether or not patients accessed early intervention programs (Jääskeläinen et al., 2013). Thus, understanding the early predictors of functional outcomes is a necessary pursuit if the promise of early intervention services is to be fully actualized. Sadly, even when full functional recovery is attained, this status may be fragile and susceptible to a course of functional relapse (Torgalsbøen & Rund, 2002). While rates vary significantly between studies and even meta-analyses, this difference can be largely attributed to the lack of consensus criteria for what constitutes functional recovery.

Despite its importance, functional impairment has been historically understudied, although research on this topic has increased since the inclusion of functioning as a diagnostic criteria in the DSM-III and later versions (Burns & Patrick, 2007). An early barrier to research on functioning was the conceptualization of functioning using the Kraeplinian model, characterized by progressive and near constant functional decline. The Kraeplinian subtype of schizophrenia was defined by continuous hospitalization, dependence on others for meeting their basic needs; a failure to engage in meaningful market employment, and poor symptom management (R. S. Keefe et al., 1988). While this conceptualization of poor outcome effectively captures the worst levels of functioning, this binary model for outcome ignores the significant variation in recovery even among those patients who are not on a “Kraeplinian course”. This approach also does not adequately address the continuum that exists in

neuropsychological functioning and social/community functioning, nor does it address the intrinsic links between the two domains (Green, 1996, 2006).

This has led to a more recent conceptualization of functional outcome that captures a continuum of disruptions that can occur from the neuropsychological level (involving deficits in working memory, attention, motor processing etc) to the social/community functioning level (including disruptions in independent living, working/education, social activity, and leisure activity) (Buchanan et al., 2011). Sumiyoshi & Sumiyoshi (2015) have suggested three scaffolded layers are required to develop positive community functioning: 1. Neurocognitive performance, 2. Functional capacity, and 3. Functional performance (Sumiyoshi & Sumiyoshi, 2015). Neurocognitive performance forms the basis of functional outcomes as the lack of intact neurocognitive skill (as discussed in previous sections) prohibits higher order processes from being possible. The second level, functional capacity, represents the ability to competently perform basic activities of daily living in a limited capacity (e.g., can describe the process of dialing a phone, using a debit card). Even if patients are unable to perform these activities in real world settings, individuals exhibiting functional capacity should possess the cognitive capacity for completing these tasks (Green et al., 2011). The third level, functional performance, suggests a patient is able to perform the activities of daily living such as working, socializing, and maintaining ones living quarters, in the real world all while managing the plethora of distractions and conflicts that are inherent in day to day life (Sumiyoshi & Sumiyoshi, 2015). Reaching the level of adequate functional performance across several domains of daily living would be considered a positive functional response to treatment in this model.

Despite increased understanding of the complexity of functional response, several barriers to studying this phenomenon remain. Particularly at the higher levels of functioning described by Sumiyoshi & Sumiyoshi (2015), poor outcome may be attributable to number of interdependent factors. For example, functional performance

is likely to be impacted by persistent negative symptoms which predict poor functional outcome in community dwelling outpatients above and beyond neurocognitive impairment (Foussias et al., 2011). While symptom remission is indeed associated with community functioning, the relationship is not robust – with evidence suggesting functional and clinical response are unique domains of outcome. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), found that use of antipsychotic medications conferred only minor improvements in community functioning (Swartz et al, 2017). Clearly, symptomatic recovery and functional recovery are disconnected with symptom remission occurring far more frequently than functional remission (Harvey et al, 2012). Similarly, reduced premorbid function which may be associated with a number of risk factors for schizophrenia, including persistent clinical symptoms and neurocognitive deficits, there is likely no single path to understanding functional outcome.

1.5 Study Rationale

Despite the methodological limitations in studying functional response (e.g., no consensus criteria), understanding and promoting functional recovery remains a valuable pursuit for EIPs. Among patients, elements of social and occupational recovery are consistently reported as primary treatment goals (rather than simply focusing on symptom remission)(Ramsay et al., 2011). Thus, the relative paucity of work assessing prognostic indicators of functional response is problematic. EIPS, despite significantly higher upfront costs, are shown to have net financial, as well as humanitarian benefits, compared to traditional schizophrenia programs (Hastrup et al., 2012; Rosenheck et al., 2016). However, the net financial benefits of these models is largely contingent upon delivering superior functioning in the critical early treatment period and reducing dependency burden over the patient's life course. Thus, the ability to identify key prognostic indicators of good versus poor outcome at the earliest possible point may aid clinicians and program administrators in EIP settings in optimizing treatment protocols for patients. By identifying the key clinical and biologic indicators of poor outcome, this would support earlier transitions to available remediation strategies (e.g., employment counselling, modified educational goals, use of clozapine). However, this goal is not without its complications. Schizophrenia pathophysiology shows disturbances at various levels of analysis, all of which may be related to later functioning. Functional outcomes in schizophrenia are impacted at multiple levels of analysis, from the micro level (e.g., neuronal communication), the meso-scale (disruptions in neural networks and cortical anatomy) and disruptions at the manifest-scale (e.g., language and behavior). Understanding how impairments at each of these levels of disruption can impact later functioning is critical to developing a holistic understanding of treatment outcome.

The present dissertation will seek to identify prognostic indicators of short term functional outcome following treatment, specifically, return to vocational activity (enrollment in employment, education, or training) and functional performance measured by the Social and Occupational Functioning Assessment Scale (SOFAS). Three

projects will be conducted to this end: In chapter 2, we will assess how disruptions at the “manifest” scale, in this case speech quality and quantity, are associated with disordered thought, and with later social and vocational functioning using automated linguistic analyses. In Chapter 3, we will assess disruptions at the “meso-scale”, by identifying how cortical anatomy, specifically gyrification and cortical thickness are associated both with baseline clinical presentation and later social and vocational functioning. Baseline T1-weighted anatomical images will be preprocessed and analyzed using Freesurfer 6.0.0 automated pipeline to assess characteristics of cortical architecture (cortical thickness and local gyrification index), and their associations with outcome. Finally, in Chapter 4, we will assess the influence of the micro-level of analysis on later functional response. 1-H magnetic resonance spectroscopy data at illness baseline will be used to assess neuro-metabolite concentration in the dorsal anterior cingulate cortex and we will then assess associations with social and vocational outcomes following treatment.

While the methodological approaches described herein are disparate, comprising automated linguistic analyses, anatomical neuroimaging, and 1-H Magnetic resonance spectroscopy, two themes bind the present works together: These projects used a unique sample of drug naïve first episode patients, and a primary focus on the oft-neglected theme of functional (specifically vocational) recovery. The use of an antipsychotic naïve sample is both unique and of methodological import. Antipsychotic use suppresses the natural variation in psychotic symptom severity, impacts speech quality and quantity (de Boer et al., 2020), and contributes to regional differences in brain structure (Nelson et al., 2018; Navari & Dazzan, 2009); By reducing these confounds in an early psychosis sample we are better able to identify the relationship between natural baseline clinical presentation and our outcomes of interest. Tying our study together with our primary outcome measures (vocational functioning at follow up) is similarly unique and represents a meaningful contribution to the extant schizophrenia literature. As mentioned in prior sections, the reduction in productivity

and heightened social services utilization among patients with psychosis is at the core of the largest economic burden associated with schizophrenia care and thus these remain highly relevant research pursuits.

1.5.1 Tracking Outcomes in Psychosis (TOPSY) Study

The data presented in this dissertation were derived from the Tracking Outcomes in Psychosis (TOPSY) study, a longitudinal, observational neuroimaging study in First Episode Psychosis (FEP). The TOPSY study is an ongoing study of drug naïve (< 2 weeks of life time antipsychotic exposure) patients experiencing their first episode of psychosis. The study includes patients who are enrolled in the Prevention and Early Intervention Program for Psychoses (PEPP) at London Health Sciences Centre, in London, Ontario Canada, and demographically matched healthy controls from the London, Ontario community. For our FEP sample, both inpatients and outpatients were eligible for the study. This data is used to study the brain processes that result in thought and language disorder and, critically, understand the factors that influence variable outcomes (both clinical and functional) seen in patients with schizophrenia using a multimodal approach.

FEP Participant inclusion was based on admission to the Prevention and Early Intervention Program for Psychoses (PEPP) at London Health Sciences Centre in London, Ontario, Canada. Enrolment was limited to patients ages 16-45, who possessed capacity to provide informed consent (determined by the clinical team and ability to express understanding of the letter of information). This broad inclusion criteria was to best capture the heterogeneous sample of FEP patients. However, a later consensus diagnosis procedure was conducted to delineate which FEP patients went on to meet clinical criteria for schizophrenia versus affective psychoses. Participants were excluded from participation if were diagnosed with a drug or alcohol dependency (according to DSM-V criteria) in the twelve months prior to enrollment (although recreational use of drugs was admissible), had suffered any head injury resulting in seizure or loss of

consciousness, were diagnosed with an intellectual disability, neurological illness, or had any implants incompatible with 7-Tesla Magnetic Resonance Imaging.

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Chapter 2: Linguistic Determinants of Functional Outcome

Preamble

Schizophrenia patients show disturbances at multiple levels of speech production (Kuperberg, 2010), and despite the difficulties conducting research in a heterogeneous illness such as schizophrenia, linguistic characteristics show promise as a prognostic indicator for conversion to psychosis, as well as relapse among treated patients (de Boer, Brederoo, et al., 2020). Despite this promise, the nature of speech disturbances are likely qualitatively and quantitatively distinct among actively psychotic vs. stable patients. Further, differences among patients exposed to antipsychotic medications have been reported (slower articulation, more pauses, shorter sentences) versus their unmedicated peers (de Boer, Voppel, et al., 2020). While the area of research assessing the prognostic value of linguistic markers in schizophrenia remains in its infancy, applying this research to identify patients at risk for poor social and vocational outcomes is warranted.

A major barrier to identifying prognostically valuable predictors of outcome in schizophrenia is a lack of research among drug naive FEPs. To address this gap in the linguistic literature, the Neuroimaging In Mental Illness (NIMI) Lab has sought to identify linguistic features of psychotic speech In a drug-naïve FEP population by analyzing three 1-minute speech samples using two automated speech analysis software programs, Cohmetrix (Graesser et al., 2004), and the Linguistic Inquiry Word Count (LIWC) (Pennebaker et al., 2015).

Using the TOPSY data set, we have completed two analyses comparing healthy controls to FEPs on their linguistic profiles, Mackinley et al. (2021) and Silva et al. (2022). In the first study (manuscript appended below), Mackinley et al. (2021) used Coh-Metrix automated speech analysis software (Graesser et al., 2004) to compare FEP patients and healthy controls on a number of variables at the word, sentence, and higher order level. In this study, patients showed reduced overall words spoken, and increases in pronoun usage. No differences on higher-order linguistic metrics (narrativity, formality,

referential cohesion, or deep cohesion) were found. Finally, a principal component analysis revealed two factors loading on linguistic connectives. The first factor “All connectives” showed positive loading on all connective types (causal, logical, temporal, contrastive, and additive) and the second factors “acausal temporal connectives” showed reduced use of causal and contrastive connectives, but used more temporal linkages and additive connections. While no significant differences emerged between patients and healthy controls on these connectives factors, higher connectives use was associated with higher scores on clinical metrics of conceptual disorganization among patients (Mackinley et al., 2021). This suggests that aberrant linguistic connective use (increased use of connective words such as “and”, “as well”, and “also”) may, in part, contribute to the clinical intuition of disorganized thought, which in turn, may result in social and occupational deficits for patients. However, the association of these variables with later functional outcomes has not been determined.

A second study, by (Silva et al., 2021), analyzed the same 3 one minute speech samples using the LIWC software package (Pennebaker et al., 2015). Silva et al compared patients and healthy controls on their use of analytic thinking style, using Bayesian statistics. Analytic thinking style is an index variable with higher scores suggesting a categorical style that is more formal and suggestive of hierarchical thinking style, and lower scores suggesting a narrative style which is more intuitive and episodic in nature. Compared to HC, patients showed reduced analytic thinking in their speech. Further, among FEPs, reductions in analytic thinking were associated with higher clinical metrics of disorganization (Silva et al., 2021). In other words, patients’ verbal responses were indicative of a more narrative and less content based pattern of speech. A higher analytic score (more categorical thinking style), is linked with academic success due to this linguistic style’s use in academic and professional settings (Pennebaker et al., 2014).Thus, it is possible that among FEP patients, analytic thinking style may be linked with later academic and occupational success, however, little evidence has been collected to assess this question.

To address this gap in the literature we assessed whether these linguistic variables, previously identified to be aberrant in psychosis or associated with worsened clinical presentation (total words spoken, all-connective, acausal connectives, pronoun use, and analytic thinking score), are associated with social and vocational functioning following 6-12 months of treatment. To this end, we used a prototypical constraint-based algorithm (PC) to identify dependencies in a variable set comprised of our linguistic factors as well as vocational status (NEET status) and follow up social and occupational functioning [SOFAS] score. The graphical probabilistic model revealed that only the total number of words spoken showed a direct association with NEET and an indirect association with SOFAS, with a second set of dependencies emerging among the remaining linguistic variables, suggesting speech production at baseline may be associated with social and vocational outcomes following treatment. The complete manuscript is appended below (Chapter 2, Manuscript 2).

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Manuscript 1: Linguistic Determinants of Formal Thought Disorder in First Episode Psychosis.

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Abstract

Aim: Thought disorder is a core feature of schizophrenia but assessment of disordered thinking is challenging, which may contribute to the paucity of mechanistic understanding of disorganization in early psychosis. We studied the use of linguistic connectives in relation to clinically quantified dimensions of thought disorder using automated speech analysis in untreated, first episode psychosis (FEPs) and healthy controls (HCs).

Methods: 39 treatment-naïve, actively psychotic FEPs and 23 group matched HCs were recruited. Three one-minute speech samples were induced in response to photographs from the Thematic Apperception Test and speech was analyzed using COH-METRIX software. Five connectives variables from the Coh-Metrix software were reduced using principal component analysis, resulting in two linguistic connectives factors. Thought disorder was assessed using the Thought Language Index (TLI) and the PANSS-8.

Results: Connective factors predicted disorganization, but not impoverishment suggesting aberrant use of connectives is specific to positive thought disorder. An independent t-test comparing low and high disorganization FEPs showed higher load of acausal temporal connectives in high disorganization FEPs compared to low disorganization FEPs (mean [SD] in high vs. low disorganization FEPs = 0.64 (1.1) vs. -0.37 (1.02) ; t=2.91, p=0.006). Factor 2 was not correlated with severity of symptoms or cognition suggesting connective use is a specific index of disorganized thinking rather than overall illness status.

Conclusions: Clinical assessment of disorganization in psychosis is likely linked to the aberrant use of connectives resulting in an intuitive sense of incoherence. In early psychosis, thought disorder may be reliably quantifiable using automated syntax analysis.

1.0 Introduction

Schizophrenia is an illness of perceptual and thought disturbances. While research on disordered thinking in schizophrenia is typically focused on unusual thought content (e.g., delusions), disturbances in the formation and expression of thought are core features of the illness. Formal thought disorder (FTD) is defined by substantial disturbances in a patient's ability to express cogent, complex thoughts (Bleuler, 1950). While not necessary for a diagnosis of schizophrenia, the presence of FTD predicts onset of psychosis in clinical high risk patients (Dominguez et al., 2010; Ziermans et al., 2014), is present in over 55% of patients in their first episode of psychosis (Roche, Lyne, et al., 2015), and its persistence is linked to worsened social/community functioning (Bowie et al., 2011; Bowie & Harvey, 2008; Roche et al., 2016), cognitive deficits and poorer clinical outcomes (Cuesta et al., 1994; Roche, Creed, et al., 2015). Despite the recognized importance of this syndrome, no effective interventions are available to reduce the burden of FTD in schizophrenia when antipsychotics are ineffective. In part, this therapeutic gap can be attributed to our lack of a clear conceptual understanding of this syndrome and its physiological basis.

FTD captures a number of non-specific thought/language anomalies (Andreasen, 1986) that are evident across a wide range of mental health and cognitive disorders including psychosis, bipolar disorder (Morgan et al., 2017), depression, and Autism Spectrum Disorder (Eussen et al., 2015), as well as among healthy controls, albeit in subtler forms (Kircher et al., 2018; Kuperberg, 2010). FTD has been assessed historically as a categorical variable (Hart & Lewine, 2017), which fails to adequately describe the breadth of dysfunction under the umbrella of FTD. By ignoring the multidimensional nature of FTD, these metrics impede the ability of researchers to identify causal link between thought disorder and its neural and cognitive basis.

A number of validated manually scored instruments have been developed to assess multiple domains of disordered thought such as the Thought Language Index (Liddle et al., 2002), Thought Disorder Index (TDI) (Solovay et al., 1986) and Thought and Language

Disorder (TALD) scale (Kircher et al., 2014). By capturing FTD as a trans-diagnostic set of features, these scales make it possible to begin the work of linking specific elements of FTD with specific neural processes. While progress has been made in this regard (Wensing et al., 2017), several barriers remain in place. First, while potentially mitigated through their manualized approach, these scales rely heavily on clinical judgement and require highly trained staff. Second, because FTD items in these scales are tailored to identify illness specific symptomology (often centered on schizophrenia), these measures may not be adequately sensitive to subtler forms of thought disorder. Finally, many of these scales can be time consuming to complete in busy clinical settings, presenting substantial pragmatic barriers to their application.

To better understand the linguistic underpinnings of FTD, recent research has leveraged automated speech analysis software. These programs allow clinicians to assess larger speech samples, across multiple linguistic domains with consistent and inexpensive results. The use of these software programs allows researchers to assess speech samples at multiple time points and levels of analysis (e.g., at the level of the word, phrase, sentence, or full speech sample) without the burdens of hand scoring. This allows researchers to assess poor conceptual integration based on traditional clinical measures of thought disorder as well as at structural language levels. Because it remains unclear whether thought disorder presents at basic linguistic or higher order levels, the ability to efficiently and simultaneously assess factors at multiple levels of analysis is advantageous.

Over the past several years these technologies have been applied in the assessment of language dysfunction in both schizophrenia (Elvevåg et al., 2010; Minor et al., 2019; Willits et al., 2018) and clinical high risk samples (Bedi et al., 2015; Gupta et al., 2018). These studies have shown speech disturbances at multiple levels of linguistic analysis ranging from basic speech descriptors (e.g., word counts) (Willits et al., 2018) up to higher order linguistic variables, such as text cohesion (Bedi et al., 2015; Gupta et al.,

2018; Willits et al., 2018). In a 2018 study, Willits et al (Willits et al., 2018) showed that schizophrenia patients used fewer causal, logical and contrastive connectives. Connectives are words used to link concepts/thoughts when speaking, and when used incorrectly the listener must exert more cognitive resources to interpret speech(Cain & Nash, 2011). However, it remains unclear whether the output from automated speech analysis software effectively captures the clinical construct of FTD or if they represent a different construct that is not clinically apparent, albeit critical for the disease process.

Because connectives are the linguistic basis upon which cohesion is built through text, we hypothesized that the aberrant use of connectives in speech samples underlies the clinical impression of thought disorder. We studied linguistic connectives in relation to clinically quantified dimensions of thought disorder using Coh-Metrix, an automated speech analysis software, in untreated first episode psychosis patients (FEPs) and healthy controls (HCs).

2.0 Method

2.1 Participants:

Data were collected from 39 treatment-naïve, psychotic FEPs recruited from the Prevention and Early Intervention Program for Psychoses in London, Ontario, Canada. All participants were in the acute phase of the illness. Additionally, we recruited 23 healthy controls from the community group matched for age, sex, and parental SES. Exclusion criteria included >2 weeks of lifetime antipsychotic exposure (the time at which antipsychotics would be expected to be fully in effect), a diagnosis of affective psychosis, active substance dependence, the presence of intellectual/ developmental disorder or the inability to provide informed consent. All participants included in the analysis were native English speakers. No controls for cognitive performance or education level were performed.

2.2 Instruments:

2.2.1 The Thought Language Index

The Thought and Language Index (TLI) (Liddle et al., 2002) is an instrument for assessing formal thought disorder under standardised conditions. Participants produce three one-minute speech samples in response to 3 photographs from the Thematic Apperception Test (Murray, 1943). Responses were scored on 8 domains: poverty of speech, weakening of goal, looseness, peculiar word usage, peculiar sentence structure, peculiar logic, distractibility, and perseveration. These domains were also used to compute 3 aggregate scores: impoverishment of thinking (the summed scores of Poverty of speech, weakening of goal, and perseveration), disorganization (the summed scores of looseness, peculiar word usage, peculiar sentence construction, peculiar logic, and distractibility), and overall thought disorder (the summed scores of all 8 domains).

2.2.2 Positive and Negative Syndrome Scale – 8 Item Scale

The Positive and Negative Syndrome Scale – 8 Item scale (PANSS-8) is an abbreviated version of the PANSS clinical assessment for psychosis with acceptable internal consistency and highly correlated with the full PANSS (C.-H. Lin et al., 2018a). The PANSS-8 was scalable at each patient contact and highly sensitive to symptomatic changes (C.-H. Lin et al., 2018a). PANSS Item P2 (conceptual disorganization) is a single item measure intended to assess FTD characterized by "disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations non sequiturs, gross illogicality, or thought block" (Kay et al., 1987) . Scored on a 1 (absent) to 7 (extreme) Likert type scale, we classified those with scores of 1-3 (absent to mild) as "Low Conceptual disorganization" and those 4-7 (moderate to extreme) as high conceptual disorganization.

2.2.3 Coh-Metrix 3.0

The Coh-Metrix (McNamara et al., 2014) system is a web-based automated speech analysis software that computes several word, sentence and passage level linguistic variables from written and spoken speech samples. The software automatically

computes a number of lower order (e.g., word counts, frequency of pronoun use, use of connectives) and higher order (e.g., narrativity, cohesion, text formality) linguistic variables (Graesser et al., 2004). We based our project on the work in Willits et al (2018), focusing primarily on the use of 5 connectives variables (See Table 2 for details). Connectives were scored based on their frequency per 1000 words spoken.

2.2.4 Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory (Oldfield, 1971) is a 12-item inventory in which participants were asked to self report their hand preference for several common house-hold/ community activities (e.g., which hand do you use to write, throw a ball). Each item is given a score of -1 for left hand preference, 0 for no preference, and +1 for right hand preference. Thus, the scale is scored from -12 (fully left handed) to +12 (fully right handed).

2.3 Procedure

This study was approved by the local Research Ethics Board and informed consent was received prior to participation. Clinical interviews, including clinical and demographic assessments, were completed by a board certified psychiatrist. Cognitive assessments and the TLI interview and rating were completed by graduate level research assistants. Speech samples were limited to 3 1-minute speech samples from the TLI interview, with researcher speech removed prior to analysis, and were blinded to participant status consistent with the procedure described by Sommer et al. (Sommer et al., 2010)

2.4 Statistical Analysis

Our analysis was completed in four steps. First, recorded and transcribed speech samples were entered in Coh-Metrix 3.0 web tool to calculate the incidence scores (use per 1000 words) for the each of the connectives variables. We then conducted a principal component analysis on the five connective variables to extract factors based on a scree plot that cumulatively explained 72.14% of variance in raw scores and compared the selected factor scores between FEP and control groups using independent t tests. We then investigated the relationship between the factor scores

and clinically observed scores using the TLI and PANSS P2. To establish specificity of these relationships, the Social and Occupational Functioning Assessment Scale (SOFAS) and cognitive scores were correlated with the factor scores.

3.0 Results

3.1 Demographic & Clinical Features

When comparing healthy controls to FEPs, no statistically significant differences existed for gender, age, socioeconomic status, or handedness (Table 1). All participants scored positively on the Edinburgh Handedness Inventory, reflecting at least mild right hand preference. As expected, there were several group level differences in cognitive and clinical scores between patient groups and healthy controls (Table 1).

Table 2.1: Demographic, Linguistic and Clinical characteristics of Healthy Controls and Patients

Variable	Healthy Control n=23	All Patients n=39	Low Disorganization Patients n=21	High Disorganization Patients n=18
	Demographic Data			
Gender (Male/Female)	17/6	32/7	16/5	16/2
Age [M (sd)]	22.08 (3.47)	23.63 (4.48)	24.37 (5.37)	22.65 (2.79)
NS-SEC[M (sd)]	3.41 (1.34)	3.76 (1.20)	3.75 (1.12)	3.78 (1.31)
Handedness [M (sd)]	10.72 (2.10)	10.33 (2.16)	10.42 (1.59)	10.22 (2.29)
	Coh-Metrix Output			
Total Words Spoken [M (sd)]	145.83 (28.54)	127.58 (35.31)*	125.55 (31.34)*	129.96 (40.35)
All-Connectives Incidence [M (sd)]	66.16 (16.31)	72.67 (25.97)	64.39 (25.41)	82.40 (23.74) *
Causal [M (sd)]	13.85 (8.73)	14.87 (9.46)	15.24 (10.28)	14.43 (8.70)
Logical [M (sd)]	32.11 (15.11)	35.36 (15.81)	30.88 (17.10)	40.61 (12.70)
Temporal [M (sd)]	8.22 (5.51)	9.28 (6.60)	5.96 (5.02)	12.39 (6.52)*
Contrastive [M (sd)]	17.11 (10.12)	18.34 (8.67)	16.90 (8.90)	19.95 (8.36)
Additive [M (sd)]	47.11 (12.27)	50.62 (19.21)	45.16 (17.58)	57.06 (19.56)
Noun Incidence [M (sd)]	212.27 (23.70)	213.94 (37.84)	217.11 (32.53)	210.21 (43.96)
Adjective Incidence [M (sd)]	48.88 (14.82)	47.41 (15.33)	48.01 (12.98)	46.69 (18.10)
Pronoun Incidence [M (sd)]	87.24 (22.66)	107.17 (24.11)**	100.52 (23.88)	115.00 (22.57)**
Narrativity [M (sd)]	0.88 (0.48)	1.08 (0.59)	0.93 (0.60)	1.24 (0.56)*
Formality [M (sd)]	0.11 (0.06)	0.36 (0.81)	0.22 (0.39)	0.52 (1.11)
Deep Cohesion [M (sd)]	-0.78 (0.94)	-0.63 (1.01)	-0.81 (1.23)	-0.41 (0.89)
Referential Cohesion [M (sd)]	0.17 (0.74)	0.11 (0.78)	-0.01 (0.74)	0.25 (0.81)
	Clinical and Cognitive Data			
DUP Months [M (sd)]	N/A	8.83 (11.86)	8.83 (13.79)	8.82 (9.11)
Antipsychotic Defined Daily Dose Equivalents	N/A	2.31 (3.68)	2.73 (3.33)	1.81 (4.10)
SOFAS [M (sd)]	81.39 (4.41)	38.60 (12.42)**	41.39 (13.35)**	34.82 (10.23)**
TLI Total [M (sd)]	0.26 (0.39)	1.39 (1.31) **	0.93 (0.91)**	1.96 (1.52)**
TLI disorganization [M (sd)]	0.17 (0.24)	0.93 (1.12) **	0.57 (0.61)*	1.35 (1.41)
TLI Impoverishment [M (sd)]	0.09 (0.21)	0.47 (0.61) **	0.35 (0.48)*	0.60 (0.72) **
PANSS-8 Total [M (sd)]	8.0 (0.00)	26.46 (7.2)**	23.66 (5.53) **	29.72 (7.69)**
PANSS-8 Negative [M (sd)]	3.0 (0.00)	6.94 (4.46)**	5.81 (3.69)**	8.27 (4.99)**
DSST [M (sd)]	68.39 (8.1)	51.83 (14.65)**	55.19 (13.70)**	47.91 (8.14)**
Trails-B [M (sd)]	56.21 (15.35)	87.21 (42.6) **	81.64 (42.95)*	93.83 (42.61)**
Category Fluency [M (sd)]	24.45 (6.44)	18.67 (5.28)**	18.95 (4.63)**	18.31 (6.14) **

M, Mean; SD, standard deviation; NS-SEC, national statistics socio-economic classification; TLI, Thought Language Index; SOFAS, Social and Occupational Functioning Assessment Score; PANSS-8, Positive and Negative Syndrome Scale – 8 Item Scale; DSST, Digit Symbol Subsitution Test; *Significantly different compared to healthy controls ($p < 0.05$); **Significantly different compared to healthy controls ($p < 0.01$).

3.2 Coh-Metrix Output

Coh-Metrix output was compared between healthy controls and patients. As expected, statistically significant differences were found between patients and controls on the number of words spoken [134.58 (35.31) vs. 115.83 (28.54); t=2.24, p=0.028]. Additionally patients showing significantly more pronoun use in their speech samples [107.17 (24.11) vs. 87.24 (22.66); t=3.13, p=0.003], but no differences were found between patients and healthy controls on higher order variables such as narrativity, formality, referential cohesion, or deep cohesion (Table 1).

When healthy controls were compared to low disorganization patients, only a reduction in total words spoken among low-disorganization patients was statistically significant [125.55 (31.34) vs. 145.83 (28.54); t=2.46, p=0.019]. Conversely, High-disorganization patients (vs healthy controls) showed significantly higher pronoun use [115.00 (22.57)vs. 87.24 (22.66); t=3.79, p=0.001], higher overall connectives use [82.40 (23.74) vs. 66.16 (16.31); t=2.53, p=0.016], higher temporal connectives use [12.39 (6.52) vs. 8.22 (5.51); t=2.07, p=0.046] and higher narrativity [1.24 (0.55) vs. 0.88 (0..48); t=2.23, p=0.032].

3.3 PCA analysis

Principal component analysis of the five Coh-Metrix based connective scores resulted in two factors (Table 2), explaining 51.6% and 20.6% of variance respectively. Factor 1 positively loaded all 5 connectives variables (overall connective use factor), and Factor 2 positively loaded temporal and additive connectives while negatively loading for causal connectives (acausal temporal linkage factor). Both Factor 1 loading and Factor 2 loaded higher among FEPs [Factor 1: M(sd)=0.10 (1.15); Factor 2: M (sd)= 0.13 (0.99)] than healthy controls[Factor 1: M(sd)= -0.09 (0.81); Factor 2: M (sd)=-0.04 (1.2), however the difference was not significant. The distribution of connectives factor 1 and factor 2 scores can be found in Figure 1 (supplemental Materials).

Table 2: Linguistic Connectives Definitions and PCA Factor Loading

Connective Variable	Variable Description	Connective factor 1	Connective Factor 2
Causal Connectives	Words that link a cause with an effect. (e.g., Because, due to)	0.703	-0.455
Logical Connectives	Words conjoining two logically linked statements (e.g., and, as well as)	0.951	-0.084
Temporal Connectives	Words that help put events in order of time (E.g., First, then, After)	0.342	0.791
Contrastive connectives	Words used to compare and contrast ideas (e.g., although, but, despite)	0.843	-0.135
Additive Connectives	Words used to add information or connect ideas (e.g., in addition, Moreover, another)	0.598	0.406

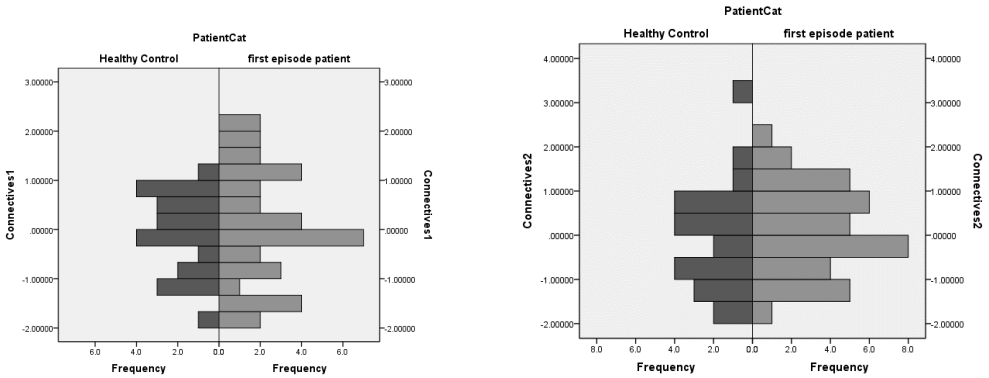

Figure 1. Distribution of Connectives Factors among Healthy Controls and Patients. **A.** Distribution of Connectives Factor 1 **B.** Distribution of Connectives Factor 2.

3.4 Relationship with clinical measures of disorganization

Correlations between linguistic connectives factors and TLI scores in FEPs showed that both linguistic connective factors were associated with the overall TLI scores among patients (Factor 1: *R=0.419 p=0.010, Factor 2:R=0.408, p=0.012),* but not among controls

(Table 3). These associations between connectives factors and TLI scores were driven by the association between connectives use and TLI disorganization sub scores (Factor 1: R=0.416, p=0.01; Factor 2: R=0.379, p=0.02). No statistically significant associations existed between connectives use and TLI impoverishment scores, suggesting that the aberrant use of connectives is associated with positive, rather than negative, elements of thought disorder. These findings persisted after controlling for gender and handedness (Table 5).

An independent t-test comparing low and high disorganization FEPs showed higher load of acausal temporal connectives in high disorganization FEPs compared to low disorganization FEPs (mean [SD] in high vs. low disorganization FEPs = 0.64 (1.1) vs. -0.37 (1.02) ; t=2.91, p=0.006).

Table 3: Correlation between Conenctives factors and Thought Language Index (TLI) Scoes Healthy Controls and First Episode Patients

Variable		**TLI: Overall** *R* (p-value)	**TLI: Impoverishment** *R* (p-value)	**TLI: Disorganization** *R* (p-value)
Healthy Control	Factor 1	-0.026 (0.91)	-0.136 (0.55)	0.079 (0.73)
	Factor 2	-.339 (0.13)	-0.371 (0.10)	-0.327 (0.14)
FEP	Factor 1	**0.419 (0.010)****	0.149 (0.38)	**0.416 (0.01)****
	Factor 2	**0.408(0.012)***	0.193 (0.25)	**0.379 (0.02)***

Table 5: Linguistic Features Healthy Controls Vs. First Episode Patients, Controlling for Gender and Handedness.

Variable		TLI: Overall *R* (p-value)	TLI: Impoverishment *R* (p-value)	TLI: Disorganization *R* (p-value)
Healthy Control	Factor 1	-0.084 (0.73)	-0.153 (0.53)	0.002 (0.99)
	Factor 2	-.385 (0.104)	-0.393 (0.096)	-0.284 (0.239)
FEP	Factor 1	**0.443 (0.008)****	0.160 (0.36)	**0.435 (0.009)****
	Factor 2	**0.410 (0.014)***	0.190 (0.27)	**0.379 (0.025)***

3.5 Specificity of Connective Factors

No correlations between connectives factors and measures of symptom severity (SOFAS, CGI-Severity) and cognition (Digit symbol substitution, Trails-B, and Category Fluency) were significant at an uncorrected threshold, suggesting that aberrant connective use is a specific index of disorganized thinking rather than overall severity of symptoms or cognitive dysfunction (Table 5). While these trends remained largely consistent following correction for gender and handedness, Factor 2 (acausal temporal connectives) was positively correlated at with Clinical Global Impression- Severity (R=0.441, p=0.017) (Table 6).

Table 5: Correlations Between Connective Use, Cognition and Severity of Symptoms

	SOFAS *R* (p-value)	**CGI-Severity** *R* (p-value)	**DSST** *R* (p-value)	**Category Fluency** *R* (p-value)	**Trails-B** *R* (p-value)
Factor 1 (overall connective use)					
Healthy Control	-0.175 (0.47)	N/A	-0.231 (0.29)	0.105 (0.66)	0.05 (0.98)
FEP:	-0.054 (0.76)	0.163 (0.336)	-0.221 (0.19)	0.022 (0.90)	0.105 (0.55)
Factor 2 (acausal temporal connectives)					
Healthy Control	0.091 (0.14)	N/A	0.098 (0.66)	0.104 (0.67)	-0.201 (0.41)
FEP	0.018 (0.92)	-0.246 (0.15)	0.171 (0.31)	-0.066 (0.97)	-0.170 (0.33)

Table 6: Correlations Between Connectives Use, Cognition and Severity of Symptoms, Controlling for Gender and Handedness

	SOFAS *R* (p-value)	**CGI-Severity** *R* (p-value)	**DSST** *R* (p-value)	**Category Fluency** *R* (p-value)	**Trails-B** *R* (p-value)
Factor 1 (overall connective use)					
Healthy Control	0.071 (0.78)	N/A	-0.445 (0.074)	0.151 (0.56)	0.023 (0.93)
FEP:	0.040 (0.84)	-0.023 (0.91)	-0.022 (0.90)	0.067 (0.78)	-0.163 (0.40)
Factor 2 (acausal temporal connectives)					
Healthy Control	-0.115 (0.66)	N/A	0.392 (0.25)	0.136 (0.60)	-0.264 (0.31)
FEP	-0.328 (0.08)	**0.441 (0.017)**	-0.206 (0.28)	0.024 (0.90)	0.229 (0.23)

4.0 Discussion

This study compared the use of linguistic connectives to traditional clinically quantified dimensions of formal thought disorder among drug-naïve FEP patients and matched healthy controls. We report 3 major findings. 1. Disorganization in FEP is characterized by excessive use of connectives 2. Connectives use during stimulus-evoked speech is correlated with disorganization, but not impoverishment, indicating the specificity of linguistic connectives to positive rather than negative thought disorder in FEP 3. Aberrant connectives use is specifically related to conceptual disorganization but not to processing speed, verbal fluency or social functioning. Thus, automated speech analysis for connectives captures a distinct facet of loosened associations that is not influenced by the cognitive and functional status of an individual. These findings suggest that aberrant use of connectives (specifically increased temporal but decreased use of causal connectives) contribute to the clinical impression of 'disorganization' and 'thought disorder' captured using instruments such as PANSS and TLI.

The importance of connectives to the clinical impression of thought disorder likely operates through one of two potential mechanisms: 1. Patients fail to elucidate the connections between meaningfully linked concepts or ideas (reduced causal, logical, or

contrastive connectives) or 2. Patients successfully, but erroneously, link ideas over time where no coherent link exists (inappropriate temporal connective use). The resulting of both mechanisms is an increased cognitive load placed on the listener to decipher the intended output of speech (Cain & Nash, 2011). If these efforts at interpreting speech fail, the result is a perception of tangentiality or incoherence, features of positive thought disorder.

We have shown that the traditional measures of disorganization (TLI & PANSS-P2) map reliably on to the specific outputs of automated speech analysis in psychosis. Automated speech analysis avoids the cost, time, and reliability issues that impact hand scoring instruments for assessing FTD, while simultaneously allowing for considerably more comprehensive analyses than classic clinician rated scales. This allows for the examination of multiple linguistic domains of thought disorder with relatively few disruptions to the clinical setting. Further, if Coh-Metrix is able to identify elements of disordered thought reliably during the first episode of psychosis, this approach could be leveraged to compare patient speech to an established corpus of speech to identify subtle longitudinal changes in speech that may be imperceptible to clinicians, allowing insights into how thought disorder evolves throughout the course of illness.

A number of limitations with the current work should be noted. Firstly, speech analyses were gathered from a provided visual stimuli. Stimulus-evoked responses likely involve unique cognitive processes that may not precisely reflect spontaneous language production. Secondly, aberrant connectives use in speech does not necessarily imply internally generated thoughts are not meaningfully connected and this unobservable thought-language gap may differ between patients and healthy controls. Finally, as we collected only a single cross-sectional speech sample during the FEP sample, it is unclear if our findings would be stable over the course of illness following exposure to antipsychotic medications, as positive thought disorder is less observable later stages of illness (Roche, Creed, et al., 2015).

Persistent positive FTD in chronic schizophrenia is linked to aberrant glutamate transmission as well as structural changes in language areas of the brain [13]. To date, it is not clear if the disorganization seen in early stages of schizophrenia is also linked to the same neural pathways. One important challenge in elucidating such neural underpinnings is the difficulty in separating positive and negative FTD during early stages of psychosis (see Palaniyappan et al., 2015). Factor analyses of symptoms in early psychosis often indicate the presence of a single dimension of Bleulerian symptoms embracing both impoverishment and disorganization (McGorry et al., 1998; Tonna et al., n.d.). The approach using linguistic connectives identifies a distinct positive FTD factor in unmedicated early stage of psychosis promises further enquiries to understand the neural underpinnings of early positive FTD.

In conclusion, FTD remains a poorly understood aspect of psychotic illness. The practical difficulty in capturing robust measures of thought disorder is an ongoing barrier to research in this area. Our work adds to the body of literature promoting automated speech analysis, and argues that the use of connectives in evoked speech could objectively identify the specific phenomenon of disorganization (positive FTD), independent of the functional and cognitive status of patients experiencing first episode psychosis. This raises the question of whether the elusive Bleulerian concept of loosening of association can now be reliably tracked across the different stages of psychosis. If this becomes feasible, we may inch closer to understanding the neural basis of a core deficit in schizophrenia.

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Manuscript 2: Assessment of Linguistic Factors during Antipsychotic Naïve first Episode Psychosis with later vocational and social outcomes in the first year of treatment.

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Abstract

Aim: Several disturbances in speech production have been identified in first episode psychosis, however it is unclear if these disturbances are indicative of poor community and vocational functioning that is a defining feature of established schizophrenia. We analyzed speech variables previously found to be aberrant during the first episode using automated speech analysis in an untreated sample of patients, and followed them up longitudinally to determine their vocational status (in or not in employment education or training - EET vs. NEET) by 6-12 months of treatment.

Methods: Three one-minute speech samples from 39 treatment-naïve, actively psychotic FEPs were analyzed using COH-METRIX and Linguistic Inquiry Word Count (LIWC) software programs. From these analyses, five metrics that were found to be aberrant among patients or associated with worsened clinical severity (connectives use, acausal connectives use, pronoun use, analytic thinking, and total words uttered) were chosen. We used a prototypical constraint-based algorithm (PC) to identify dependencies in our variable set. This set comprised of vocational status (NEET, follow up social and occupational functioning [SOFAS] score) and speech variables (total words spoken during a picture description task, analytic thinking score, the use of any connectives, rate of use of connectives without causal links, and pronoun use). We also included PANSS at the time of presentation, parental socioeconomic status and processing speed as covariate to control for disease severity or latent variables that may hold more explanatory power on functioning than speech.

Results: The graphical probabilistic model revealed that only the total number of words spoken showed a direct association with NEET and an indirect association with SOFAS, with a second set of dependencies emerging among the remaining linguistic variables (analytic thinking, pronoun use, acausal connectives & temporal connectives). The primary (speech-only) model outperformed models including parental socioeconomic status, processing speed or both as latent variables.

Conclusions: The total number of words spoken at baseline was the only variable that showed causal dependencies with the primary outcome measures (social and vocational functioning at follow up). This suggests impoverished speech, even at subclinical levels, may carry long-term prognostic value and warrant clinical consideration when treating first-episode psychosis.

1.0 Introduction

Schizophrenia is an illness of disordered thought, with symptoms often reflected in disturbances in language and communication(Kuperberg, 2010). While an impairment of verbal communication is one of several diagnostic features of schizophrenia, with a strong posited genetic component (DeLisi, 2001), not all patients with schizophrenia exhibit clinically identifiable disordered speech. Speech disturbances, referred to as formal thought disorders (FTD), can be classified as positive or negative FTD. Positive FTD includes phenomenon such as derailment, tangentiality, or in more severe cases, neologisms or even complete incoherence (schizophasia). Alternatively, negative FTD captures the characteristic poverty of speech that many patients experience (Kuperberg, 2010). While several scales have been developed with the goal of identifying these elements of speech, such as the scale for thought language and communication (TLC) (Andreasen, 1986) or the Thought Language Index (TLI) (Liddle et al., 2002), many of the speech disturbances in psychosis are too subtle to be captured by clinicians during a cross-sectional clinical interaction (Palaniyappan, 2022).

Recent work has focused on identifying subtler forms of speech variation in naturalistic speech among schizophrenia samples, a goal that has been aided by the proliferation of automated linguistic analysis tools. The utilization of these automated speech analysis software programs allows complex analysis of speech without the burdens (and expense) of manual scoring. Automated linguistic analyses have allowed researchers to identify disturbances in multiple levels of speech in schizophrenia, from phonological, morphological, syntactic, and pragmatic levels(Murphy & Benítez-Burraco, 2016), and have been utilized in predicting psychosis onset in at risk populations (Bedi et al., 2015).

While it is intuitive that social and vocational outcomes may relate to one's verbal abilities, as the ability to interact in a socially desirable way with customers and potential employers is conditioned upon basic verbal skills, the body of research demonstrating this link in schizophrenia have several limitations that preclude the use

of linguistic features in functional prognostication. Firstly, much of this work has been based on language impairments in experimental, rather than naturalistic, paradigms where the semantic space is defined by the researcher (Alonso-Sánchez et al., 2022) [e.g. using verbal fluency tests (Addington & Addington, 2000; Rempfer et al., 2003)]. Secondly, even studies in which unconstrained speech is assessed, objective aspects of conversations are not considered; instead, the clinically judged construct of thought disorder is employed. While these studies have observed shared variance between functional outcomes and negative FTD (specifically poverty of speech and content) (Bowie & Harvey, 2008; Wilcox et al., 2012), unexpected observations also exist in this regard (Roche et al., 2016), likely due to the difficulties surrounding the clinical assessment of formal thought disorder. Thirdly, most studies to date make cross-sectional correlations between functioning and verbal assessments; there is a notable lack of longitudinal data to clarify whether the verbal deficits temporally precede (and thus lie on the causal pathway of) poor functioning seen in schizophrenia. Furthermore, functional outcomes in many prior studies have been conflated with severity of psychopathology when using tools such as Global Assessment of Functioning (Roche et al., 2016), and a lack of satisfactory definition of social dysfunction (Marggraf et al., 2020; Oeztuerk et al., 2022). In addition, exposure to antipsychotics over a long period of time alters the nature of speech and our ability to assess FTD (de Boer et al., 2020), thus necessitating the study of minimally treated or drug naive subjects. Demonstrating this relationship will be of critical value in improving clinical decisions during early intervention based on long-term prognostic outlook, which at present is challenging to assess. To address this crucial gap, we sought to identify linguistic features of psychotic speech in an untreated FEP sample using a computational linguistic approach called parts-of-speech tagging implemented through Cohmetrix (Graesser et al., 2004), and the Linguistic Inquiry Word Count (LIWC) (Pennebaker et al., 2015).

In a prior cross-sectional analysis on this sample of untreated subjects, Mackinley et al. (2021) used Coh-Metrix automated speech analysis software (Graesser

et al., 2004) to compare FEP patients and healthy controls on a number of variables at the word, sentence, and higher order level. In this study, patients showed reduced speech production (number of words) and higher pronoun use compared to their healthy control counterparts but did not differ in a variety of other higher-order linguistic metrics (narrativity, formality, referential cohesion, or deep cohesion). When connective use was analyzed using data driven principal factor analysis, two factors, one with a positive loading on "all connective types" (causal, logical, temporal, contrastive, and additive) and the second "acausal temporal connective factor" reflecting reduced use of causal and contrastive connectives, but higher use of temporal linkages and additive connections emerged. While patients and healthy controls employed these connective factors in a comparable manner during the picture description tasks, patients with higher connectives use had higher scores on clinically rated conceptual disorganization (Mackinley et al., 2021). This suggests that aberrant linguistic connective use may contribute to the clinician's detection of disorganized thought.

In an overlapping cross-sectional sample, we (Silva et al., 2021) analyzed the picture description speech samples using the Linguistic Inquiry Word Count (LIWC) software package (Pennebaker et al., 2015) to determine the relative proportion of content words and function words. From this parts-of-speech tagging, we determined Pennenbaker's Analytic Thinking scores (higher scores suggesting a well-formed hierarchical thinking style suitable for academic expressions, and lower scores suggesting a narrative style which is more intuitive and episodic in nature) (Pennebaker et al., 2014). A higher analytic score (more categorical thinking style), is linked with academic success due to this linguistic style's use in academic and professional settings (Pennebaker et al., 2014). We observed that compared to HC, patients showed reduced analytic thinking in their speech. Further, among FEPs, reductions in analytic thinking were associated with higher clinical metrics of disorganization (Silva et al., 2021). This suggests that less structured, less content-based speech may contribute to the clinician's detection of disorganized thought. Thus, it is possible that among FEP

patients, analytic thinking styles are associated with later academic and occupational success; however, little evidence to assess this question has been gathered.

With longitudinal functional outcome data from this cohort, we aim to ascertain the role of connectives, analytic thinking index, total number of words, and frequency of pronouns on vocational status and social and occupational functioning ascertained after 6 months of treatment in an early intervention setting. Given the prior observations indicating 'negative FTD' relates more strongly to functional outcomes than 'positive FTD', we expected a reduction in total number of words used during a picture description will be predictive of later functional outcomes. To this end we applied a Bayesian approach called prototypical constraint-based algorithm (PC) that uses directed acyclic graphs (Spirtes et al., 2001; Tsagris, 2018) to identify dependencies among the baseline linguistic variables and vocational status or social functioning after 6-12 months of treatment in an early intervention program for psychoses. We assessed the contribution of other explanatory variables such as parental socioeconomic status and speed of cognitive processing using probabilistic models of functional outcome. We quantified social functioning using the widely used Social and Occupational Functioning Assessment Scale (SOFAS) as a continuous measure, and a macroeconomic indicator of productivity in young adults reflecting participation in active Employment Education or Training (EET vs. not-EET or NEET) status as a categorical measure, as employed in our previous brain imaging study (MacKinley et al., 2022).

2.0 Method

2.1 Participants:

Data were collected from 39 treatment naïve FEP patients recruited from the Prevention and Early Intervention Program for Psychoses in London, Ontario, Canada,as reported in a previously published manuscript (MacKinley et al., 2021). All participants were in the acute phase of the illness, with fewer than two weeks of antipsychotic exposure lifetime. The mean lifetime defined daily dose was M=2.31, SD=3.68, with n=14 being completely drug-naive(36%). Over the subsequent year, patients were longitudinally followed with assessments of social and occupational functioning

completed when clinically stable between 6 and 12 months following the initial assessment. All participants used in the present analysis were native English speakers.

2.2 Clinical and Linguistic Assessment Procedure

The local Research Ethics Board (Western University) approved all study procedures, and all patients provided informed consent before participating. All patients were enrolled in a first-episode psychosis program over the next 12 months, and we ascertained their social and vocational status between 6 to 12 months after entering treatment. Due to the need for multiple information sources, not all patient follow-ups were assessed at precisely the same time point after the onset of illness.

Licensed psychiatrists conducted all clinical interviews and rating scales to determine illness severity, and rule out exclusionary diagnoses (substance abuse, neurologic disorders). Graduate-level research assistants completed cognitive assessments and the TLI interview and rating. During the TLI procedure, three one-minute speech samples were induced in response to photographs from the Thematic Apperception Task (Murray, 1943) and were blinded to participant status consistent with the procedure described by Sommer et al. (Sommer et al., 2010).

The Positive and Negative Syndrome Scale – 8 Item (PANSS-8), which is highly correlated with the full 30-items PANSS (Lin et al., 2018), was utilized to measure the severity of clinical symptoms. Functional assessments were based on multiple sources of information (patient interviews, information from the psychiatrist providing care, case managers, and when required information from family members). Measures of social and occupational functioning were assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) (Rybarczyk, 2011) at baseline and follow-up. The SOFAS is a single-item measure of functioning scored between 1 (indicating a persistent inability to maintain minimum even basic function) and 100 (superior functioning in a wide range of activities). In our study, SOFAS scores considered current functioning (rather than the highest level of functioning over the past year). Vocational assessments were conducted using a binary NEET status (not in employment education or training).

Patients were deemed to be NEET (vocationally inactive) if they were unemployed and not in any form of schooling/education for more than half of the time since the onset of treatment for psychosis. Individualsclassified as EET were engaged in work or school for more than half of the duration of treatment (vocationally active). This definition considers a longer period than the 1-week period used by the Organization for Economic Co-Operation and Development (OECD) (*Youth and the Labour Market - Youth Not in Employment, Education or Training (NEET) - OECD Data*, n.d.), but is consistent with its use in early intervention services for psychosis (Iyer et al., 2018; Maraj et al., 2019). When inconsistencies between patient and care provider accounts were noted, a consensus was reached among the members of the research team.

2.3 Instruments:

2.3.1 Linguistic Inquiry Word Count

Linguistic Inquiry Word Count Software (LIWC 2015 Edition) uses a computational-lexical approach, which provides summaries of psycholinguistic dimensions (i.e., analytic thinking score) and pre-defined content word themes (e.g., negative emotion words) derived from psychometric rates. In the two-step process, LIWC analyzes the current target word contained in texts comparing and matching every single word against master dictionaries using its own language corpora composed of "almost 6,400 words, word steams, and selected emoticons from a sample of ~181,000 text files". Secondly, a standard LIWC computes the percentage of co-occurrences. LIWC has recently gained attention in several research areas establishing the relationship between linguistic-thinking styles and both personality traits, and mental health conditions.

2.3.2 Coh-Metrix 3.0

Coh-Metrix (McNamara et al., 2014) is a web-based automated speech analysis software that computes basic and higher-level linguistic variables from written and spoken speech samples. The software automatically computes several lower order (e.g., word counts, frequency of pronoun use, use of connectives) and higher order (e.g.,

narrativity, cohesion, text formality) linguistic variables (Graesser et al., 2004). While initially implemented for the analysis of larger text segments, the software has been applied in the analysis of brief language samples in clinical populations previously (Gupta et al., 2018). Though there are no requirements for minimum number of words for applying Coh-Metrix to study texts, analyses of readability and cohesion have been generally reported for written materials with 100 words or above (Latiefi & Gierl, 2020; Maamuujav et al., 2021). The incidence scores are based on frequency of occurrence of different parts of speech (e.g. pronouns, connectives etc.) in the units of numbers per 1000 words. We based our project on the work in Willits et al (2018) with the focus of Coh-Metrix output on the frequency of connectives use as described in MacKinley et al. (2021).

2.4 Statistical (Bayesian) Analyses

For descriptive analyses, we used the JASP software (JASP version 0.16.3, 2022) to report Bayes factors against the null model (BF_{10}). Briefly, if $BF_{10} < 2$, we accepted the null hypothesis, whereas if BF > 2 provides support for the alternative hypothesis. To answer the research question, we used a prototypical constraint-based algorithm (PC) (Spirtes et al., 2001; Tsagris, 2018) within the context of a Bayes network (a probabilistic graphical model) to identify dependencies in a set of variables. This set comprised NEET (6-12 months), SOFAS score (6-12 months), total words spoken, analytic thinking score, all connectives score, acausal connectives score, and pronoun use (all at baseline). We also included PANSS-8 total score as a nuisance variable to control disease severity at the time of linguistic data collection. The algorithm yielded a Bayes network upon which we applied an expectation maximization algorithm (Wu, 1983) to perform maximum likelihood estimation of parameters (parameters learning). Finally, we made a series of inferences (conditional probability queries in terms of causal and evidential reasoning) aiming to explain the relationships between our variables of interests (total words spoken, analytic thinking, connectives use, and pronoun use).

3.0 Results

When baseline characteristics of patients who went on to be vocationally active (EET) were compared to patients that went on to be vocationally inactive (NEET), no evidence for group differences were observed in regards to medication exposure, duration of untreated psychosis, age, sex, parental SES, or the use of cannabis alcohol or tobacco, or symptom severity at baseline. As expected given the overlapping nature of the SOFAS scale and vocational activity, very strong support was found that NEET patients differed from EET patients in measures of follow up SOFAS score (BF_{10} = 55.50; EET mean = 65.00, SD = 10.54; NEET mean = 46.47, SD =18.28). There was marginal evidence that patients who speak more words at baseline would go on to be vocationally active (BF_{10} = 2.42; EET mean = 123.22, SD = 38.50; NEET mean = 104.40, SD = 24.19). Finally, we report moderate evidence that those that perform better on the Digit Symbol Substitution Test (DSST), a measure of processing speed, would go on to be vocationally active (BF_{10} = 3.32; EET mean = 57.87, SD = 14.72; NEET mean = 46.92, SD = 12.14). No differences were found on other linguistic variables of interest (Table 1).

TABLE 1. Demographic and Linguistic Characteristics of Sample

Variable	All Patients n=39	Patients Not in Education Employment or Training (NEET) n=18	Patients Engaged in Employment education or Training (EET) n=21	BF_{10}	95% Highest Density Interval
Demographic and Clinical variables					
Sex (Male/Female)	32/7	16/2	16/5	1.00	-1.72, 0.77
Age [M (sd)]	22.53 (4.76)	23.58 (6.02)	21.58 (3.15)	0.60	-0.955, 0.25
NS-SEC[M (sd)]	3.76 (1.20)	4.28 (1.07)	3.25 (1.02)	1.11	-1.14, 0.12
DUP in Months [M (sd)]	8.82 (11.86)	7.57 (8.21)	10.00 (14.67)	0.32	-0.58, 0.54
Defined Daily Doses[M (sd)]	2.31 (3.68)	2.39 (3.65)	2.27 (3.80)	0.36	-0.53, 0.59
Non-antipsychotic Meds (Y/N)	9/30	3/15	6/15	1.16	-1.59, 0.77
Tobacco Smoker (Yes/No)	11/25	7/11	5/16	1.00	-1.61, 0.80
CAST score [M (sd)]	13.5 (6.59)	15.13 (6.65)	11.87 (6.34)	0.35	-1.07, 0.25
AUDIT-C [M (sd)]	2.64 (3.12)	2.07 (2.22)	3.31 (3.90)	0.53	-0.34, 0.99
PANSS-8 Total [M (sd)]	26.46 (7.21)	27.44 (6.65)	25.62 (7.71)	0.40	-0.79, 0.36
PANSS-8 Positive [M (sd)]	13.08 (2.98)	13.44 (2.72)	12.74 (3.24)	0.39	-0.77, 0.38
PANSS-8 Negative [M (sd)]	7.76 (4.46)	8.33(4.52)	7.21 (4.44)	0.40	-0.79,0.37
CGI-Severity [M (sd)]	5.34 (1.09)	5.44 (0.86)	5.26 (1.28)	0.35	-0.71, 0.44
SOFAS Baseline [M (sd)]	38.31 (12.50)	34.40 (8.35)	41.10 (14.32)	1.27	-0.10, 1.16
SOFAS 6-12 Month [M (sd)]	55.74 (17.46)	46.47 (18.28)	65.00 (10.54)	**55.50**	0.39, 1.81
DSST [M (sd)]	52.40 (14.42)	46.92 (12.14)	57.87 (14.72)	**3.32**	0.06, 1.34
Avg Months to NEET assessment [M (sd)]	7.95 (2.89)	8.17 (3.38)	7.75 (2.41)	0.34	-0.69, 0.45
Linguistic Variables of Interest					
Total Words Spoken	115.08 (34.03)	104.40 (24.19)	123.22 (38.5)	**2.42**	0.01, 1.29
Analytic Thinking Score	55.27 (21.65)	57.94 (22.24)	53.25 (21.52)	0.35	-0.69, 0.45
All Connectives	0.095 (1.16)	-0.08 (1.61)	0.22 (1.17)	0.33	-0.50, 0.64
Acausal Connectives	0.128 (0.99)	0.08 (0.79)	0.17 (1.14)	0.38	-0.39, 0.76
Pronoun use/ thousand words	107.17 (24.11)	105.86 (19.93)	108.17 (27.83)	0.33	-0.50, 0.64

Note: M, Mean; SD, standard deviation; DUP, Duration of Untreated Psychosis; CAST, cannabis abuse screening test; AUDIT-C, Alcohol use disorders identification test; PANSS, Positive and Negative Syndrome Scale – 8 Item Scale; CGI-Severity, Clinical Global Impression – Severity; SOFAS, Social and Occupational Functioning Assessment Score; BF, Bayes Factor.

4.2 Bayesian analyses

Whereas a causal network was established among the linguistic variables of interest (the two connectives factors, pronoun use, and analytic thinking style), the

graphical probabilistic model revealed that only the total number of words showed a direct association with NEET and an indirect association with SOFAS (Figure 1)**.** The expectation maximization algorithm converged (Log likelihood = -712.39). We further investigated whether this model better explained the data than a null model. To this end, we applied the expectation maximization algorithm to a model without the direct and indirect relationships identified above. Bayesian information criterion numbers (BIC) confirmed that the converged null model (Log likelihood = -723.28, BIC = 1512) underperformed the model estimated via the PC algorithm (BIC = 1504).

The number of words one employs during a descriptive task may vary based on factors such as social environment during early development (specifically parental SES)(Palaniyappan, 2021) and cognitive capacity indexed by processing speed (Brébion et al., 2018) both of which may also affect the later vocational outcomes. To address this, we undertook a specific model comparison approach with self-reported parental socioeconomic status and digit symbol substitution score (a proxy for processing speed) added into our model with 4 contingencies and compared using the BIC values. The first model (M1) comprised total words conditioned upon both the DSST and SES. In the second model (M2), total words were conditional on only DSST. In the third model, total words were conditional on SES. Finally, in model 4 (M4) neither DSST nor SES influence the total number of words (Figure 2). The model comparison procedure yielded M4 as the best model (BIC_{M1} = 1777, BIC_{M2} = 1770, BIC_{M3} = 1774, **BIC_{M4} = 1767).** This indicates that despite the putative role of processing speed and SES in vocational outcomes among patients, the role of reduced speech production is best considered as an independent predictor.

Directionalities in the graph (Figure 1) indicate that, the NEET score is explained by both the total number of words and the SOFAS score. Interestingly, once the NEET score is known the number of words and SOFAS scores are independent of each other. In consequence, the directionalities in the graph allow us to estimate the probability distribution of NEET given an observed SOFAS score and the total number of words

(conjointly). For example, for a patient that produces 48 words on average, the probability of NEET =1 is 79.8 %. On the other extreme, if the patient produced 211 words, they would have NEET = 0 with 99% chance. Finally, in the midpoint of the observed distribution of word count, a patient following in the 50 percentile (median = 113), a NEET =1 would have 64.8% chance. The directionalities of the Bayes network also allow us to estimate the probability of SOFAS at follow up given the total number of words observed at the time of first assessment. Specifically, with 48 words spoken we could estimate a follow up SOFAS with a distribution of (m = 55, sd = 10.9). With a median number of words spoken (113 words) we would expect a similar score (m = 56, sd =11). However, improvements in follow up SOFAS scores can be seen in individuals with high speech production (211 words spoken) could expect an elevated SOFAS score (m=65, sd =10) relative to their peers.

Finally, In a subgroup analysis of patients (n=22) who also had completed the Category Fluency test (animals), our data suggest that baseline category fluency (number of correct items) did not differ notably between EET and NEET patients (BF_{10} = 1.163; EET mean = 19.69, SD = 4.36; NEET mean = 16.33, SD = 4.27). However, category fluency score did correlate with the total number of words spoken (r=0.56, BF_{10} = 7.52). This suggests that word generation during naturalistic speech has a specific prognostic value in predicting social and vocational outcomes in first episode psychosis, while being in alignment with estimated fluency from a constrained cognitive test context.

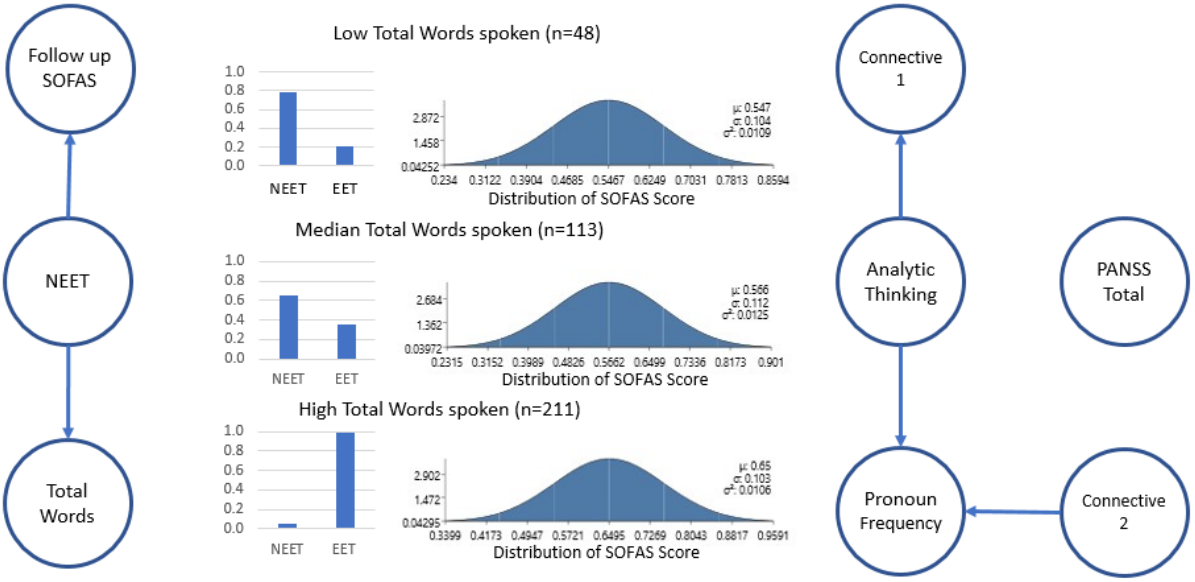

Figure 1. Bayes network that resulted from the application of the PC algorithm. Only the total number of words directly relates to NEET and indirectly relates to SOFAS. Furthermore, whereas the PANSS score was independent of all the other variables, the remaining predictors (Analytic thinking, Total connectives, acausal connectives, pronoun use) show conditional dependencies among themselves. Binarized NEET/EET Probability and distribution of predicted SOFAS scores are shown based on Low, Median and High number of words spoken. **SOFAS, Social and Occupational Functioning Assessment Scale; Connectives 1, All connectives use; Connectives 2, Acausal Connectives use; PANSS, Positive and Negative Syndrome Scale 8-Item Version; NEET, Not in Employment, Education or Training); EET, Engaged in employment education, or training.*

4.0 Discussion

This study sheds light on how the way we speak when experiencing acute psychosis may provide insight into our occupational/functional outcomes in the first year of early intervention. We report three major findings: (1) Speech production (total number of words spoken) during a 3-minute descriptive task at the time of first presentation with psychosis, explained significant variance in NEET status after 6-12 months of treatment. (2) Measures of parental socioeconomic status and processing speed did not explain this relationship, and (3) the linguistic features included in our analysis (connectives, pronoun use, and analytic thinking scores) formed their own causal network (i.e. inter-related) but were not related to vocational or social outcomes.

Thus, the ability to find a productive vocational status following the experience of psychosis relates to the number of words an individual manages to deploy during a discursive task of describing a picture to another person, even controlling for parental social background, one's personal speed of processing information and linguistic style of expression, and the severity of core symptoms (PANSS-8 total) . These findings provide an objectively detectable and intuitive speech metric that requires no clinical judgment as a prognostic marker of functional outcome. This takes rater-related factors out of consideration when considering prognosis, potentially complementing clinical decisions that may require an assessment of longer-term outcomes (e.g., duration of case management, employment and placement support).

Individuals with robust speech production had a 'protective' effect with respect to functional deterioration. While those with median speech production (113words) still had an above chance level of poor vocational outcomes (65% NEET), the effects of high speech production on vocational outcomes were far more positive; our modelling would predict that patients with speech production on the upper tail of the distribution (211 words) to have a 99% chance of being vocationally active. There are several hypotheses that could explain this association between the abundance of speech production with good vocational outcome. First, patients with high speech production are far less likely to have broader dysfunction in other negative domains. Poverty of speech has been consistently associated with affective flattening (Foussias et al., 2014) and reduced symptom remission in negative domains (Yalincetin et al., 2017), as well as likely a marker for underlying cognitive deficits (Fervaha et al., 2016). While this contributes a strong case for why lower speech production is likely to impair vocational prospects, it fails to make an affirmative case for good outcomes among those producing higher speech. The benefit of speech production to good vocational prospects is therefore likely related patients with more speech production being rated as more socially adept and desirable by peers and employers. In both healthy control and patient samples, social skills are highly correlated with gaining and retaining competitive

employment (Tsang et al., 2000). Among patient population, the social threshold for employment may in fact be more pronounced as patients are more likely to be involved in service sector and routine/non-technical occupations where customer or client relations are of primary importance. This potential explanation warrants investigation. While 'verbosity' may not be readily modifiable among clinical samples, social skills training as part of employment support in first episode psychosis clinics may yield more robust results among patients who are on the cusp of functioning.

Antipsychotic medications may reduce articulation speed and reduce sentence length in patients with psychosis; in our sample, we are not able to assess the effect of 6-12 months of treatment on speech as we lacked sufficient longitudinal data. In our sample, patients with higher speech production tend to do better over time, despite no systematic differences in antipsychotic exposure at baseline. This suggests that patients with superior verbal output at baseline may maintain adequate speech production despite any adverse treatment effects, thus achieving superior vocational outcomes.

Our study has several strengths including the assessment of minimally treated FEP subjects, the use of objective linguistic analysis and a careful control of confounders. Nevertheless, several limitations warrant consideration. We did not have sufficient longitudinal speech data to assess the stability of 'verbosity' over time in this sample. We also lacked information on many mediators of educational/vocational success e.g., parental support, workplace mentorship and motivational factors. As a result, our results pertaining to the value of word counts in forecasting later functioning should be considered complementary information rather than being the best of all baseline predictors of functioning. Such a conservative interpretation also fits with effect-size noted in the primary Bayesian analysis (BF>2 relating number of words to NEET status). Nevertheless, the use of acyclic graph models on longitudinal data allows us to draw causal inferences (Pearl, 2014) from observational design.

To conclude, we call for including the rate of word production during routine clinical assessments of first episode psychosis. Our results suggests that this may be an inexpensive approach that carries prognostic value relevant for functional recovery.

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Chapter 3: Cortical Anatomy and its association with clinical severity and vocational outcomes in psychosis

Preamble

While our previous chapter assessed linguistic production (manifest/behavioral scale) as a prognostic indicator of later functioning, in chapter 3, we are assessing how disruptions in brain structure (meso-scale changes) relate to baseline clinical severity and later functional outcomes. Specifically, we assessed two features of gross cortical anatomy that have shown consistent associations with schizophrenia/psychosis pathophysiology: cortical gyrification (see review: Matsuda & Ohi, 2018) and cortical thickness (Zhao et al., 2022).

Gyrification, the process by which the lissencephalic brain takes on its characteristic folded morphometry, begins at roughly 10 weeks gestation reaching its peak within the first 1-2 years of life, and is therefore considered to be a biomarker of early neurodevelopmental insult (Sasabayashi et al., 2021). While much of the early work on gyrification within the schizophrenia literature suggested that reduced gyrification may be a marker of neurodevelopmental anomaly in psychosis, these findings were largely reported in samples with a higher chronicity of illness. As first episode data has accumulated, more evidence has suggested that increased cortical gyrification is more are more commonly reported in early illness suggesting that hypergyrification is infact the biomarker for illness susceptibility, and that gyrification may interact with chronicity of illness (Sasabayashi et al., 2021).

Alternatively, cortical thickness is an established marker of neurodegeneration associated with psychosis pathophysiology. While clinical high-risk and first episode patients typically show few differences in measures of cortical thickness when compared to healthy controls, among more established schizophrenia samples wide spread reductions in cortical thickness are reported and are associated with worse clinical presentation and community functioning (Zhao et al., 2022). Again indicating that cortical morphometry likely interacts with illness chronicity/ exposure to antipsychotic medications.

Given the considerable variation in cortical architecture based on chronicity of illness and exposure to antipsychotic medication, analysis of anatomical predictors of clinical severity and vocational outcome at the antipsychotic naïve first episode state are warranted. In the appended manuscript, we analyzed baseline cortical thickness and gyrification and assessed associations with baseline clinical severity and later vocational functioning. To our knowledge, this is the first study to tie baseline cortical anatomical features with vocational response following treatment.

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Manuscript: Association between Aberrant Gyrification, Symptom Severity and Social and Vocational Functioning in Drug-Naive First Episode Psychosis

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Abstract

Background: Schizophrenia is a disorder of cerebral connectivity associated with disturbances of cortical development. In patients with established illness, widespread defects in gyrification alongside cortical thinning are seen, yet the status of gyrification among first episode samples and the prognostic value of gyrification on later functioning has been largely unknown. As antipsychotics are associated with cortical thinning, which has secondary effects on cortical folding, we investigated the anatomical distribution of gyrification in antipsychotic naïve first episode patients, and report associations with baseline clinical severity and later functioning.

Methods: We performed automated surface-based morphometric assessment of gyrification on 3-dimensionally reconstructed cortical surfaces across multiple vertices that cover the entire cortex. We recruited a sample of 65 antipsychotic naïve first episode psychosis patients and 33 healthy controls group matched for age, sex, and parental socio-economic status. After comparing patients to controls in a cortex wide analysis, we assessed associations between patient gyrification patterns and baseline clinical characteristics from the Positive and Negative Syndrome Scale (8-Item version). Finally, we assessed associations between gyrification at baseline with functional outcomes assessed 6-12 months after the initial scan. Assessment of functional outcomes included The Social and Occupational Functioning Assessment Scale (SOFAS) as well as assessment of vocational activity defined using "Not engaged in employment education or training (NEET)" criteria.

Results: After adjustments for intracranial volume and gender, patients showed increased gyrification in the right precentral gyrus (Cluster inclusion at $p = 0.005$). Among patients, more severe positive and negative symptoms were associated with increased bilateral fronto-temporal gyrification (Cluster inclusion at $p = 0.005$). Only negative symptoms were associated with changes in cortical thickness, with more severe negative symptoms being associated with increased cortical thickness in the left

temporal pole and middle temporal gyrus. Finally, higher gyrification in parietal regions of the right hemisphere at baseline was associated with vocational inactivity following 6-12 months of treatment. After adjusting for individual differences in baseline functioning, higher gyrification trended toward association with lower follow-up SOFAS scores superior parietal regions in the right hemisphere, however, this association only survived with cluster inclusion set at $p = 0.05$.

Conclusion: Our findings add to an emerging body of evidence suggesting increased gyrification may be a feature of early psychotic illness. Further, for the first time to our knowledge, we show associations between increased gyrification with later functional deficits. These findings warrant further longitudinal investigations to establish their prognostic value in psychosis.

1.0 Introduction

Schizophrenia is an illness of perceptual and thought disturbances characterized by disruptions in cortical connectivity and structure that are largely attributable to disordered development (R. M. Murray et al., 2017; Rapoport et al., 2012). The cortical architecture of the adult brain is largely the result of a substantial expansion of surface area during development which, in conjunction with restraints of intracranial volume, necessitates considerable folding or gyrification (White et al., 2010). The axonal tension theory describes gyrification as the result of strong axonal connections between cortical regions maintaining proximity between these regions, resulting in the formation of gyri. Whereas relatively less connected regions are able to drift apart more readily during the brain's expansion which results in the formation of sulci (Van Essen, 1997). Because this process typically reaches its peak at roughly 66-80 days post gestation (Zilles et al., 2013) and is sensitive to developmental aberrations (Engelhardt et al., 2015; Hendrickson et al., 2017; Wu et al., 2020), it is postulated that gyrification may represent a surrogate marker for disruptions in neuronal connectivity during early development.

A number of studies have assessed gyrification abnormalities in relation to schizophrenia over the previous 2 decades. However, much of this literature has been focused on established schizophrenia, which has typically show decreased gyrification (hypogrification) relative to healthy controls (Bonnici et al., 2007; Kulynych et al., 1997; Palaniyappan & Liddle, 2012; Sallet et al., 2003; Vogeley et al., 2000). While some contradictory evidence did suggested that patients may experience an increase in regional gyrification (Vogeley et al., 2000), overall, chronic schizophrenia appears to be related to reduced gyrification and cortical thickness among patients (See review by White & Hilgetag, 2011). This relationship, however, appears to be inverted among first episode patients (FEPs) or early schizophrenia (<2 years). In a study by Sasabayashi, patients with first episode or recently diagnosed schizophrenia showed cortex wide increases in gyrification (Sasabayashi et al., 2017). This work which used the LGI

approach is consistent with earlier findings from the first episode literature, suggesting a link between FEP and hypergyrification (Harris et al., 2004; C. C. Schultz et al., 2010, 2013; Tepest et al., 2013). However, these findings are tempered by competing literature suggesting no difference in gyrification exists between early psychosis patients and healthy controls. In one study of adolescent schizophrenia patients, hypergyrification was noted at baseline, but the gyrification among patients appeared to reduce with chronicity of illness (Palaniyappan et al., 2013). Overall, the literature suggests that disease-phase may have a significant impact on observed gyrification in patients versus controls, whereby hypergyrification may be a developmental marker of illness susceptibility, with loss of brain tissue and commensurate loss of gyrification due to degenerative/neurotoxicity of psychotic illness being present in late illness. This notion of illness-duration dependent gyrification was recently modelled by Sasabayashi (2021).

Identifying patterns of gyrification in early, particularly untreated, psychosis is key to understanding the dynamic nature of cortical architecture over the course of schizophrenia. If widespread abnormalities in gyrification are present, this may reflect a deviation in underlying neurodevelopmental processes. Based on the theory of neurodevelopment, a theoretical dose response relationship between the degree of anatomical deformity and disease severity should be identifiable. The putative model of LGI longitudinal changes in Sasabayashi (Sasabayashi et al., 2021) suggests that patients with more significant clinical symptomology should theoretically be showing hypergyria in early illness, with reductions in gyrification being present among more clinically impaired patients in chronic samples.

While limited, researchers have attempted to correlate patterns of gyrification with specific clinical symptoms in prior studies. Among FEP samples, samples increasing severity of positive symptom severity was associated with increased gyrification in the right temporal pole, right insula, and right parahippocampal gyrus (Sasabayashi et al., 2017) suggesting a link between increased gyrification and the presence of positive

symptoms. However, among established schizophrenia samples results were mixed, symptoms on paranoid dimensions (suspiciousness, somatic concern, and grandiosity) were associated with higher gyrification, while negative symptoms were associated with reduced gyrification (Sallet et al., 2003). However, these early findings should be interpreted with caution, as much this work requires replication. Indeed, more recent work in schizophrenia and schizotypal patients have shown no clear relationship between clinical symptom severity and patterns of gyrification (Sasabayashi et al., 2020). However, the failure to assess the relationship between clinical severity and gyrification in an anti-psychotic naïve sample is a substantial limitation of the extant literature. Medication substantially reduces the symptom variance compared to untreated samples; biasing previous work toward the null hypothesis and likely contributing to divergent findings.

To add to the literature investigating gyrification & cortical thickness in first episode schizophrenia and its associations with clinical variables, we undertook an automated assessment of gyrification in multiple vertices across 3-dimensionally reconstructed cerebral surfaces in a sample of 98 individuals, 65 antipsychotic naïve first episode psychosis patients, and 33 healthy controls using a 7T MRI scanner. By assessing patients without exposure to significant antipsychotic use (less than 2 weeks) we are able to assess the impacts of gyrification on the development of schizophrenia without confounds of medication or chronicity of illness. Further, in the present study we analyzed the entire cortical surface using a vertex-based approach. This allowed us to detect defects in regions across the cortex, rather than limiting our analysis to specific regions of interest. Finally, to determine if gyrification defects were associated with specific clinical metrics, we conducted a series of general linear models (GLMs) comparing local gyrification indices to symptom severity among patients. Because our study was not confounded by the use of medication adherence nor by a temporal gap between the collections of clinical and scan data, we were able to directly assess how gyrification may influence clinical presentation during the natural progression of

psychotic illness, and how these cortical characteristics at baseline may impact functional response following treatment.

2.0 Methods

2.1 Participants:

Our sample consisted of 65 patients with anti-psychotic naive first episode psychosis and 33 healthy controls. The Western University Research Ethics Board (REB) approved the study, and all participants provided written informed consent. Clinicians from the emergency department and outpatient mental health clinics initially referred the patients for this study. The responsible clinicians confirmed patient capacity to provide informed consent, and written consent was obtained following the presentation of the letter of information approved by the REB. Consensus diagnosis of schizophrenia was made following three months of treatment in accordance with the procedure of Leckman et al.(Leckman et al., 1982) using all available information, including a review of case files and initial clinical interviews. Patients who were diagnosed with a primary affective disorder were removed from our sample prior to analysis. All patients were antipsychotic naive (defined as less than 14 days of lifetime antipsychotic exposure) and in their first episode of psychosis. The mean lifetime antipsychotic exposure equated to 2.3 Defined Daily Doses, using the process defined by Leucht et al. (2016). Our sample had a mean duration of untreated psychosis of 6.4 months. Individuals with neurologic disorders, current substance dependence, major head injuries, or any implants incompatible with MRI were excluded. Patient's initial assessments were conducted on the same day of the scans. Healthy controls were recruited from the local community via advertisements and included 33 individuals (21 men) free of any psychiatric or neurologic disorder, group-matched for age and parental socioeconomic status (measured using National Statistics — Socio Economic Classification) (Rose et al., 2005) to the patient group. Controls had similar exclusion criteria to patients; with the additional exclusion of any current axis 1 or 2 psychiatric condition, or first degree relatives with a psychotic illness.

2.2 Clinical Procedure:

A clinical battery was conducted by either a research psychiatrist or trained psychometrist. The clinical battery was used to assess patient symptom severity and to ensure that control subjects were free from current Axis I disorders and history of either psychotic illness or neurologic disorder. To assess symptoms of psychosis The Positive and Negative Syndrome Scale – 8 Item (PANSS-8) was used (C.-H. Lin et al., 2018a). The PANSS-8 is an abbreviated version of the 30 Item PANSS clinical assessment of symptomology in schizophrenia and psychosis with acceptable internal consistency and highly correlated with the full PANSS (C.-H. Lin et al., 2018a). Items are scored on a 1 (absent) to 7 (extreme) Likert type scale. The PANSS-8, in our analysis was considered as a total score (Summed scores of all 8 items), a PANSS-positive subscale (combined scores of items P1-delusions, P2 – Conceptual disorganization, & P3- hallucinations), a PANSS-Negative Subscale (the combined scores of N1- Blunted or flat affect, N4- passive social withdrawl, and N-6 impoverishment of speech) as well as through individual PANSS-8 Items and their association with local gyrification index.

In addition to the PANSS-8 the clinical global impression- severity (CGI-S) item was administered following the PANSS-8. The CGI-S is a single item metric of clinical severity (Busner & Targum, 2007). This item asks the clinician “given your total clinical experience with this clinical population, how mentally ill is the patient at this time?” The item is scaled in a likert-type format from 1(normal/not Ill) to 7 (Among the most severely ill patients). This single item is intended to tap the clinician’s gestalt perception of severity including clinical measures, functioning and distress/social factors. Finally, the Calgary Depression Scale and Young Mania Rating Scale were administered to identify any affective features.

2.3 Image Acquisition and Processing:

Measurements were collected using a Siemens MAGENTOM 7-Tesla head-only MRI scanner (Siemens, Erlangen, Germany) with an in-suite designed head coil (8-channel

transmit, 32-channel receive). The scanning protocol included T1-weighted image acquisition using a 0.75mm isotropic magnetization-prepared two rapid acquisition gradient echo (MP2RAGE) sequence (TR = 6000 ms, TI1 = 800 ms, TI2 = 2700 ms, flip-angle 1 (α1) = 4°, flip-angle 2 (α2) = 5°, FOV = 350 mm × 263 mm × 350 mm, Tacq = 9 min 38 s, iPATPE = 3 and 6/8 partial k-space). Head motion was minimized using cushion pads and through verbal cuing at the beginning of the procedure. A quality check to exclude motion artifacts was carried by researchers independently using predefined criteria. Surface extraction was completed using FreeSurfer version 6.0.0. The preprocessing was performed as described by Dale and colleagues. Cortical thickness is calculated through this automated pipeline as the minimum distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl, 2012). We obtained local gyrification indices (LGIs) using the method of Schaer and colleagues, with images reconstructed through the Freesurfer pipeline (Schaer et al., 2012). This method is a vertex-wise approach which gives a ratio of the inner folded contour to the outer perimeter of the cortex. A pial surface is first obtained before an outer "hull" surface is generated by means of a morphological closing operation, which ensures that the local curvature at all points on the outer hull surface is less than the curvature of a 15-mm radius sphere (a radius chosen to ensure that the hull surface does not dip into the sulci). This hull surface acts as the outer perimeter while the original pial surface provides the inner perimeter. Both inner and outer surfaces are tessellated with numerous vertices. For each vertex on the outer surface, a spherical ROI is created with the vertex as the center and a standard 25-mm radius.

2.4 Analysis

Each vertex-wise LGI measurement of the participants' surface was mapped on a common spherical coordinate system (fsaverage) using a spherical transformation. Maps were analyzed unsmoothed, with intergroup analysis using a general linear model controlling for the effect of sex and intracranial volume to estimate differences in

gyrification between patients and healthy controls each vertex of the right and left hemispheres. For GLM analyses restricted to patients, analyses were run uncorrected for covariates. We used the Query Design Estimate Contrast (QDEC) tool in the Freesurfer 6.0.0 program to generate the contrasts. We then performed Monte Carlo permutation cluster analyses with 10 000 simulations to identify significant clusters with vertex-wise group differences (cluster inclusion threshold $p = 0.005$). To produce a visual display of the group comparison, we used the reconstructed grey–white boundary of the fsaverage image, which allows anatomic landmarks to be illustrated clearly.

3.0 Results

There were no significant differences in age or parental socio-economic status between patients and controls, although healthy controls had a higher proportion of females ($x^2 = 3.79$, p= 0.051), (Table 1), and thus, sex was controlled for in group analyses. As expected, patients showed higher clinical severity.

Table 1: Demographic and Clinical Characteristics of Healthy Controls and Patients

Variable	**Healthy Control n=33**	**Patients n=65**
	Demographic Data	
Gender (Male/Female)	21/12	53/12*
Age [M (sd)]	21.61 (3.37)	22.86 (4.74)
NS-SEC[M (sd)]	3.14 (1.40)	3.34 (1.29)
NEET Status (NEET/EET)	1/32	31/34**
Edinburgh Handedness [M (sd)]	10.72 (2.10)	10.33 (2.16)
	Clinical Data	
DUP Months [M (sd)]	N/A	8.83 (11.86)
Antipsychotic Defined Daily Dose Equivalents	N/A	2.31 (3.68)
SOFAS [M (sd)]	82.03 (4.77)	40.97 (12.33)**
PANSS-8 Total [M (sd)]	8.0 (0.00)	19.40 (9.11)**
PANSS-8 positive [M (sd)]	3.0 (0.00)	12.09 (2.68)**
PANSS-8 Negative [M (sd)]	3.0 (0.00)	7.12 (4.09)**
CGI- Severity	1.00	5.21 (0.93)**

M, Mean; SD, standard deviation; NS-SEC, national statistics socio-economic classification; SOFAS, Social and Occupational Functioning Assessment Score; PANSS-8, Positive and Negative Syndrome Scale – 8 Item Scale; CGI-Severity, Clinical Global Impression – Severity; *Significantly different compared to healthy controls ($p < 0.05$); **Significantly different compared to healthy controls ($p < 0.01$).

3.1 Group Comparison:

When assessing group differences between patients and healthy controls with cluster inclusion set at P<0.01, a modest cluster revealing hypergyrification was identified in the precentral gyrus in patients relative to controls (p<0.0056), after controlling for intracortical volume and gender (Figure 1). In our sample this group difference was lateralized, with this cluster of hypergyrification among patients only surviving correction in the right hemisphere (Table 2).

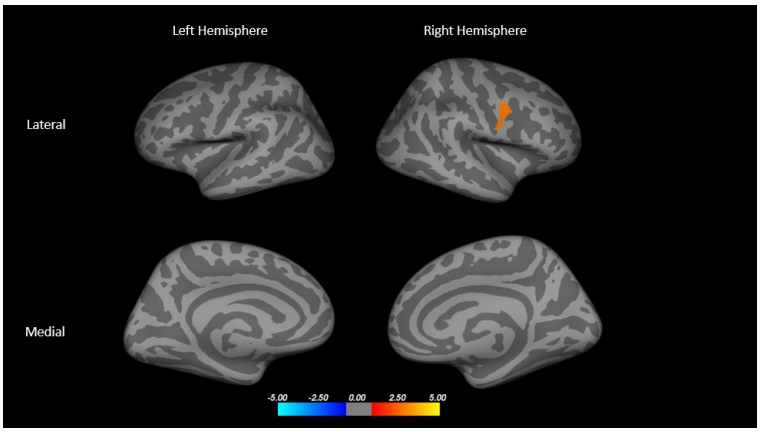

Figure 1: Significant cluster (P<0.001) showing hypergyrification in the right precentral gyrus of first episode psychosis patients vs. healthy controls.

Table 2. Cluster showing group differences in Local Gyrification Index between healthy controls and First episode Psychosis Patients

	GLM Cluster R-Value	Talaraich coordinate of the centroid			Cluster size, mm^2	Cluster- wise probability
		x	*y*	*z*		
Right Precentral Gyrus	2.25	58.1	3.8	26.5	340.68	0.0056

3.2 Cortical Architecture association with Clinical Variables in First Episode Psychosis

To assess the links between clinical variables and LGI among patients, general linear models (GLMs) were conducted. These GLMs were restricted to first episode patients with Monte Carlo Null-Z simulations set at 2.3 (P<0.005) (See Table 3 for all significant clusters). When comparing Clinical Global Impression – Severity score to LGI, our analysis revealed two significant clusters of hypergyrification. Cluster 1 was

centered on the right precentral gyrus, extending to the posterior central gyrus, with Cluster 2 centering on the right medial-orbital frontal gyrus, extending into the rostral anterior cingulate (Figure 2). There were no significant differences in cortical thickness.

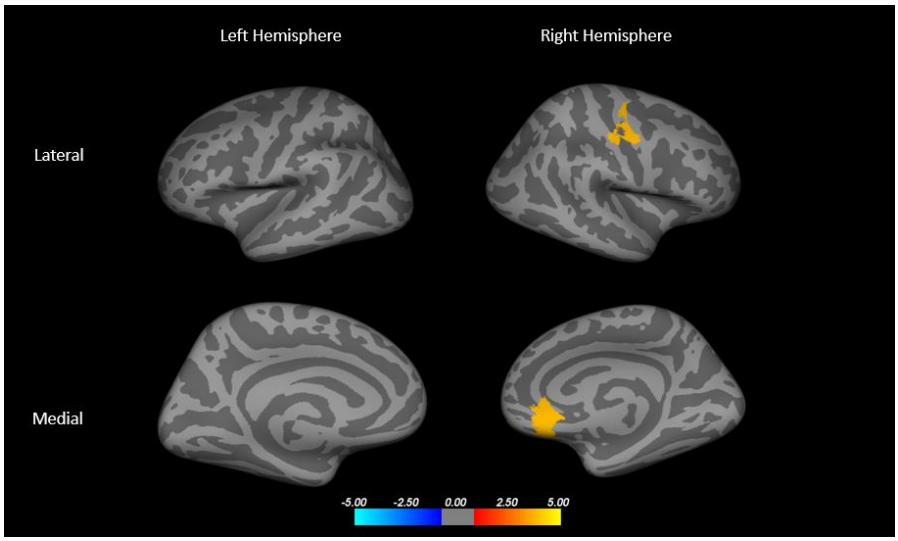

Figure 2. Significant clusters showing a positive association between Clinical Global Impression-Severity index and local gyrification index.

When this analysis was applied to the PANSS-8 clinical ratings, the overall score on the PANSS-8 was positively associated with hypergyrification in two clusters: one cluster centered on the posterior cingulum of the left hemisphere, extending upwards to the precuneus and paracentral gyrus, and a second cluster in the right superior frontal gyrus (Figure 3A). When we restricted the symptoms to the positive symptom subscale (hallucinations, delusions, and conceptual disorganization), higher symptom burden was associated with several clusters of hypergyrification (Figure 3B). In the left hemisphere, a cluster was identified in the supramarginal gyrus ($R=4.0$, $p < 0.0001$) extending into the postcentral gyrus. In the right hemisphere two clusters were identified in the precentral gyrus (Cluster 1: $R=4.0$, $p<0.0001$; Cluster 2: $R=3.0$, $p=0.018$), with a third smaller cluster identified with a primary centroid in the lateral orbito-frontal gyrus ($R=1.63$, $p=0.021$), extending into the medial orbito-frontal gyrus. No associations were found between positive symptom severity and cortical thickness.

Analyses of the association between gyrification and the negative symptom subscale of the PANSS-8 yielded similar findings, with clusters appearing bilaterally. In the left hemisphere, analyses revealed two significant clusters showing positive correlations between gyrification and symptom severity: one in the fusiform gyrus, and a second in the precentral gyrus extending into the superior frontal gyrus (Figure 3C). In the right hemisphere, two significant clusters were found, one in the precentral gyrus, and a second in the caudal middle frontal gyrus. The two clusters were near contiguous, with evidence of hypergyria extending from the caudal middle frontal gyrus-extending inferior into the opercularis, and posteriorly through the precentral and postcentral gyrus (Figure 3C). Further, negative symptom burden was associated with statistically significant increases in cortical thickness in the temporal pole and middle temporal gyrus (Figure 3D; Table 4).

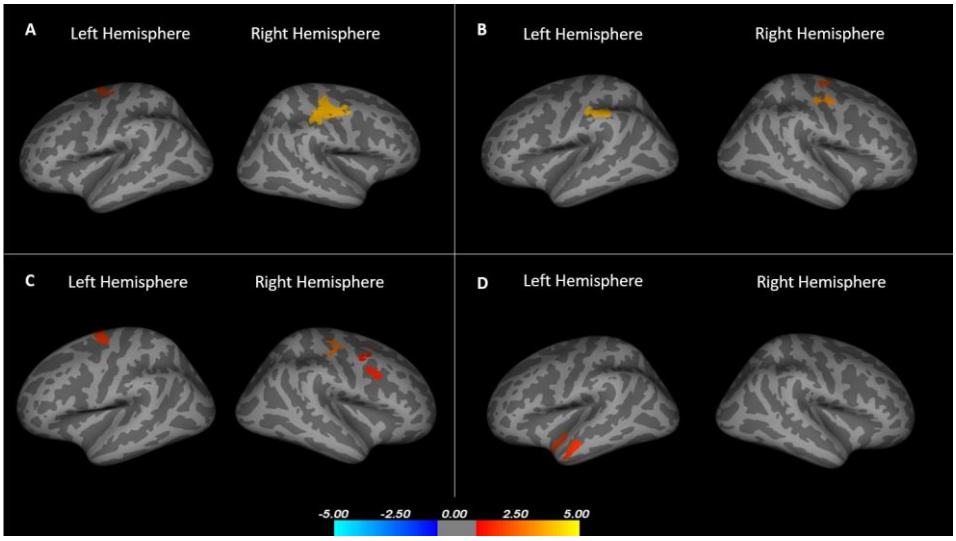

Figure 3: A) Clusters with significant association between PANSS Total Score and gyrification **B)** Clusters with significant association between PANSS-Positive symptom scores and gyrification **C)** Clusters with significant association between PANSS-Negative symptom scores and gyrification **D)** Clusters showing positive associations between increased baseline PANSS-Negative symptom score and cortical thickness

After restricting analyses to single symptom items, several clinical features were revealed to be significantly associated with LGI (for complete list: See in Table 2). The association between worsening symptom profiles and regional hypergyrification persisted through most single domain analyses, with no evidence of an association between symptomatology and hypogyria in our sample (Figures available in supplemental materias). Only passive social withdrawal (PANSS-N4) showed significant associations with bilateral increases in cortical thickness (Supplemental Figure 5).

3.3 Association between Cortical Architecture at Baseline and Later Functional Response

When assessing associations between baseline cortical architecture and vocational functioning at 6-12 months follow-up (NEET vs EET), with cluster inclusion set at $p<0.005$, increases in gyrification in the bilateral inferior parietal region and right parsorbitalis were associated with NEET status at 6-12month follow up (Figure 4). No differences in cortical thickness were observed between NEET and EET patients.

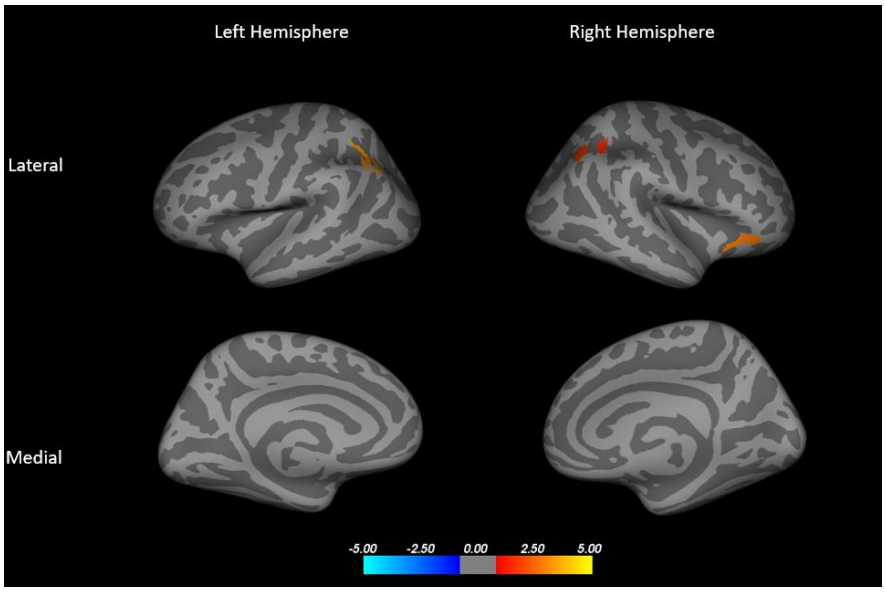

Figure 4: Clusters showing statistically significant positive associations between baseline local gyrification index and vocational inactivity after 6-12 months of treatment.

When we expanded this assessment of baseline gyrification with later functional response to include follow up SOFAS scores, adjusting for individual differences in baseline functioning, higher gyrification trended toward association

with lower follow-up SOFAS scores in superior parietal regions in the right hemisphere, however, this association only survived with cluster inclusion set at p = 0.05. No association between cortical thickness and follow-up SOFAS scores were observed.

Table 3. Clusters Showing Correlation in a General Linear Model with Clinical Metrics:

	GLM Cluster R-Value	Talaraich coordinate of the centroid			Cluster size, mm^2	Cluster- wise probability
		x	*y*	*z*		
CGI-Severity						
Right Precentral gyrus	4.00	40.2	-10.9	42.6	1160.23	0.0001
Right medial orbitofrontal	4.00	6.3	33.5	-19.9	533.30	0.0001
PANSS-Total						
Right Precentral Gyrus	4.00	40.2	-10.9	42.6	1563.39	0.0001
PANSS-Positive						
Left Supramarginal	4.00	-57.0	-34.2	40.4	507.07	0.0001
Right Precentral	4.00	40.2	-10.9	42.6	455.02	0.0001
Right Precentral	1.74	27.7	-14.4	60.2	221.43	0.018
Right lateralorbito-frontal	1.63	15.0	19.7	-23.7	211.97	0.021
PANSS-Negative						
Right Precentral	4.00	40.2	-10.9	42.6	893.47	0.0001
Right Caudal middlefrontal	3.52	32.7	10.6	31.1	362.12	0.0003
Left fusiform	2.49	-30.2	-68.0	-13.4	338.99	0.0032
Left precentral	1.65	-26.7	-13.4	53.9	243.54	0.02
PANSS- P2						
Right Medial Orbito Frontal	1.37	6.3	33.5	-19.9	187.54	0.043
Left Lateraloccipital	2.03	-28.4	-94.9	-4.7	282.49	0.009
PANSS-P3						
Right Rostral Middle Frontal	2.02	23.5	42.7	23.3	248.94	0.0084
Right Inferior Temporal	1.91	57.8	-47.7	-18.1	240.84	0.011
Left caudal middle frontal	4.00	-30.8	9.3	53.6	956.46	0.0001
Left Post Central Gyrus	4.00	-49.5	-23.9	37.3	899.91	0.0001
Left Rostral Middle Frontal	3.70	-30.3	46.4	10.8	447.02	0.0002
Left Rostral Middle Frontal	2.11	-38.8	28.0	33.6	291.24	0.007
Left Paracentral	1.87	-16.1	-36.6	49.9	265.92	0.013
PANSS-N1						
Right Caudal Middle Frontal	4.00	32.7	10.6	31.1	547.99	0.0001
Right Superiortemporal	1.59	65.2	-17.0	3.0	208.00	0.025
PANSS-N4						
Right Precentral Gyrus	4.00	40.2	-10.9	42.7	2140.64	0.0001
Left precentral gyrus	1.46	-26.7	-13.2	53.9	171.00	0.035
NEET Status						
Left inferiorparietal	3.09	-34.2	-68.3	45.1	398.72	0.0008
Right Parsorbiatlis	2.85	44.7	29.3	-13.4	308.9	0.001
Right Inferiorparietal	1.88	33.3	-61.9	45.6	236.37	0.012
Right Inferiorparietal	1.54	35.1	-50.8	37.2	203.94	0.028

*Threshold for inclusion in a cluster was $p = 0.005$. CGI, Clinical Global Impression; PANSS, Positive and Negative syndrome scale, P2, Conceptual disorganization; P3, Hallucinations; N1, Blunted affect; N4, passive social withdrawal; NEET, Not in education employment or training.

Table 4. Cluster showing significant relationship between cortical thickness and clinical symptoms in First episode Psychosis Patients

	GLM Cluster R-Value	Talaraich coordinate of the centroid			Cluster size, mm^2	Cluster- wise probability
		x	*y*	*z*		
PANSS-Negative						
Left temporal Pole	2.19	-36.6	11.3	-32.7	406.7	0.006
Left middle temporal	1.86	-53.8	-12.3	-21.1	359.2	0.013
PANSS-N4						
Left Superior temporal	3.52	-48.0	-11.6	-9.6	589.21	0.0003
Left Middle temporal	3.30	-49.9	-3.6	-24.8	567.05	0.0005
Left Entorhinal	1.56	-31.6	-5.4	-33.5	321.75	0.027
Right Superior temporal	4.0	49.4	-6.4	-11.9	634.10	0.0001
Right lingual	1.74	9.2	-60.9	2.6	356.33	0.018

4.0 Discussion

Using a surface-based vertex-wise morphometric approach, we observed a significant increase in gyrification among FEP patients compared with healthy controls. This hypergyria was lateralized to the right hemisphere, in the precentral gyrus. Additionally, we discovered several associations between clinical symptoms and gyrification. This is a unique finding from an antipsychotic naïve sample, with clinical metrics taken on the same day as the scan. This suggests that the natural presentation of psychotic symptoms (i.e., the progression in the absence of therapeutic intervention with medication) are linked with the severity of gyrification. Finally, we did not identify any differences in cortical thickness between patients and controls, and only found cortical thickness to be associated with negative symptoms among patients.

While the extent of the hypergyria among FEP patients (vs. controls) in our sample was modest and localized to the right hemisphere, our work is consistent with previous literature regarding clinical high risk (T. Das et al., 2018; Harris et al., 2007) and first episode psychosis samples (Sasabayashi et al., 2017; Schultz et al., 2010, 2013;

Tepest et al., 2013; Zuliani et al., 2018). The increasing evidence for hypergyria in pre-clinical and early psychosis provides additional support for the neurodevelopmental origins of schizophrenia. While directly investigating hypergyrification as a posited sequela of early developmental insult has limitations, the link between gyrification and early development is clear. Experimental data has shown differential rates of neuronal proliferation and tangential expansion (Rakic, 1988; Ronan et al., 2014; Xu et al., 2010) as well as the strength of axonal tensions (Toro & Burnod, 2005; Van Essen, 1997) in early development are the primary drivers of cortical folding in the mammalian brain. Thus any insult during this critical period of cortical expansion in the first several months' gestation, is likely to result in aberrant gyrification and potentially lead to significant downstream neuropsychiatric consequences. While not tested in the current study, given the proposed mechanism of gyrification, it is possible that the aberrant neurodevelopment that contributes to anomalies in gyrification may also be linked to the cortical dysconnectivity identified in first episode samples (Cao et al., 2018; Satterthwaite & Baker, 2015; Woodward & Heckers, 2016). Thus the influence of neurodevelopment on both anatomical and functional connectivity metrics may in part explain the associations with clinical metrics described below.

When our analysis was restricted to FEP patients, general linear models showed several significant associations between gyrification and metrics of disease severity. Overall clinician ratings of illness severity were associated with increased folding in frontal and parietal areas of the right hemisphere. While any specific conclusions about the relationship between specific clusters of hypergyria and clinical characteristics should be made with caution, the association between clinical severity and anatomical disturbance in the medial orbitofrontal cortex (Walton et al., 2018) and the precentral gyrus (Xiao et al., 2015) have previously been reported. With previous work suggesting volumetric disturbances in the orbitofrontal cortex of schizophrenia patients (Lacerda et

al., 2007), and both volumetric (Xiao et al., 2013; Zhou et al., 2005) and connectivity (Li et al., 2019; Zarei, 2018) disturbances in the precentral gyrus of schizophrenia samples.

When analyses focused more directly on symptom severity, our findings suggest positive symptoms are associated with bilateral increases in gyrification. This is consistent with previous work by Sasabayashi et al. (Sasabayashi et al., 2017). Our work identified several new significant clusters, suggesting the link between positive symptoms and gyrification may be more diffused throughout cortical structures than previously understood. In addition to the increased gyrification of the precentral gyrus and orbitofrontal regions relating to ratings of clinical severity, we also report a significant cluster of hypergyria in the left supramarginal gyrus.

When limited to negative symptoms, our study found that overall negative symptomology was associated with increased gyrification bilaterally. While the findings of hypergyrification were predominantly located in frontal and parietal regions, similar to associations with positive symptomology, we also revealed a significant cluster of hypergyria in the left fusiform. The presence of abnormality in the fusiform has previously been identified in schizophrenia samples (Jung et al., 2021; Lee et al., 2002), and may underlie emotion and facial processing deficits key to negative symptomology. We also identified evidence of increased cortical thickness in both the temporal pole and middle temporal gyrus, regions that may be associated with socioemotional processing (Herlin et al., 2021) and semantic processing (Davey et al., 2015, 2016) respectively. Our finding however trends in the reverse direction of previous literature where negative symptoms have been associated with volumetric deficits in both chronic and first episode (Bergé et al., 2011) samples, and reductions in gyrification (Sallet et al., 2003). While this inconsistency with the broader literature is noteworthy, it is likely that this is related to the drug naïve, first episode nature of our sample.

To our knowledge, the present study is the first to present findings associating drug naïve first episode psychosis patient's gyrification with later functional outcomes following 6-12 months of treatment. We reported bilateral increases in gyrification in the inferior parietal lobe, as well as the right parsorbitalis among patients who were not involved in vocational activity in the first year of treatment. In a systemic review of the role of the parietal lobe in schizophrenia, Yildiz et al. (2011) have argued that schizophrenia patients with disturbances in parietal structures (both from connectivity and volumetric studies) may be associated with greater deficits in working memory and self-conceptualization. These factors are potentially linked to our observations of occupational inactivity following treatment. While our patients did not show any signs of tissue loss, this is relatively consistent with previous literature suggesting that tissue loss may be associated with the onset of psychotic symptoms, rather than conferring vulnerability to psychosis (Borgwardt et al., 2008). Thus follow up imaging on patients to assess anatomical trajectories and their associations with functional response is warranted.

We also note that greater levels of gyrification are typically associated with corresponding increases in cortical thickness in healthy adults (Gautam et al., 2015), yet this relationship was not broadly identifiable in our sample. Despite hypergyria being associated with all symptoms and later outcomes in our study, the only corresponding increase in cortical thickness was the aforementioned findings in the temporal pole and middle temporal gyrus among patients exhibiting higher negative symptom burden. While this is inconsistent with some previous FEP studies (Crespo-Facorro et al., 2011; Janssen et al., 2009), our sample was unique due to the drug naïve acute phase of illness. While gyrification may represent a stable marker of neurodevelopmental vulnerability (Sasabayashi et al., 2017), cortical thinning may be among the earliest identifiable neurodegenerative processes, beginning even before patients present to clinical settings, and worsening throughout the course of illness (Rodriguez-Perez et al.,

2020). It is plausible that in addition to hypergyria more diffused cortical thickening was present during development, and this tissue loss had already begun to take effect prior to our assessment, thus we were unable to identify any previously present association positive symptom burden. This early tissue loss likely underlies the findings in established schizophrenia cases showing reduced gyrification (Bonnici et al., 2007; Kulynych et al., 1997; Palaniyappan & Liddle, 2012), and is consistent with the model of early hypergyria followed by progressive tissue loss and hypogyria described by Sasabayashi et al (2021). This reduction in cortical thickness, and later gyrification, is consistent with the theory of neuroprogression (Kapczinski et al., 2014), and may indeed represent an neuro-adaptive response from acute to more stable phase of illness (Palaniyappan & Sukumar, 2020), that would exist regardless of medication status (Liu et al., 2020; Nelson et al., 2020). This suggests the need for longitudinal investigation of the association between gyrification, cortical thickness, and treatment response.

While this study had a number of unique strengths (7T- MRI, antipsychotic naïve sample, relatively low duration of untreated illness), a few limitations warrant discussion. First, by its cross sectional nature, this study is unable to directly assess questions surrounding whether the posited trajectories over the course of illness represent neurodegenerative or neuro-adaptive responses to illness. To this end, future studies should assess whether longitudinal changes in anatomical characteristics are related to changes in symptom severity as patients transition from the acute to stable phase of illness, thus providing evidence for a neuro-adaptive response to psychotic illness. Further, the cross sectional nature of this study did not allow the research team to assess the long term clinical relevance of these anatomical features, such as predicting response to treatment or influence on later functional outcomes. Future work should consider assessing how baseline neuroanatomy among antipsychotic naïve patients relates to later clinical response.

4.1 Conclusion

Using a cortex-wide analysis, we found increased LGI in the right precentral gyrus of first-episode schizophrenia patients relative to controls. While these findings were relatively localized compared to previous studies, this finding adds to the growing evidence for early developmental abnormality in diverse cortical areas in schizophrenia patients in a drug-naive sample. Our findings also provide a detailed analysis relating clinical severity to gyrification in schizophrenia patients. These findings suggest that symptoms severity, particularly positive symptom severity, may be related to aberrant gyrification in several clusters throughout the cortex.

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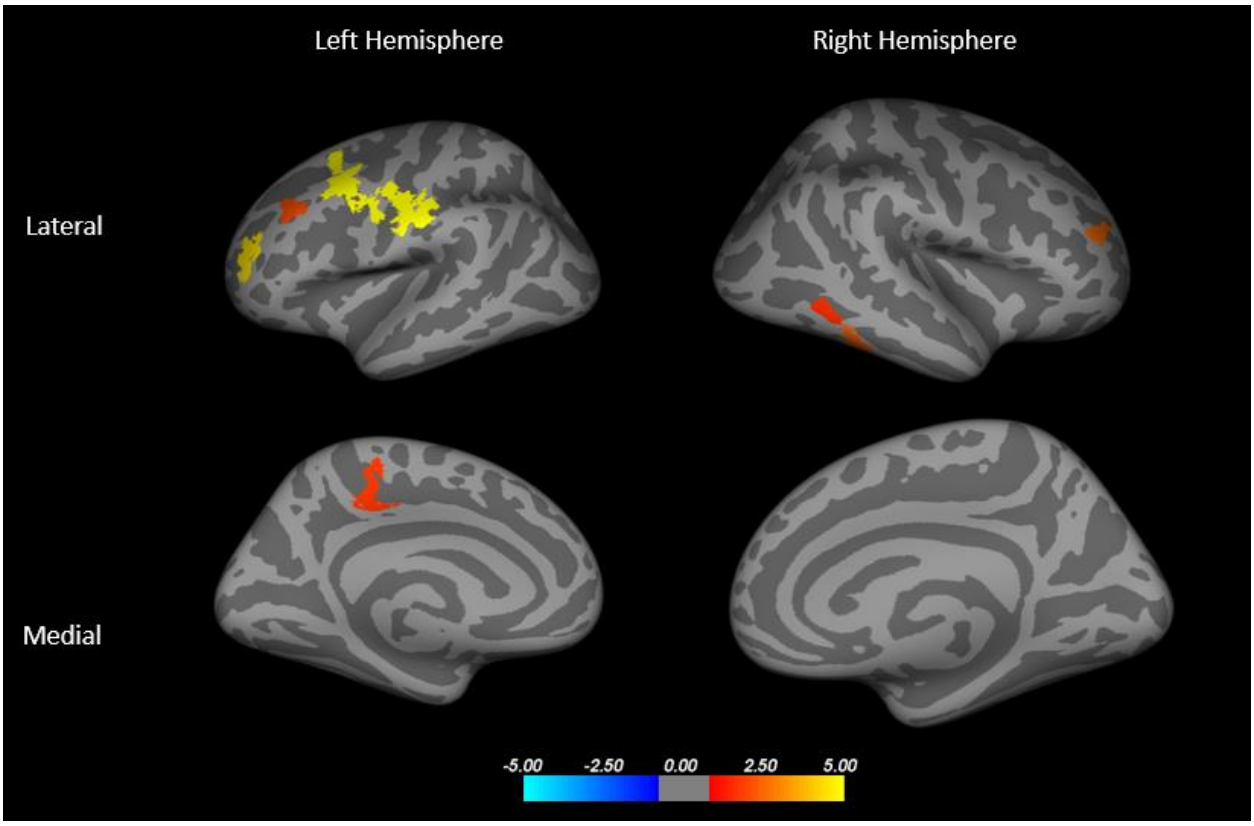
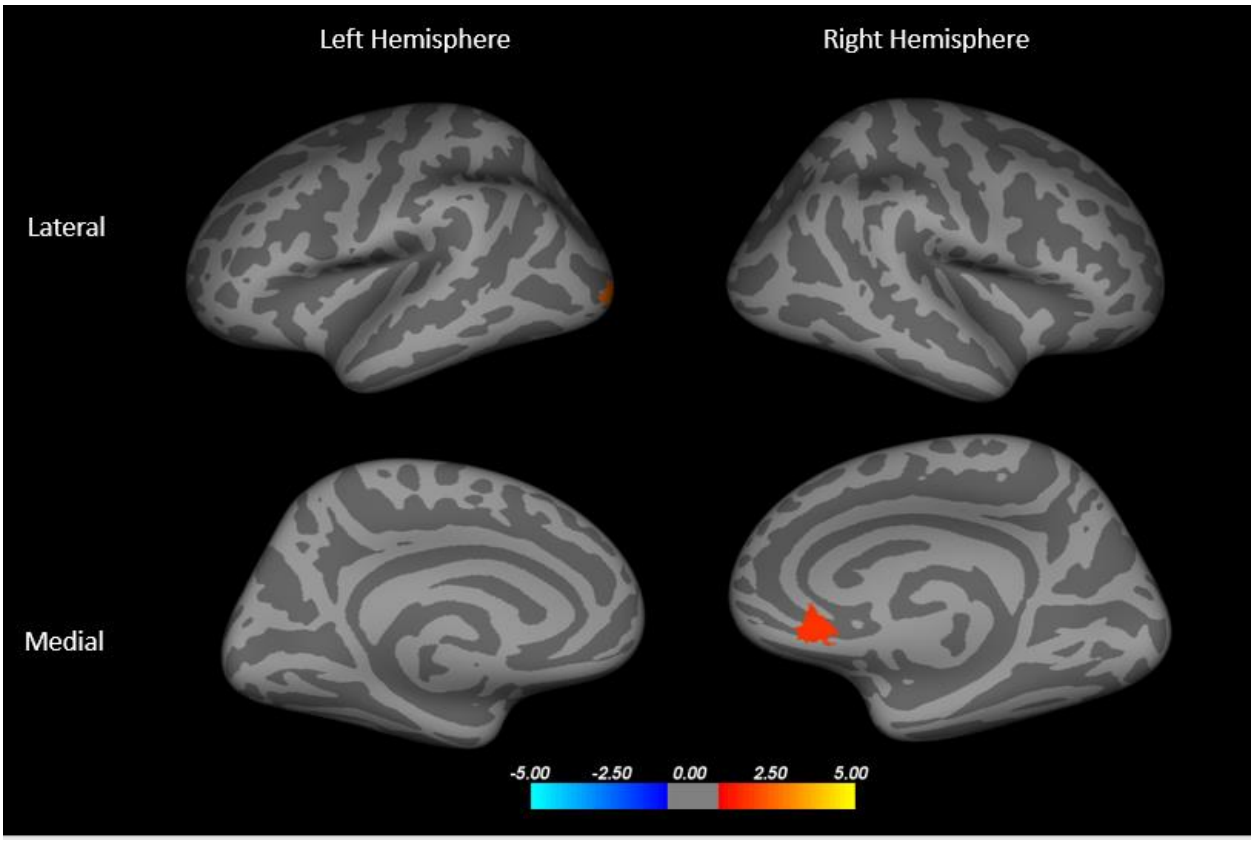
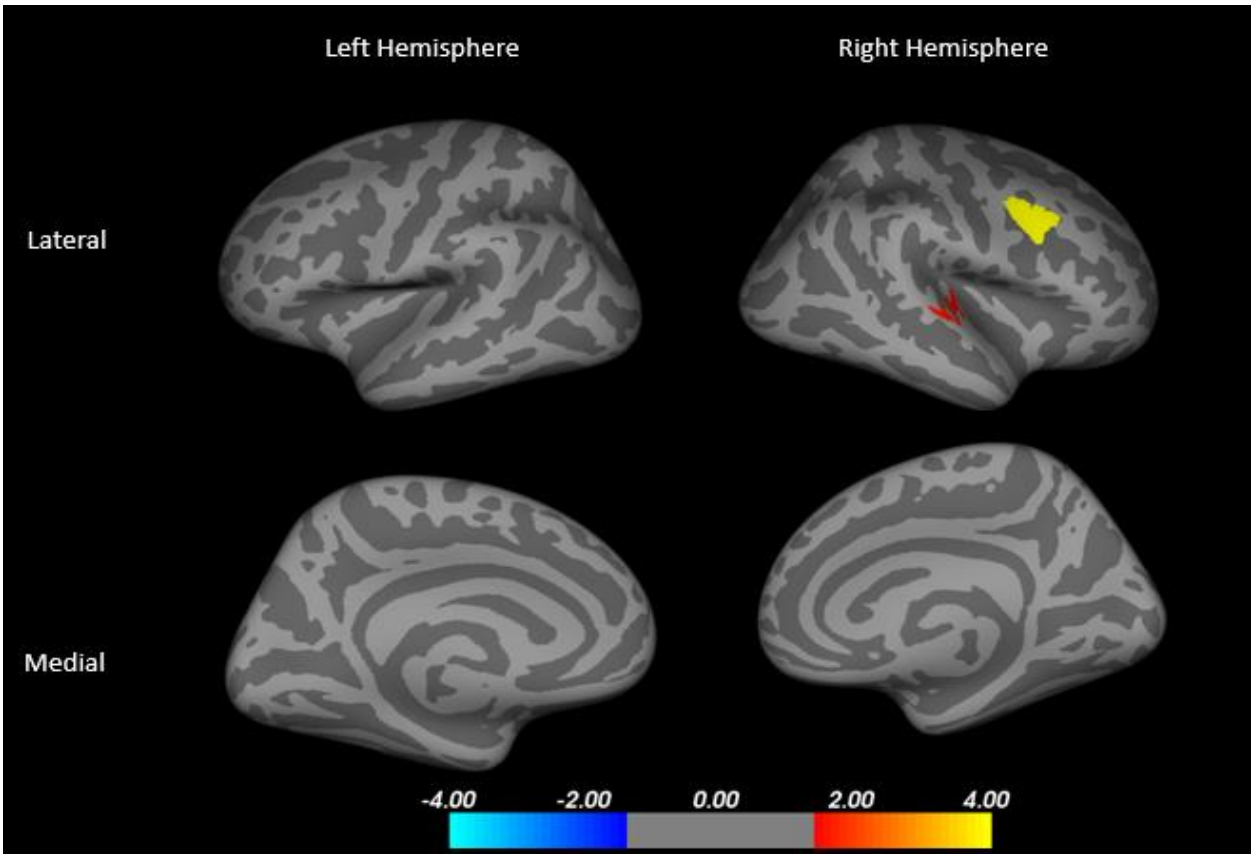
6.0 Supplementary Materials



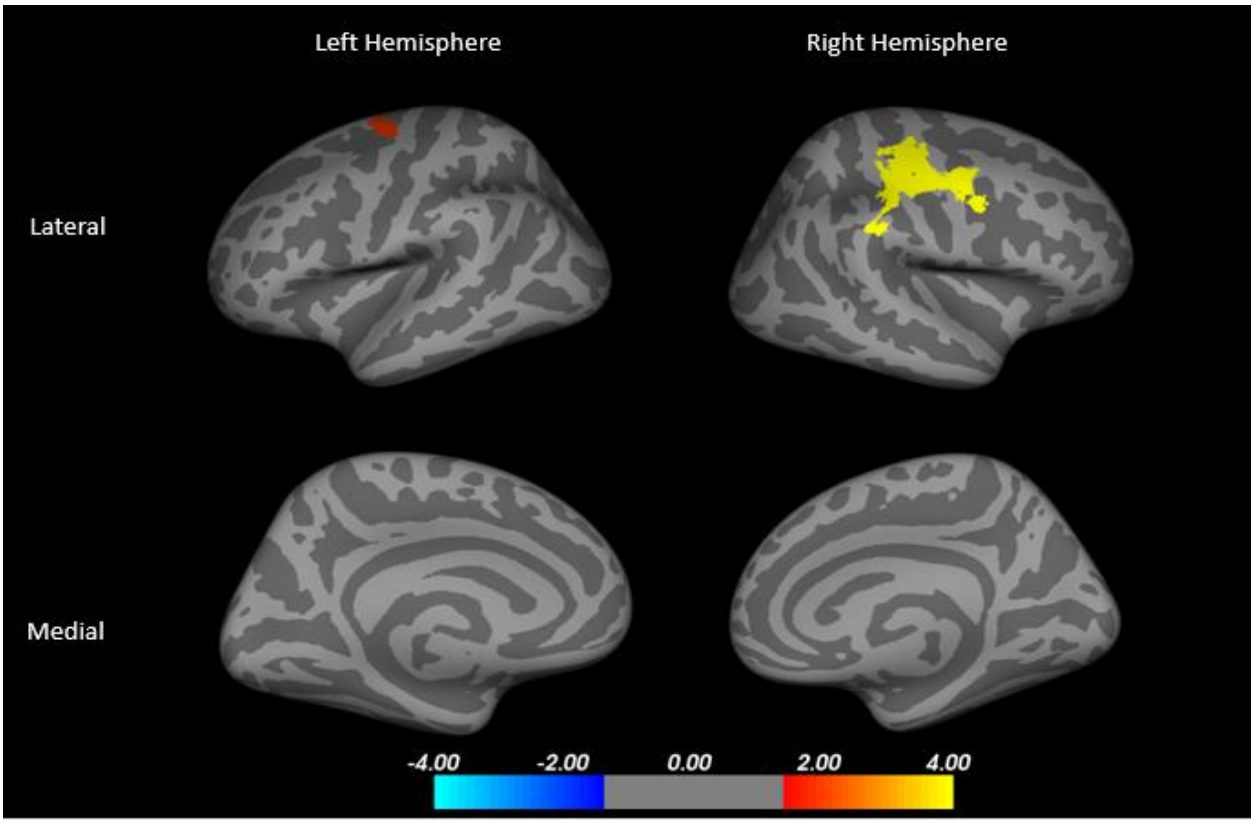
Supplemental Figure 1: Cluster showing statistically significant associations between severity of hallucinations (PANSS-P3) and increased gyrification among patients in the right rostral middle frontal, right inferior temporal gyrus, and the left caudal middle frontal gyrus, left post central gyrus, let rostral middle frontal gyrus and left paracentral gyrus.



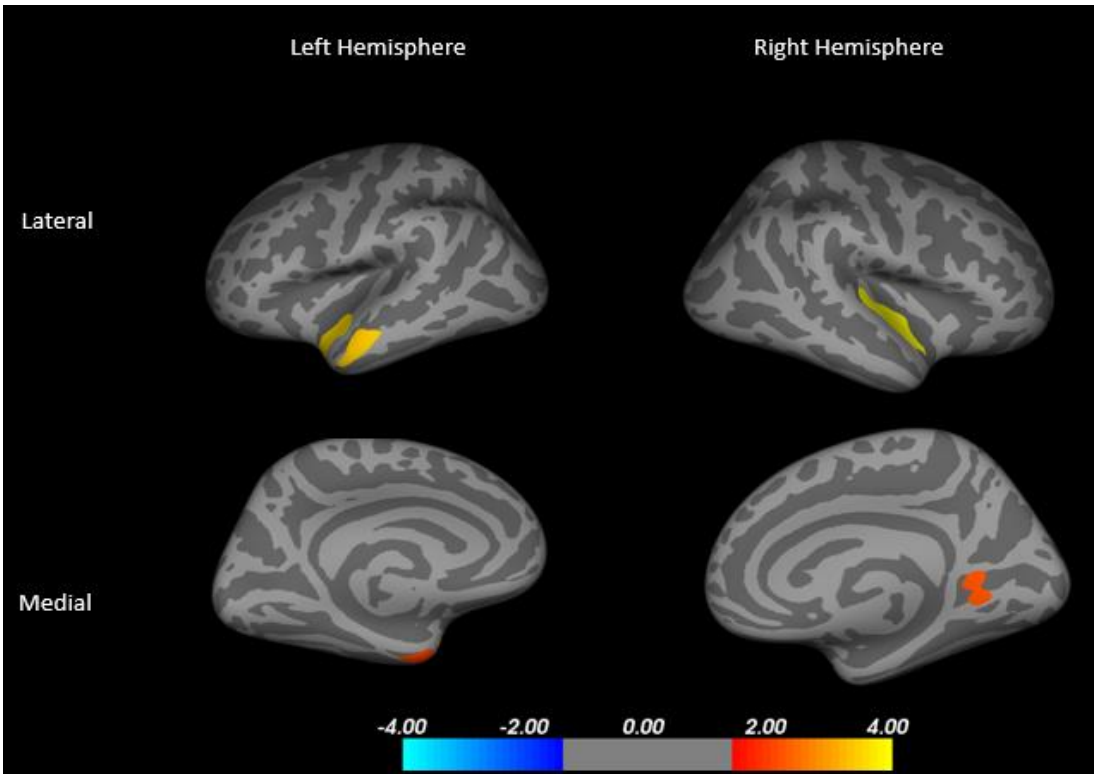
Supplemental Figure 2: Cluster showing statistically significant associations between conceptual disorganization (PANSS-P2) and increased gyrification in the left lateral occipital gyrus and the right medial orbitofrontal gyrus among first episode psychosis patients



Supplemental Figure 3: Cluster showing statistically significant associations between blunted affect (PANSS-N1) and increased gyrification in the right caudal middle frontal gyrus and right superior temporal gyrus among patients



Supplemental figure 4: Cluster showing statistically significant positive associations between passive social withdrawal (PANSS-N4) and increased gyrification among patients in the bilateral precentral gyrus.



Supplemental Figure 5: Clusters showing statistically significant associations between passive social withdrawal (PANSS-N4) and increased cortical thickness among patients

Chapter 4: Glutathione and Vocational Outcome in First Episode Psychosis

Preamble

In previous chapters, we have assessed abberations in both linguistic factors (manifest-behavior scale), and cortical anatomy (meso-scale) and their corresponding effects on both clinical severity as well as social and vocational outcome. In chapter four, our final manuscript will focus on the micro-scale of analysis by addressing how neuro-metabolite concentrations, specifically glutathione in the dorsal anterior cingulate cortex, may be associated with early vocational response.

While several well established predictors of poor functional outcome exist such as higher duration of untreated psychosis (Marshall et al., 2005) and persistent negative symptomology (Foussias & Remington, 2010), these factors do not present an actionable mechanism for early intervention, which has resulted in a focus on molecular mechanisms that may allow clinicians to reduce functional impairment in psychosis. Researchers have turned to investigating oxidative stress as one such putative mechanism underlying poor functioning. Glutathione, the brains primary antioxidant, has been investigated as a molecule with the potential to offset oxidative stress and improve functional outcomes in patients with FEP. Previous work has shown higher blood glutathione to be associated with reduced cognitive deficits (Martínez-Cengotitabengoa et al., 2014) and brain volume loss in early psychosis(Fraguas et al., 2012), suggesting a potentially modifiable pathway to improve functioning in the first episode of psychosis.

To our knowledge, no prior study has assessed the association between in-vivo measurements of intra-cortical glutathione at illness onset with later social and vocational outcomes in a sample of FEP patients. In the subsequent manuscript, we assessed this question by measuring glutathione in the dorsal anterior cingulate cortex and its associations with social and vocational response in the first year of treatment.

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Manuscript: Central oxidative stress and early vocational outcomes in first episode psychosis: A 7-Tesla Magnetic Resonance Spectroscopy study of glutathione

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Abstract

Background: Following the first episode of psychosis, some patients develop poor social and occupational outcomes, while others display a pattern of preserved functioning. Evidence from preclinical, genetic and biochemical studies suggest a role for high oxidative stress in poor functional outcomes among patients. The measurement of intracortical glutathione (GSH) using magnetic resonance spectroscopy (MRS) enables investigation of the relationship between central antioxidant tone and functional outcomes at the time of first episode psychosis (FEP). We hypothesized that patients with higher central antioxidant tone at first presentation will have better functional outcomes in early stages of illness.

Methods: We scanned 57 patients with FEP and 30 matched healthy controls and estimated GSH resonance using 7-Tesla MRS. We minimised the confounding effects of illness chronicity, long-term treatment exposure and metabolic complications by recruiting patients with <2 weeks of lifetime antipsychotic exposure on average and followed up this cohort for the next 1 year to determine functional outcomes.

Study results: Patients who achieved employment/education or training status (EET) in the first year, had higher GSH at the baseline than healthy controls. Social and occupational functioning assessment scale (SOFAS) scores were also significantly higher in patients with higher GSH levels at the outset, after adjusting for various confounds including baseline SOFAS. Patients who were not in EET did not differ from healthy subjects in their GSH levels.

Conclusion: Our observations support a key role for the central antioxidant tone in the functional outcomes of early psychosis.

Keywords: antioxidant, employment, schizophrenia, functioning, anterior cingulate

1.0 Introduction

For patients with schizophrenia, the probability of functional recovery is highest at the early stages of the illness, around the time of the first psychotic episode(Addington, 2007; Dama et al., 2019; Henry et al., 2010); when a chronic pattern of the illness gets established, the chances of functional recovery greatly diminish, with only a small sub-group (~13%) recovering at this stage (Jääskeläinen et al., 2013; Norman et al., 2018). Currently, we do not know what mechanistic processes underlie these diminishing returns in recovery rates over time. Several clinical characteristics (e.g., the presence of negative, disorganised symptoms, cognitive deficits(Santesteban-Echarri et al., 2017)) have been observed in association with poor functional outcomes; in particular, the degree of functioning at first presentation (baseline or premorbid) explains a significant amount of variance in long term functional outcomes(Díaz-Caneja et al., 2015; O'Keeffe et al., 2019; Velthorst et al., 2017) . Despite their explanatory power, these clinical associations do not offer an actionable mechanistic marker that can be harnessed for therapeutic purposes. There is an urgent need to understand the neurobiological factors that contribute to differences in functional outcomes in early stages of illness.

One promising approach to study variable outcomes in psychosis is quantifying the relative burden of oxidative stress experienced by patients during the first psychotic episode(A. J. Murray et al., 2021). Fournier and colleagues utilised a data-driven stratification procedure on a cohort of patients with early psychosis and identified a subgroup with superior functional outcomes; this subgroup was characterised by lower levels of oxidative stress markers (especially glutathione peroxidase) in the blood(Fournier et al., 2017). Lower baseline blood levels of glutathione (GSH), a major antioxidant, predict later cognitive deficits(Martínez-Cengotitabengoa et al., 2014) as well as brain volume loss in early psychosis(Fraguas et al., 2012). While peripheral markers of oxidative stress correlate with concentration of the primary intracortical antioxidant glutathione(Xin et al., 2016), a direct link between central glutathione levels and functional outcome in first episode psychosis (FEP) is yet to be demonstrated. Wood and

colleagues(Wood et al., 2009) reported a 22% increase in medial temporal GSH levels in first episode psychosis; in a sub-sample from this study, treatment related increase in GSH was associated with a gain in global functioning scores(Berger et al., 2008). In a small group of individuals with various mental health difficulties indicating a high-risk state for psychosis, we recently demonstrated higher GSH levels measured using magnetic resonance spectroscopy (MRS) from the dorsal anterior cingulate cortex (ACC) in those with better social and occupational functioning(Jeon et al., 2021). Given the prior reports relating higher ACC GSH levels in high-risk state with baseline functioning(Jeon et al., 2021), and in early stages of psychosis with later treatment response(Dempster et al., 2020) and resistance (Coughlin et al., 2020), we hypothesized that ACC GSH levels measured at the onset of first episode psychosis, before treatment initiation, predicts later functional outcomes in the first year of early intervention.

Early functional outcome status is a well-established indicator of long-term course of schizophrenia(Harrison et al., 1996, 2001). An exciting translational possibility of linking GSH levels with functional outcomes in psychosis, is the availability of targeted treatments that can improve intracortical GSH in patients. Several clinical trials have reported on the safety and efficacy of the glutathione precursor N-acetylcysteine (NAC) in patients with psychosis(Yolland et al., 2020). These trials (6 RCTs)(Yolland et al., 2020) indicate that NAC produces a modest, but significant improvement in cognitive deficits and negative symptoms (critical determinants of poor functional outcomes), when used as an adjunct to antipsychotics. Thus, in patients with psychosis, a deficit in intracortical GSH is likely to be a potentially modifiable pathway of poor outcomes.

2.0 Methods

2.1 Participants:

The sample for the present analysis consisted of 72 new referrals to the PEPP (Prevention and Early Intervention for Psychosis Program) at London Health Sciences Centre. After exclusions were made due to missing/poor quality scan data (n=15; n=11

withdrew from scan, n=4 incorrect voxel placement due to movement in scanner), our final sample consisted of 57 patients (48 males/9 females) (Table 1). All participants provided written, informed consent prior to participation as per approval provided by the Western University Health Sciences Research Ethics Board, London, Ontario. Inclusion criteria for study participation were as follows: individuals experiencing first episode psychosis, with not more than 14 days of cumulative lifetime antipsychotic exposure, no major head injuries (leading to a significant period of unconsciousness or seizures), or known neurological disorders, and no concurrent substance use disorder. There were no explicit instructions to abstain from substances to participate in the study. Patients on non-antipsychotic prescription medication were not excluded (See Supplementary Table 1 for medication class by group).

The mean lifetime total defined daily dose days (DDD × days on medication) for antipsychotic use was 1.80 days with 27 patients (47.4%) being completely antipsychotic naive at the time of scanning. Of those who had started antipsychotic treatment, (N=30; 52.6%), the median total defined daily dose days was 2.81 days (range of 0.4–14 DDD days). Patient consensus diagnosis was established using the best estimate procedure described by Leckman et al.(Leckman et al., 1982) following 6 months of treatment. Diagnoses were made based on the Structured Clinical Interview for DSM-5.

Healthy control subjects (n=30) were recruited through posters and word of mouth advertising. Healthy control subjects had no personal history of mental illness, no current use of medications, and no first-degree relatives with a history of psychotic disorders. Healthy controls were group matched to the FEP cohort for age and parental socio-economic status (the National Statistics Socioeconomic Classification: five-class version(Rose & Pevalin, 2003)). Similar to their FEP counterparts, those with a history of substance use disorders in the past 12 months, significant head injury or neurological disorders were excluded.

2.2 Clinical Measures:

A clinical examination was conducted during the baseline assessment (the same day imaging was performed) by a research psychiatrist for patients or a trained rater for healthy controls. The clinical battery was used to assess patient symptom severity, substance use and to ensure that control subjects were free from current psychiatric disorders and history of either psychotic illness or neurologic disorder. To address substance use in the 6 months prior to our initial scan, the 6-item Likert-type Cannabis Abuse Screening Test (CAST)(Legleye, 2018) was used, in addition to self-reports of alcohol consumption using the Alcohol Use Disorders Identification Test – 3 Item version (AUDIT)(Saunders et al., 1993) and regular nicotine use (yes or no).

To assess symptoms of psychosis the Positive and Negative Syndrome Scale – 8 Item (PANSS-8) was used(C.-H. Lin et al., 2018b). The PANSS-8 is an abbreviated version of the 30 Item PANSS clinical assessment of symptomology in schizophrenia and psychosis with acceptable internal consistency and highly correlated with the full PANSS(C.-H. Lin et al., 2018b). Items are scored on a 1 (absent) to 7 (extreme) Likert type scale, assessing both positive (P1-delusions, P2 – Conceptual disorganization, & P3-hallucinations), and negative domains (N1- Blunted or flat affect, N4- passive social withdrawal, and N6- impoverishment of speech).

Additionally, the Social and Occupational Functioning Assessment Scale (SOFAS) was administered at baseline and follow up between 6-12 months after the acute phase of psychosis. The SOFAS is a single item measure of functioning scored between 1 (persistent inability to maintain minimum functioning without external support) and 100 (superior functioning in a wide range of activities). The SOFAS ratings of social and occupational functioning were made independent of symptom severity. In our study SOFAS was taken with consideration for current functioning (rather than highest level of functioning over the past year).

We obtained baseline SOFAS on the same day MRI data were acquired. The patients enrolled in the PEPP clinic were followed up for the next 12 months. We ascertained their Vocational status using NEET criteria (not in employment, education, or training) and follow up scores after 6-12 months of treatment following the acute phase of illness. The functional assessment was based on multiple sources of information: patient interviews, information from the attending psychiatrist, nurse/ social work case managers and, where required, information from family members documented in clinical charts. Due to the need for multiple information sources, not all patients were assessed at the same point after their illness onset, but the vocational (NEET) status of the cohort between the window of 6-12 months was captured, in addition to baseline and follow up assessment of cross sectional functioning using SOFAS. Patients were classified as NEET (vocationally inactive) if they were unemployed and not in any form of schooling/education for more than half of the time since the onset of treatment for psychosis. Individuals who were engaged in work or school for more than half of the duration of treatment were classified as EET (vocationally active). This definition considers a longer time frame (up to 6 months) than the 1-week period used by the Organisation for Economic Co-Operation and Development (OECD(Youth and the Labour Market - Youth Not in Employment, Education or Training (NEET) - OECD Data, n.d.)), in line with its use in early intervention services for psychosis(Iyer et al., 2018; Maraj et al., 2019). A consensus was reached within the research study team when discrepancies noted in reported functioning between patient's accounts and those of care providers.

2.3 MRS assessment

The complete MRS protocol for this study has been described in overlapping sample (37/72 patients overlap) previously published from this research project by Dempster and colleagues(Dempster et al., 2020). Metabolite concentrations were estimated using single-voxel ^{1}H-MRS data acquired with a Siemens MAGNETOM 7.0T head-only MRI scanner (Siemens, Erlangen, Germany) using an 8-channel transmit/32-channel receive head coil at the Center for Functional and Metabolic Mapping of Western

University in London, Ontario. A 2.0 × 2.0 × 2.0 cm (8 cm^3) voxel was placed on the bilateral dorsal ACC using a two-dimensional anatomical images acquired in the sagittal direction (37 slices, TR = 8000 ms, TE = 70 ms, flip-angle (α) = 120°, thickness = 3.5 mm, field of view = 240 × 191 mm). The posterior end of the voxel was set to coincide with the precentral gyrus and the caudal face of the voxel coincided with the most caudal location not part of the corpus callosum. The angulation of the voxel was determined to be tangential to the corpus callosum (Figure 1). A total of 32 water-suppressed spectra were acquired using a semi-LASER ^{1}H-MRS pulse sequence (TR = 7500 ms, TE = 100 ms) during each scan session, while participants were at rest. A long echo time was used during this study as it was demonstrated by Wong and colleagues that optimal GSH quantification alongside a higher spectral quality of glutamate signal is obtained when using long echo time for the semi-LASER sequence at 7-Tesla field (Wong et al., 2018) (also see (Jeon, 2019)). An additional benefit of a long echo time is the removal of any macromolecular contribution, increasing the precision of our spectral fitting and quantification procedures.

Phase and frequency corrections were applied to our MRS data using MATLAB tools developed by Near and colleagues(Near et al., 2015) after which they were averaged into a single representative spectrum. The spectrum then underwent QUALITY Deconvolution and Eddy Current Correction (QUECC)(Bartha et al., 2000a) and Hankel Singular Value Decomposition (HSVD)(van den Boogaart et al., 1994) post-processing for line shape deconvolution and residual water signal removal. The software fitMAN(Bartha et al., 1999) was used for spectral fitting, which included 17 brain metabolites in its echo time specific prior knowledge fitting template. Barstool(Wong, 2019) was used for quantification and included corrections for T_1 and T_2 relaxations of gray matter, white matter, and CSF via partial volume segmentation calculations. MRS quality was assess using Cramer-Rao lower bounds (CRLB) for each metabolite fit. No significant differences were observed in spectral linewidth or SNR_{NAA} was seen among the three groups of interest (healthy controls, FEP-NEET and FEP-EET) (see supplementary

Table 2). Cramer-Rao lower bound (CRLB) thresholds for study inclusion was <10% for glutamate and <25% for glutathione, though the majority of CRLB values were much closer to half of that threshold (Supplemental Table 3).

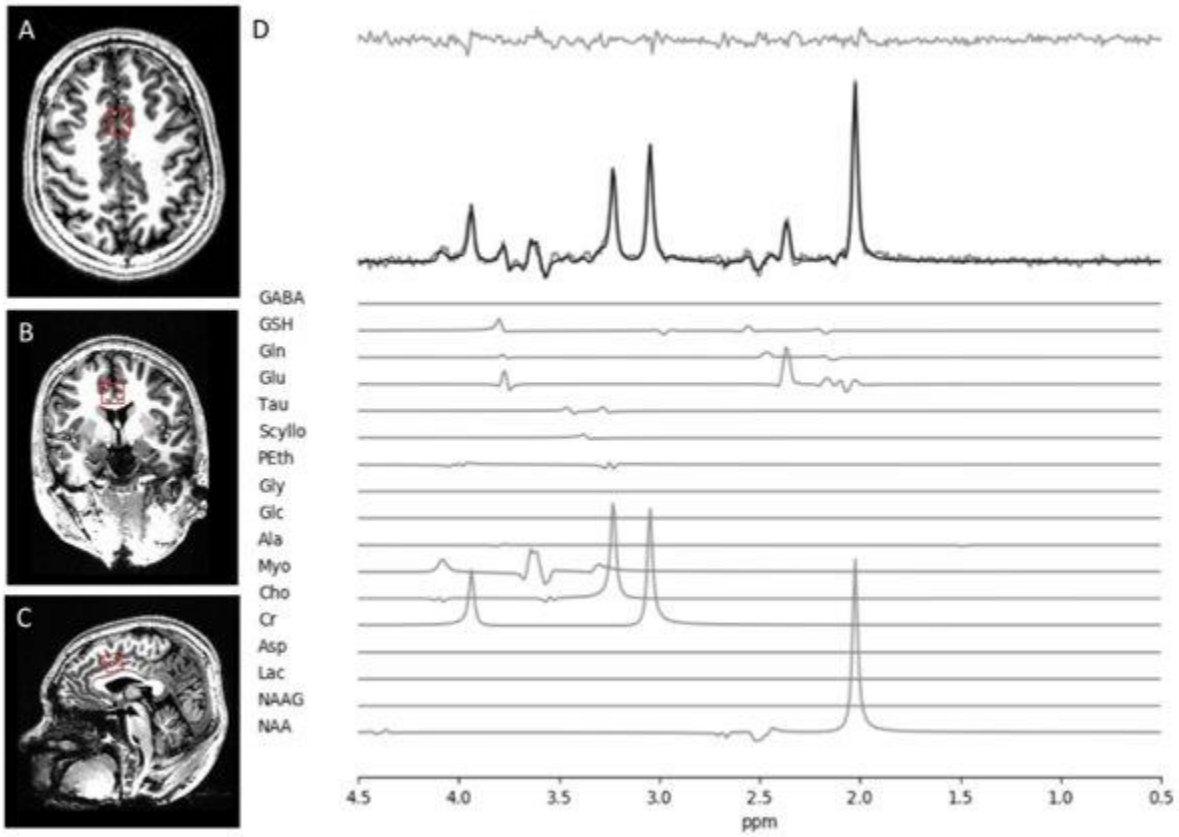

Figure 1: Illustrative example of the voxel placement on the dorsal ACC. A) Dorsal Brain View B) Posterior view C) Sagittal view D) A representative spectrum

2.4 Statistical analyses

We used IBM SPSS Statistics version 24 for all analyses. First, the primary hypothesis of a relationship between NEET status in the first year and glutathione was tested using *a one-way ANOVA*, with healthy controls, NEET and EET patients as 3 groups

of interest. Second, within the patient group, a bivariate correlation between follow-up SOFAS scores and GSH measurement was conducted, with bootstrapping for generating p-values and confidence intervals. We also tested if GSH levels retain their ability to predict follow-up SOFAS, after adjusting for the variance explained by baseline functioning (SOFAS at the time of MRS scanning), age and sex as covariates. Finally, we excluded patients without a clear diagnosis of schizophrenia by 6-12 months assessment and tested the relationship between GSH and SOFAS and NEET.

3.0 Results

When comparing healthy controls to FEPs, no statistically significant differences existed for age, parental socioeconomic status or alcohol use, although males (x^2= 4.83, p=0.028), and smokers (x^2=6.62, p=0.01) were over-represented and self-identified cannabis use frequency (CAST scores: t=5.72, p<0.01) was higher in the patient sample (Table 1). No significant differences in baseline demographic, medication, cannabis or alcohol use, or clinical differences were identified between EET and NEET patients, apart from baseline SOFAS scores, which were higher among EET patients (t= 2.23, p= 0.031). Alcohol, tobacco and cannabis use were not associated with GSH, baseline SOFAS, or follow up SOFAS scores (see Supplementary Table 4). Both EET and NEET groups showed a mean gain in SOFAS scores over the follow-up period, but the gain was higher in the EET group (EET=21.66 (14.49), and NEET= 12.00 (14.99)) t=2.07, p=0.045). Including demographic data of subjects without useable MRS data (n=15) did not affect this profile (Supplementary Table 5).

Table 1: Demographic and Clinical Characteristics of Healthy Controls versus total patient population, and NEET patients versus EET patients

Variable	Healthy Control n=30	All Patients n=57	HC vs Patient	EET Patient n=31	NEET Patient n=26	EET vs NEET
	Demographic Data					
Sex (Male/Female)	19/11	48/9	**x^2= 4.83, p=0.028**	25/6	23/3	x^2= 0.65, p=0.42
Age [M (SD)]	21.57 (3.45)	22.75 (4.28)	$t_{(85)}$=1.5, p=0.14	22.16 (3.92)	23.46 (5.29)	$t_{(55)}$=-1.10, p=0.274
Parental NS-SEC [M (SD)]	3.20 (1.42)	3.34 (1.27)	$t_{(80)}$=0.47, p=0.64	3.31 (1.11)	3.42 (1.38)	$t_{(51)}$=0.47, p=0.64
Avg Months to NEET assessment	N/A	9.00 (4.38)	N/A	8.90 (3.96)	10.04 (4.79)	$t_{(55)}$=1.79, p=0.08
CAST Score	6.13 (0.73)	12.38 (5.94)	**$t_{(75)}$=-5.72, p<0.01**	12.00 (5.88)	12.76 (6.09)	$t_{(45)}$=0.49, p=0.625
AUDIT-C	2.77 (2.10)	2.25 (2.63)	$t_{(79)}$=0.91 p=0.37	2.79 (2.69)	1.61 (2.46)	$t_{(49)}$=0.1.61, p=0.12
Smoker (Yes / No)	0/30	11/46	**x^2=6.62, p=0.01**	5/26	6/20	x^2=0.44, p=0.51
	Clinical Data					
DUP [M (SD)]	N/A	5.63 (5.74)	N/A	5.60 (5.80)	5.67 (5.82)	$t_{(53)}$=-0.04, p=0.97
Antipsychotic Defined Daily Dose Equivalents	N/A	1.80 (2.81)	N/A	1.62 (3.03)	1.79 (2.09)	$t_{(55)}$=-0.06, p=0.96
Other Psychotropic Medication (yes/no)	N/A	13/57	N/A	9/31	4/26	x^2= 1.42, p=0.22
Baseline SOFAS [M (SD)]	82.92 (4.20)	41.04 (12.48)	**$t_{(77)}$=16.30, p<0.001**	44.38 (14.31)	37.00 (8.45)	**$t_{(52)}$=2.22, p=0.03**
Follow-up SOFAS [M (SD)]	N/A	59.34 (13.70)	N/A	67.68 (10.08)	48.37 (9.44)	**$t_{(42)}$=6.47, p<0.001**
PANSS-8 Total [M (SD)]	8.0 (0.00)	24.98 (5.76)	**$t_{(82)}$=13.8, p<0.01**	24.07 (4.95)	26.13 (6.57)	$t_{(52)}$=-0.83, p=0.41
PANSS-8 Positive [M (SD)]	3.0 (0.00)	12.35 (2.32)	**$t_{(82)}$=18.6, p<0.01**	12.03 (2.44)	12.75 (2.15)	$t_{(52)}$=-0.94, p=0.35
PANSS-8 Negative [M (SD)]	3.0 (0.00)	7.22 (4.17)	**$t_{(82)}$=5.67, p<0.01**	6.63 (3.76)	7.96 (4.61)	$t_{(52)}$=-0.86, p=0.39
CGI- Severity	1.00	5.19 (0.97)	**$t_{(81)}$=23.15, p<0.01**	5.10 (1.13)	5.29 (0.75)	$t_{(52)}$=-0.85, p=0.40

M, Mean; SD, standard deviation; NS-SEC, national statistics socio-economic classification; CAST, Cannabis Abuse Screening Test; DUP, Duration of untreated Psychosis in Months; NEET, Not engaged in employment education or training; EET, Engaged in employment education or training; SOFAS, Social and Occupational Functioning Assessment Score; PANSS-8, Positive and Negative Syndrome Scale – 8 Item Scale; PANSS-8 Positive, Positive and Negative Syndrome Scale total score for positive symptom items; PANSS-8 Negative, Positive and Negative Syndrome Scale total score for negative symptom items; CGI-Severity, Clinical Global Impression – Severity.

3.1 Glutathione Results

Patients (as a whole group) showed significantly higher glutathione levels versus controls (FEP= 1.68 (0.36), HC= 1.49(0.32); t (85) = 2.46, p = 0.016). As sex was differently distributed between patients and controls, we included sex as a covariate along with diagnosis but noted no significant effect of sex [F(1,84)=0.62, p=0.43], but patient status continued to predict higher GSH levels [F(1,84)=6.61, p=0.012], after adjusting for sex. When comparing the 2 subgroups of patients (NEET/EET) and controls in a one-way ANOVA, glutathione levels were significantly different among the 3 groups (FEP-NEET, FEP-EET and HC) at the $p<0.05$ level [F(2,84)= 4.55, p= 0.01]. Post hoc comparisons using the Sidak test indicated that the mean GSH levels for FEP-EET subjects was significantly higher than healthy controls [[Mean(SD) of GSH: FEP-EET= 1.76(0.37), HC= 1.49(0.32); p=0.01]. However, FEP-NEET subjects [M (SD) =1.60 (0.34)] did not significantly differ from the healthy controls (p= 0.25) or FEP-EET (p= 0.57) (Figure 2).

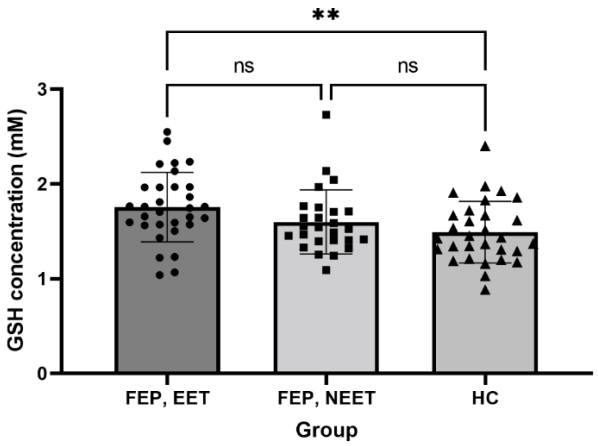

Figure 2: Relationship between Glutathione concentrations (GSH) levels among healthy controls, patients involved in vocational activity (EET) and patients not involved in employment, education, or training (NEET). Statistically significant differences were observed between EET patients and healthy controls.

Analyses restricted to the FEP group revealed GSH measured at baseline predicted the follow-up SOFAS scores (R^2 =0.17, F (1,42)= 8.45, p= 0.006). When covariates age, sex and baseline SOFAS scores were added, the regression model continued to be significant and GSH was the only variable that predicted follow-up SOFAS (R^2= 0.29, F(4,36)= 3.67,

p= 0.013; note n=41 for this analysis as 3 subjects lacked baseline SOFAS scores). GSH levels (β= 0.36, p= 0.016) showed the strongest association out of all independent predictors for follow-up SOFAS, after adjusting for the variance explained by baseline functioning (β= 0.19, p= 0.22), age (β= -0.21, p= 0.15) and sex (β= 0.17, p=0.27). The correlation between adjusted GSH levels and follow-up SOFAS is displayed, stratified by NEET status, in Figure 3 (See Supplementary Table 6 for further regression models demonstrating specificity of GSH - follow-up SOFAS relationship and Table 7 for expanded list of available metabolites and associations with SOFAS scores).

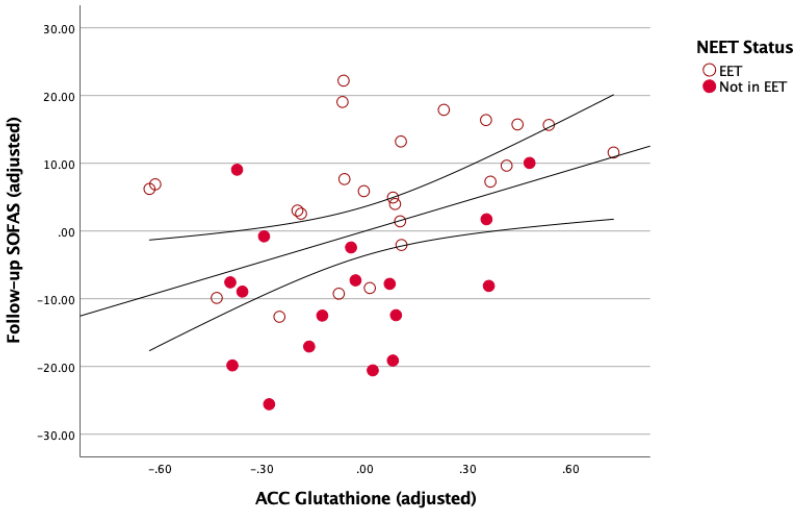

Figure 3: Association between anterior cingulate cortex (ACC) glutathione concentrations and 6-12 months follow up Social and Occupational Functioning Assessment Scale (SOFAS), adjusted for age, sex, and baseline SOFAS. Total sample size = 41 (3 subjects lacked baseline SOFAS scores).

3.2 Analysis restricted to first episode schizophrenia only

Finally, we repeated the above analysis in a subset of patients with a consensus diagnosis of schizophrenia/schizoaffective disorder by 6-12 months, after excluding 5 subjects with major depressive disorder, schizophreniform or bipolar disorder (FES n= 39). Glutathione levels continued to differ significantly among the 3 groups (FES-NEET, FES-EET and HC) at the p<0.05 level [F(2,79)= 4.16, p= 0.02]. Post hoc comparisons using the Sidak test indicated that the mean GSH levels for FES-EET subjects was still significantly higher than healthy controls [[Mean(SD) of GSH in FES-EET = 1.75(0.36), HC= 1.49(0.32);

p= 0.016]. As in the fuller FEP sample , FES-NEET subjects [M(SD) = 1.59(0.35)] did not significantly differ from the healthy controls (p= 0.26) or FES-EET (p= 0.67).

Within the FES group, GSH measure at baseline was positively correlated with follow-up SOFAS scores r(39)= 0.38 [bootstrap 95% CI: 0.15-0.61], p= 0.017. GSH levels, in combination with age, sex and baseline SOFAS scores, continued to predict follow-up SOFAS in the FES group at a trend level, (R^2= 0.24, F(4,32)= 2.47, p= 0.06; note that the total n=37 for this analysis as 2 subjects lacked baseline SOFAS). GSH level (β= 0.32, p= 0.05) continued to be the most prominent independent predictor of the follow-up SOFAS, after adjusting for the variance explained by baseline functioning, age and sex (β= 0.10-0.23, all p> 0.16).

3.3 Prognostic relevance based on binarized GSH levels

To provide clinically relevant information to a patient with FEP whose GSH values have been quantified as described in this study, we performed a median split analysis of the patient group based on ACC GSH values of the entire sample (median= 1.586mM). We then compared the low-GSH and high-GSH FEP groups on the clinically relevant variables of NEET status and SOFAS at follow-up. The proportion of patients with FEP who were vocationally active (i.e., EET) significantly differed based on their baseline GSH status, with high-GSH FEP reporting 68% (23 of 34) in EET, while low-GSH FEP reporting 35% (8 of 23) in EET (Fisher's exact p= 0.018). This translated to an odds ratio of 3.92 (95%CI: 1.34-11.2), and a relative risk of 1.95 (95%CI: 1.13-3.7) in favour of being in employment, education or training if an individual with FEP belonged to the high, instead of low-GSH group at the outset. The mean follow-up SOFAS scores for high-GSH FEP was also significantly higher than low-GSH FEP [Mean(SD) of SOFAS: high-GSH= 62.7(12.9), low-GSH= 53.5 (13.4); t (42)= 2.24; p= 0.03].

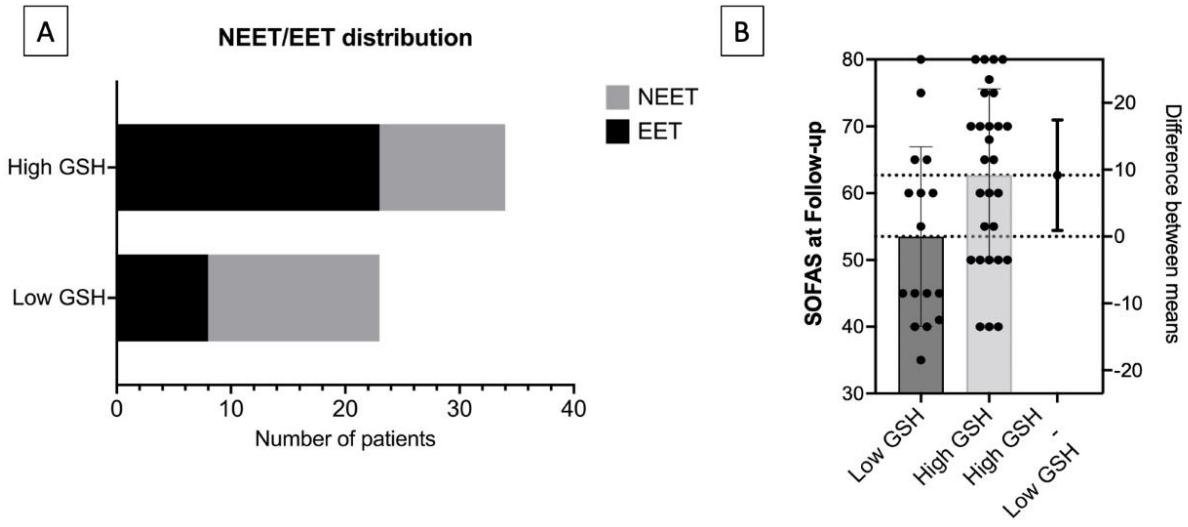

Figure 4: A) Visualization of vocational NEET/ EET distribution of First Episode Psychosis patients, based on high versus low GSH grouping B) Comparison of mean SOFAS score among high vs low GSH grouping.

4.0 Discussion

Using 7T MRS to measure GSH concentration from ACC in untreated FEP subjects followed up over 1 year period, we report 2 major findings: (1) GSH levels are higher in patients in an education, employment or training status than healthy controls; and (2) the baseline GSH levels predict later socio-occupational functioning over and above what can be predicted from baseline functioning, indicating a specific mechanistic role for the central antioxidant in the outcome trajectories following first psychotic episode. Patients with GSH levels that were lower than the median values in the sample were at approximately two times higher risk of being vocationally inactive, with approximately 10 points lower scores in SOFAS. This relationship was specific to GSH, as other metabolites did not relate to vocational functioning (Supplementary Table 3).

Our observed relationship between lower GSH levels and lower SOFAS scores and NEET status is consistent with several prior reports. In an overlapping sample, we previously reported a predictive relationship between low GSH and delayed response to antipsychotics(Dempster et al., 2020). Lack of early response is a critical indicator of long-

term poor outcomes in schizophrenia(Carbon & Correll, 2014; Derks et al., 2010; Lambert et al., 2008). In line with studies linking lower GSH to higher residual symptom burden(Kumar et al., 2020), negative symptoms(Matsuzawa et al., 2008) and cognitive deficits(Wang et al., 2019) in schizophrenia, our observation highlights a prominent 'pathoplastic' role for antioxidant status in shaping the outcomes of this illness. In fact, a recent 7T-MRS study of the ACC reported that patients who fail first-line antipsychotic treatments are more likely to have an intracortical GSH-deficit(Yang et al., 2021). In our study, the presence of higher ACC GSH in FEP may indicate the overall superior treatment responsiveness in this cohort, given their untreated status. Such higher GSH levels have been previously reported in other brain regions in FEP(Berger et al., 2008; Wood et al., 2009). Our observations also establish that the predictive value of GSH relates to 'stable' functioning that emerges 6-12 months later; not the SOFAS scores during acute illness which may be determined predominantly by the florid nature of the presenting psychotic symptoms.

The small to medium effect size difference in patients vs. healthy controls comparison underscores the considerable heterogeneity in intracortical GSH levels in psychosis, in line with several 3T MRS studies that did not report a notable group difference in the ACC(T. K. Das et al., 2019) as well as other regions(Iwata et al., 2021; Lesh et al., 2021). This indicates that a more nuanced interpretation is required with respect to GSH levels in this illness (Palaniyappan, Park, et al., 2021). A meta-analysis of variance that includes the current sample, indicates that inter-individual variability in ACC GSH is increased in patients with psychosis(Palaniyappan, Sabesan, et al., 2021). The observed heterogeneity may relate to individual differences (i.e., subgroups of patients with high or low GSH levels) or stage-specific differences (acute excess, followed by later deficit) (Palaniyappan, Park, et al., 2021). While several exogenous factors may also affect antioxidant levels, there is no evidence for a major role for these confounders in explaining aberrations in glutathione pathway in psychosis(Ballesteros et al., 2013).

An important strength of our study is its longitudinal nature; with the temporal information we can establish that higher GSH levels at the outset predict superior socio-occupational functioning seen over the next 1 year among patients. But a major limitation is the availability of a single time point of GSH levels and lack of data on adherence to treatment throughout the observation period. To establish a more conclusive causal inference, we need longitudinal follow-up studies that capture multiple time points from untreated early stages of psychosis to a stable phase when functional outcome trajectories become more established. Long term follow-up of experimental studies with patients in early stages of psychosis that receive adjunctive NAC will also be illuminating in this regard. We also lacked peripheral and genotyping measures of antioxidant capacity in this cohort; while these measures are more accessible than 7T-MRS, they do not consistently reflect intracortical GSH(Coughlin et al., 2020; Gawryluk, 2011; Zhang et al., 2017). Finally, our inferences are limited to illness-related vocational functioning and not generalizable to vocational functioning in healthy subjects, which may not depend on one's GSH levels.

It is important to note that both schizophrenia and antipsychotics can affect T2 of neurometabolite signal amplitudes(Bracken et al., 2013), but this effect may not affect all metabolites(Tunc-Skarka et al., 2009) and may be age, region and tissue dependent(Kirov et al., 2008). In our study, we estimated metabolite concentrations based on the ratio of metabolite signal amplitude and water amplitude for all reported metabolites. For our reported GSH specific results to be ascribed to a T2-related effect at long-TE, a specific T2 related GSH-water differential must have occurred. Nevertheless, we recommend study-specific measurement of metabolite T2 relaxation times in future studies.

We conclude that in patients with first episode psychosis in whom intracortical GSH levels are higher during the acute phase of psychosis, functional outcomes are superior to those with lower levels, over the next 1 year. Thus, ACC GSH measure may be a useful indicator of resilience to oxidative stress and functional recovery after first

episode of psychosis. Taken together with prior MRS studies from established cases of schizophrenia indicating a profile of treatment failures and residual symptoms in patients with intracortical GSH-deficit, our observation makes a compelling case to investigate the role of pre-emptive antioxidant interventions in early stages of psychosis.

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6.0 Supplementary Materials

Supplementary Table 1: Breakdown of non-antipsychotic psychotropic medications for all patients, and by vocational status.

Medication Class	All Patients (n=57)	EET Patients (n=31)	NEET Patients (n=26)
Antidepressant	7 (12.3%)	4 (12.9%)	3 (11.5%)
Benzodiazepine	4 (7%)	3 (9.7%)	1 (3.8%)
Quetiapine*	3 (5.3%)	1 (3.2%)	2 (7.7%)
Stimulants	2 (3.5%)	2 (6.5%)	0 (0.0%)

EET, Patients engaged in employment, education or training; NEET, Patients not employed in employment education or training

*Quetiapine included as a non-antipsychotic medication if dose was subthreshold for antipsychotic effects, and patients were not taking other antipsychotic medications at the time (where quetiapine would be captured in DDD)

Supplementary Table 2: Comparison of Linewidth, Signal to Noise Ratio and Cramer-Rao Lower bound values by group.

	Linewidth (Hz)	**SNR_{NAA}**	**$CRLB_{Glu}$**	**$CRLB_{GSH}$**
HC (n=30)	7.4 ± 1.1	188.1 ± 35.8	3.2 ± 0.7	9.6 ± 2.2
EET (n=21)	7.8 ± 1.4	183.9 ± 48.7	3.5 ± 1.1	9.9 ± 3.2
NEET (n=26)	7.5 ± 1.5	170.5 ± 40.2	3.7 ± 1.2	11.5 ± 4.4

HC, Healthy Control; EET, Patients engaged in employment, education or training; NEET, Patients not employed in employment education or training; SNR, Signal-to-Noise Ratio; NAA, N-Acetylaspartate; CRLB, Cramer-Rao Lower Bound; Glu, Glutamate; GSH, Glutathione. No significant differences were observed in spectral linewidth (EET vs. NEET, p = 0.32; HC vs EET, p = 0.15; HC vs NEET, p = 0.78) or SNR_{NAA} (EET vs. NEET, p = 0.25; HC vs EET, p = 0.70; HC vs NEET, p = 0.09) among on the three groups.

Supplementary Table 3: Metabolite Concentrations and Cramer-Rao Lower Bound Values by Group. ANOVA comparing HC, EET and NEET metabolite concentrations and T-test Comparing NEET vs EET Groups

	Healthy Control (n=30)		EET Patient (n=31)		NEET Patient (n=26)		One-way ANOVA	NEET vs. EET T- test
Metabolite	**Mean**	**CRLB**	**Mean**	**CRLB**	**Mean**	**CRLB**		
NAA [M (sd)]	10.21 (2.05)	0.97 (0.44)	10.99 (1.52)	1.11 (0.63)	10.57 (1.94)	1.25 (0.91)	F=1.39, p = 0.25	t=0.92, p=0.35
Creatine [M (sd)]	8.36 (1.54)	1.22 (0.23)	9.25 (1.40)	1.31 (0.36)	8.92 (1.61)	1.35 (0.39)	F =2.69, p = 0.078	t=0.80, p=0.42
Choline [M (sd)]	2.40 (0.48)	1.74 (0.38)	2.62 (0.45)	1.85 (0.50)	2.53 (0.57)	1.94 (0.63)	F =1.51, p = 0.23	t=0.62, p=0.53
Myo-inositol [M (sd)]	4.61 (1.08)	3.84 (0.88)	4.74 (1.21)	4.10 (1.35)	4.68 (0.84)	4.42 (1.30)	F =.113, p = 0.89	t=0.20, p=0.84
Scyllo-inositol [M (sd)]	0.26 (0.10)	22.61 (11.85)	0.41 (0.16)	16.39 (5.45)	0.37 (0.14)	17.34 (6.39)	**F =10.43, p = 0.001**	t=0.94, p=0.35
Glutamate [M (sd)]	6.51 (1.37)	3.17 (0.72)	7.04 (1.26)	3.53 (1.08)	6.63 (0.81)	3.62 (1.12)	F =1.64, p =0.20	t=1.41, p=0.16
Glutamine [M (sd)]	1.00 (0.38)	22.42 (15.06)	1.19 (0.41)	21.26 (11.73)	0.96 (0.36)	24.29 (18.51)	**F =3.17, p =0.047**	**t=2.27, p=0.03**
Glutathione [M (sd)]	1.49 (0.32)	9.59 (2.23)	1.76 (0.37)	9.94 (3.16)	1.60 (0.34)	10.72 (3.42)	**F=4.55, p= 0.013**	t=1.63, p=0.10

CRLB, Cramer-Rao Lower Bound; *HC* healthy controls, *EET*, Patients engaged *CRLB*, Cramer-Rao Lower Bound; *HC* healthy controls, *EET*, Patients engaged in employment education or training; *NEET*, Patients not engaged in employment education or training at follow up*; NAA*, N-acetyl aspartate; *M*, Mean; *SD*, standard deviation;

Note: Mean (SD) concentration reported in mM; CRLB Mean (SD) units are measured in %.

Supplementary Table 4: Association Between Drug-use, SOFAS, and Glutathione concentrations Among First Episode Psychosis Patients

Drug Type	SOFAS Baseline	SOFAS Follow up	Glutathione
CAST score	r= -0.16, p=0.28 (n=44)	r= 0.12, p=0.50 (n=34)	r=0.067, p=0.66 (n=47)
Tobacco Use	t=-0.04, p=0.783 (n=54)	t= 0.03, p=0.848 (n=44)	t=0.54, p=0.590 (n=57)
AUDIT Score	r=0.26, p=0.07 (n=48)	r=0.26, p=0.12 (n=38)	r=0.172, p=0.23 (n=51)

CAST Score, Cannabis Abuse Screening Tool score*; AUDIT*, Alcohol Use Disorders Identification Test. Tobacco use was a binary item (yes/no).

Supplementary Table 6: Linear block regression results table, assessing variables association with follow up Social and Occupational Functioning Assessment Scale scores in First Episode Psychosis (Total sample size n= 40, as 1 patient lacked PANSS, and 3 lacked baseline SOFAS scores)

	Model 1			**Model 2**			**Model 3**			**Model 4**		
Variable	B	β	Sig.	B	β	Sig.	B	β	Sig.	B	β	Sig.
Glutathione	15.81	0.39	**0.01**	13.4	0.33	**0.03**	13.3	0.40	**0.04**	16.45	0.40	**0.01**
Age				-0.47	-0.17	0.26	-0.65	-0.23	0.15	-0.56	-0.20	0.19
Sex				4.71	0.13	0.42	4.40	0.12	0.45	6.49	0.18	0.27
SOFAS_BL				0.27	0.26	0.11	0.17	0.16	0.44	0.03	0.03	0.91
PANSS_Pos							-0.76	-0.14	0.50	-0.40	-0.07	0.71
PANSS_Neg							-0.48	-0.16	0.31	-0.19	-0.06	0.68
DSST										0.32	0.33	0.06
R^2	0.148			0.288			0.316			0.389		
Adjusted R^2	0.126			0.207			0.192			0.255		

SOFAS_BL, Baseline Social and Occupational Functioning Assessment Scale; *PANSS_Pos*, Positive and Negative Syndrome Scale 8-item version positive item total*; PANSS_Neg*, Positive and Negative Syndrome Scale 8-item version negative item total; DSST = modified Digit Symbol Substitution Test to assess speed of processing (as described in Rathnaiah et al.(Rathnaiah et al., 2020)). As symptom burden as well as processing speed are important predictors of functioning(Dickinson et al., 2007), we wanted to demonstrate that the specificity of GSH-SOFAS relationship withstands the adjustment for the variance in processing speed in our patient sample.

Supplementary Table 7: Pearson Correlation between metabolite concentrations and baseline SOFAS scores (n=53), follow-up SOFAS scores (n=44), and Change in SOFAS scores (n=41) after follow up among first episode psychosis patients

Metabolite	SOFAS Baseline	SOFAS Follow up	SOFAS Change
NAA [M (sd)]	r=-0.05, p= 0.75	r=0.09, p= 0.55	r=0.04, p= 0.78
Creatine [M (sd)]	r=-0.11, p= 0.41	r=0.09, p= 0.54	r=0.15, p= 0.35
Choline [M (sd)]	r=-0.03, p=0.80	r=0.07, p=0.64	r=0.05, p=0.73
Myo-inositol [M (sd)]	r=0.01, p=0.95	r=0.12, p=0.45	r=-0.02, p=0.91
Scyllo-inositol [M (sd)]	r=0.15, p=0.29	r= 0.14, p=0.36	r=0.11, p=0.50
Glutamate [M (sd)]	r=-0.11, p=0.44	r=0.12, p=0.42	r=0.15, p=0.33
Glutamine [M (sd)]	r=0.09, p=0.48	r=0.29, p=0.06	r=-0.07, p=0.66
Glutathione [M (sd)]	r=0.04, p=0.72	**r=0.41, p=0.006**	r=0.20, p=0.22

M, Mean; *SD*, standard deviation; *NAA*,N-acetylaspartate; *SOFAS*, Social and Occupational Functioning Assessment Score.

5.0 Chapter 5: General Discussion

Throughout this dissertation, we performed a series of analyses assessing baseline predictors of later functional outcome. Specifically, we assessed whether linguistic characteristics, cortical anatomical features, and neuro-metabolite concentrations among patients were associated with baseline clinical severity and later vocational status and social and occupational functioning. While the methods applied in our analyses are well established in the field of psychosis research, their application in a sample of drug naive first episode psychosis patients, the focus on vocational outcome, and the longitudinal design has provided several novel insights into the critical determinants of functional response in psychosis.

In this chapter, we will revisit the key findings from the prior chapters and discuss some broader implications of this line of work as it pertains both to future research pursuits as well as to broader policy and clinical treatment paradigms.

5.1 Summary of Findings

In chapter 2, we presented two manuscripts assessing variables at the manifest scale, specifically elements of produced speech. In manuscript 1, we used output of automated linguistic analysis to determine if linguistic features of acutely psychotic patients differed between patients and healthy controls. Additionally, we assessed whether any linguistic variables were associated with the severity of symptomology. This work revealed that, compared to healthy controls, patients used fewer words than controls overall, used more pronouns in describing neutral scenes (particularly personal pronouns), and that the use of linguistic connectives predicted disorganization. However, this use of connectives was not correlated with severity of other hallmark symptoms (i.e., delusions or hallucinations), cognition or overall social/occupational functioning at presentation suggesting connective use is a specific index of disorganized thinking / positive thought disorder.

In the second manuscript of chapter 2, the linguistic features above (connectives, number of words spoken, and pronoun use), along with analytic thinking

score (a linguistic feature shown to be aberrant in our sample by Silva et al (2021)), were entered into a prototypical constraint-based (PC) algorithm. The PC algorithm yielded a Bayes network (a probabilistic graphical model) showing that while the pure linguistic metrics (connectives, pronouns, analytic thinking) formed a causal network among each other, only number of words spoken (speech production rather than performance) explained vocational inactivity and social functioning after 6-12 months of treatment. Due to considerations that the number of words one employs during a descriptive task may vary based on the social environment during early development (Palaniyappan, 2021) and cognitive capacity (Brébion et al., 2018), we completed subsequent analyses comparing the inclusion of parental socioeconomic status and processing speed as potential latent variables. Despite the inclusion of processing speed and parental SES, (both independently and in combination) the model assessing the influence of speech production without these factors was the most robust in our model comparison. This suggests that the role of reduced speech production is best considered as an independent predictor of early vocational outcomes in first episode psychosis.

In chapter 3, we considered a different scale of measurement in relation to functional outcomes. Moving from the behavioral/speech characteristics of patients (manifest-scale), we assessed how disruptions in brain structure (meso-scale changes) may affect functional outcomes. In this chapter we assessed cortical features from T-1 weighted anatomical MRI that are known to be associated with both early and late developmental insult – specifically cortical thickness and local gyrification index (LGI). Increased LGI in the right precentral gyrus was present in patients compared to healthy controls. When this analysis was restricted to patients only, general linear models revealed associations between wide spread increases in gyrification and worsened clinical presentation at illness onset. While we report no differences between patients and healthy controls on measures of cortical thickness, we reported an association between more severe negative symptoms and increased cortical thickness in the left temporal pole and middle temporal gyrus in analyses limited to patients.

In analyses assessing longitudinal functional outcomes, hypergyrification in parietal regions of the right hemisphere at baseline was associated with vocational inactivity following 6-12 months of treatment.
After adjusting for individual differences in baseline functioning, higher gyrification in superior parietal regions of the right hemisphere trended toward an association with lower follow-up SOFAS scores, however, this association was weak in that it only survived with a liberal cluster inclusion set at $p = 0.05$.

Finally, in chapter 4, we analyzed data at the micro-level of analysis, assessing the impact of neuro-metabolite concentrations in the dorsal anterior cingulate cortex (dACC) on later functional response. We used 7T-magnetic resonance spectroscopy (MRS) with a voxel placed in the dACC to examine how brain metabolite concentrations, specifically glutathione (GSH), affected later social and vocational outcome. Patients, who were vocationally active in the first year of treatment, had significantly higher GSH at illness onset than healthy controls. Follow up SOFAS scores were also significantly higher in patients with higher GSH levels at the outset, after adjusting for various confounds including baseline SOFAS. Patients who were not engaged in employment did not differ from healthy subjects in respect to their GSH levels. This suggests that a surge in antioxidant concentrations early in the psychotic illness may be protective against the neurotoxic effects of acute illness.

5.2 Strengths

Arguably, the largest strength of this dissertation is the untreated status of patients included at the initial observation, and the associated antipsychotic naivety of this dataset. While some minimal antipsychotic exposure was reported (typically less than 3 days on average), restricting inclusion to individuals with less than 2 weeks of life time antipsychotic exposure has two major benefits. First, by assessing antipsychotic naïve patients, we were able to identify symptom severity in the un-impeded course of psychosis. Medication substantially reduces the symptom variance compared to untreated samples; biasing previous work using medicated first episode patients toward

the null hypothesis. Further, several of the baseline prognostic indicators we evaluated in our sample, including speech production (de Boer et al., 2020) and cortical architecture (Nelson et al., 2018), are known to be impacted by antipsychotic medications. However, while the impact of antipsychotics on neuro-metabolite concentrations broadly is understood, glutathione may not be directly impacted by antipsychotic use (Ivanova et al., 2015). By reducing or eliminating this major confound in our analyses, we are better able to understand the true relationship between baseline features and later functional response.

Similarly, our use of ultra-high field strength (7T) MRI and MRS data collection was unique, with limited studies assessing drug-naïve psychosis patients at 7T. The primary benefit in utilizing ultrahigh field strength MRI is a striking increase in signal-to-noise ratio (SNR) (Ladd et al., 2018). When analysing cortical anatomy, higher field strength allows for more precise delineation of grey-white matter boundaries, with lower field strengths potentially over-estimating thickness values (Lüsebrink et al., 2013). This ability to accurately delineate the grey-white matter boundary is a foundational element in accurately calculating both local gyrification indices and cortical thickness. Similarly, the use of high field strength on spectroscopy fidelity is substantial, with higher field strengths resulting in improved separation of metabolite peaks allowing for more precise spectral fitting, and thus increased quantification precision (Bartha et al., 2000). This benefit is most pronounced when examining low concentration metabolites (such as glutamate and glutamine), which are indistinguishable at lower field strengths (Mekle et al., 2009; Tkáč et al., 2009).

Finally, given the nature of following up patients in first-episode psychosis samples, we have also developed a relatively large cohort for our analyses, with a variety of available methods for analysis. With the untreated patient populations ranging in size within this dissertation from n=39 (chapter 2) to n=65 (chapter 3), this work possessed adequate statistical power to reduce type 2 error that likely plagues smaller studies in first episode psychosis (n typically <30). This unique data set also

afforded the opportunity to analyse prognostic indicators of good versus poor outcome at several levels of analysis using unique methodologies. The resulting impact was a more holistic understanding of both the complexities of prognostication, as well as the opportunities for future interventions.

5.3 Limitations

5.3.1 Lack of Continuous Follow up Measurement

While these results have contributed meaningfully to understanding early prognostic indicators of poor vocational functioning, we note a number of limitations. Data collection only assessed patients at two time points: at baseline and upon collection of functioning outcomes (6-12 month follow up). While this type of follow up provided a unique prognostic perspective, the lack of continuous measurement of clinical variables poses a number of potential problems. We were unable to conduct measurement of patient antipsychotic medication or adherence following the baseline assessment. Consistently, early response to medication (Carbon & Correll, 2014) and medication adherence (Ascher-Svanum et al., 2006) are found to be the primary drivers of good outcomes in first episode psychosis. Thus, while no systematic baseline differences in early antipsychotic exposure were found in our study, the potential that our independent variable's relationships with vocational and social functioning is moderated by differences in medication profiles warrants consideration. Further, we did not collect data indicating whether our baseline variables were associated with clinical response/symptom remission at the time of our functional response measurement. While this was not the focus of our study, identifying if these factors are also predictive of clinical remission or are specific predictors of vocational functioning warrants consideration.

5.3.2 Dichotomized Outcome

The use of a dichotomous outcome measure of NEET versus EET status has limitations. Dichotomized vocational status is a gross measurement of overall vocational functioning and fails to account for the complex biological, psychological and social mechanisms that influence a patient's vocational status. Impairments in vocational

functioning may be linked to disturbances at neurocognitive or clinical domains, more complex functional capacity level, or at a higher social/ functional performance level as explained by Sumiyoshi and Sumiyoshi (2015). While using a dichotomous variable does provide limited context, our analyses included data from the Social and Occupational Functioning Assessment scale, which assesses functioning in other domains. We reported consistent associations between NEET and follow up SOFAS, which while predictable given their overlapping nature, provides face validity that engagement in vocational activity is indeed a useful measure of overall functioning.

Arguably, the largest limitation of the dichotomized NEET/EET categorization is that this metric fails to acknowledge the potentially devastating effects of chronic underemployment. While vocational activity is critical to reducing the burden of schizophrenia, this metric fails to identify the degree to which patients are underemployed relative to their premorbid functioning (specifically relative to their educational and occupational histories). Patients who were employed at reduced hours, or in a role below their predicted capacity (e.g., professional school graduate working in service sector positions) would still be classified as having a "good outcome" by a dichotomized metric, while still contributing to the considerable reduction in economic productivity described by Goeree et al. (2005). Further, even among patients who have achieved full employment, EET/NEET status is susceptible to disruption given the recurring episodic nature of psychosis during the first episode (Byrne, 2007). While vocational activity appears to decline following the first episode of psychosis (Marwaha & Johnson, 2004), and thus our measurement of early vocational response may not be sustained, patients who experience better functional response following early treatment are far more likely to experience improved functioning long term (Golay et al., 2021), particularly when medication adherence is maintained (Ascher-Svanum et al., 2006). Thus, while dichotomized vocational outcomes are unable to account for underemployment and may be susceptible to disruption, NEET status is still likely a robust indicator of both short and longer-term functional prognosis.

Despite these limitations, vocational engagement may contribute to the maintenance of overall functioning, beyond what is expected from clinical care alone. The activation, social engagement, and structure provided by vocational engagement likely functions as informal behavioural therapy for both clinical and non-clinical populations (Modini et al., 2016). For decades, research has indicated a strong positive relationship between simple employment status and outcomes for patients with serious mental illness. Post hospital admission, nearly all patients (97%) who were able to retain employment avoided readmission to the hospital. Alternatively, among the non-working cohort, less than half were able to avoid readmission (Brown et al., 1958). While there are likely several factors confounding this relationship, patients with severe mental illness self-report that involvement in paid employment supports recovery, contributes to the development of coping strategies and self-esteem, and provides a sense of meaning to one's life, much as it does for non-clinical samples (Dunn et al., 2008). Further, these qualitative results have been echoed by quantitative findings suggesting that patients involved with vocational activity experience lower symptomology, better functioning, reduced rates of relapse, and reduced health care utilization (Adebiyi et al., 2018; Drake et al., 2013; Schennach, Obermeier, et al., 2012; Schennach, Riedel, et al., 2012). While selection effects are likely at play, and questions regarding the direction of these associations exist, the mere act of obtaining and maintaining employment is a directly measurable treatment goal that presents significant clinical, economic and humanitarian benefits. Thus, despite the limitations of a dichotomized vocational status variable, it also functions as a strong composite measure of "good functioning" and represents a valid treatment goal in early treatment.

5.4 Clinical Augmentation strategies

When applying the findings of this dissertation to the broader clinical care of first episode psychosis patients at risk for poor functioning, a number of potential avenues worth continued exploration emerge. Over the past several decades, several augmentation strategies in schizophrenia care have been developed, yet often are

underutilized until a largely intractable chronic course of poor functioning is established. If clinicians utilize these augmentation strategies earlier in the course of illness for patients at risk of poor outcome, even modest direct benefits can have a significant downstream effect on functioning.

The identification of a causative link between speech production and functional response following treatment, suggests that speech production should be monitored closely at illness onset. Specifically, clinicians may consider using an automated speech analysis software and a brief naturalistic language assessment tool to identify deficits in speech production that fall below the threshold of typical clinical rating scales, but may no less impede functional improvement. However, this would require the development of robust speech norms across varying languages, and a method of rapid comparison for this technique to be utilized. In cases where reduced speech production is identified, relying exclusively on first line pharmaceutical treatment may be inadequate (Aleman et al., 2017). While no direct treatment for poverty of speech exists, when speech production fails to improve with first-line antipsychotic treatments, second line treatments such as clozapine may be warranted. Largely due to the severe side effect profile, clozapine is underutilized (Nucifora et al., 2017), yet it is the most effective antipsychotic in addressing primary negative symptoms, with some evidence suggesting direct (though modest) benefits to speech production among patients who were non-responsive to previous antipsychotic trials (Subramanian et al., 2017). Similarly, cortical stimulation strategies may be implemented to address negative symptoms, including poverty of speech, with varying success. ECT for example, has been shown to be effective in the reduction of schizophrenia symptoms in general (Zierhut et al., 2021), and in reducing poverty of speech specifically (Ipekcioglu et al., 2018). Unfortunately, like clozapine, ECT is largely reserved for treatment refractory schizophrenia. While less invasive forms of cortical stimulation, such as repeated transcranial magnetic stimulation (rTMS) are available, their direct impacts on negative symptoms and speech production

in schizophrenia samples are less clear(Aleman et al., 2018), with stronger effects among more severe patients (Shi et al., 2014).

Unfortunately, patients who are prescribed either clozapine or cortical stimulation are typically experiencing the most functionally impaired course of illness, and thus are unlikely to experience significant benefits to their vocational prospects with the modest expected improvements. However, if continued emphasis is placed on identifying key predictors of functional prognosis, and clinicians are able to identify patients who are on the cusp of good functioning, the earlier use of these augmentation strategies may be warranted in some cases, despite the potential for adverse events.

Our work on speech production indicated that the most verbose patients experienced more positive vocational outcomes, rather than deficits experienced by those with significantly impoverished speech. While the association between poor outcomes and poverty of speech is understood to be related to reduced symptom remission in negative domains (Yalınçetin et al., 2016), and underlying cognitive deficits (Fervaha et al., 2016), these findings fail to make an affirmative case for good vocational outcomes among those producing more speech. The benefit of high speech production to vocational prospects, may instead, be tied to ratings of these patients as more socially adept and employable. In both healthy control and patient samples, social skills are highly correlated with gaining and retaining competitive employment (Tsang et al., 2000). This suggests a potential utility of social skills training (such as communicative-pragmatic training (Bosco et al., 2016)) and employment support in first episode psychosis clinics to improve vocational outcomes, particularly among patients who are on the fringes of employability. Social skills training has been previously identified as an effective strategy in offsetting mild negative symptoms in patients (Turner et al., 2018), and may improve clinical ratings of occupational performance (Ercan Doğu et al., 2021). When employment and social support were applied to real world vocational outcomes, substantial improvements to outcomes were identified

(Rinaldi et al., 2010), even among patients with a more chronic course (Cheng & Yen, 2021). Social and employment skills training programs may therefore provide opportunities for patients who would otherwise not experience the long term benefits of employment.

We also note in chapter 2, a putative causal link between processing speed and employment status using Bayes Factor (BF_{10} = 3.52; EET mean = 57.87, SD = 14.72; NEET mean = 46.92, SD = 12.14). Similarly, in chapter 4, our Linear block regression results showed that in a model predicting follow up SOFAS scores (included glutathione, age, sex, baseline sofas, PANSS-Positive sub score, PANSS-Negative sub score, and digit symbol substitution scores), DSST scores were marginally significant (β=0.33, p=0.06) at predicting follow up SOFAS. While not directly part of the present dissertation, these findings suggest that processing speed has a strong likelihood of being related to later functional outcomes in our sample, which is consistent with the extant literature (Dickinson et al., 2007; Dickinson & Coursey, 2002; Ojeda et al., 2008). While significant deficits in processing speed are ubiquitous in schizophrenia samples (Dickinson et al., 2007), Initial evidence suggests that cognitive remediation may be able to play a minor role in offsetting these effects (Sartory et al., 2005). In a systematic review, inpatients who underwent cognitive remediation training did show significant improvements in processing speed, with some indication that this is related to social and vocational functioning (Cella et al., 2020). It is highly likely that the combination of cognitive remediation skills in conjunction with social skills and employment training will help improve job performance and is likely to improve vocational engagement over time.

Finally, in chapter 4, we briefly discussed the modifiability of intra-cortical glutathione levels. Several clinical trials have reported on the safety and efficacy of the glutathione precursor N-acetylcysteine (NAC) at boosting intracortical GSH levels in both psychosis, and other clinical samples (Holmay et al., 2013). While it's impact on vocational functioning has not been assessed, the use of NAC as an adjunct treatment to

antipsychotics has been shown to lead to statistically significant improvements in both clinical symptoms and working memory among patients with psychosis(Yolland et al., 2020). While these results are promising, the effects are modest, likely due to higher than average variability in ACC GSH levels in patients with psychosis (Palaniyappan et al., 2021). It is plausible that a subset of patients exhibiting anti-oxidant deficits in first episode psychosis are primarily reaping the potential benefits of NAC. By identifying and addressing these deficits early in the treatment course, before oxidative damage accumulates, we may be able to improve the clinical, cognitive, and downstream functional deficits experienced by patients. To establish a more conclusive causal inference, we need longitudinal follow-up studies that capture multiple time points from untreated early stages of psychosis to a stable phase in NAC treated and placebo groups. Further, evaluation of potential positive interactions between NAC use and additional psychosocial augmentation are warranted.

It is worth nothing when linking biological (microsystem) features to vocational/functional outcomes, efforts should be taken to consider how these narrow patient factors interact with the macro level/ exosystem (i.e., the broader social context of a patient) in forming observed relationships (see: bio-ecological model, Bronfenbrenner & Ceci, 1994). For example, at the individual level when experiencing a healthy state, a compensatory effect of certain social contexts (e.g., superior parental socioeconomic functioning) may offset a particular biologic risk (such as hypergyrification or low GSH), precluding the identification of this risk factor in analyses. However, patients may experience reductions in this compensatory process, revealing the underlying deleterious biological influence (micro-macro level link). Similarly, during widespread social constraints that fundamentally limit opportunities to all (e.g., pandemic, recession) the role of otherwise trivial biological influences on individual differences in outcome may emerge because of ‘two hits’ –a biologic risk in addition to the constrained social environment. Similarly, certain advantageous social environments (e.g. a period generalised economic uplifting) may reduce the influence of external

factors on individual functional outcomes, but will result in a corresponding increase in the magnitude of effect of microsystem influences have on community functioning. In this regard, our findings linking microsystem to functional/social outcomes do not imply that improving superior functional outcomes necessitates a micro-level or biological change. Instead, this conceptual framework suggests various points of interventions at biological, psychological and sociologic levels.

Ultimately, though no single (currently available) intervention seems to radically increase employment rates (or broader community functioning) among patients with first episode psychosis or schizophrenia, there is a lot of reason for optimism. Firstly, augmentation strategies, though individually limited in their magnitudes of effect, may play a critical role in altering the functional trajectory of patients where progress has otherwise stalled. Secondly, the apparent failure of current strategies, in part, relate to our inability to sensitively identify and quickly interrupt the pathways that lead to these poor outcomes. Focussing in on prognostic indicators of good versus poor functional response can identify the patients most likely to develop functional benefits from adjunct treatment approaches, and improve the success s rates of focussed interventions.

5.5 Conclusions

The manuscripts within this dissertation have presented several novel findings. To our knowledge, we are the first to report in early psychosis 1. A causal association between baseline speech production and later vocational engagement, 2. Associations between gyrification and later vocational engagement, and 3. Associations between glutathione in the dorsal anterior cingulate cortex and later vocational and social functioning. These findings may represent the early steps in identifying clinically useful prognostic classifications to identify patients at risk for poor vocational outcomes. Continued efforts to subtype patients based on their prognostic profiles may allow clinicians to augment typical treatment approaches earlier in the course of illness, before a chronic and debilitating course is established, possibly altering the trajectory of

a patient's illness and reducing their disability burden for the remaining decades of their lives.

5.6 Additional Work from the Tracking Outcomes in Psychosis (TOPSY) Study

While the work included within this dissertation represents a range of methods utilized across the TOPSY study, it by no means covers the breadth of investigation from this ongoing project. A number of projects utilizing data from the TOPSY study have been published. For readers interested in a more comprehensive understanding of the TOPSY study and lines of inquiry within, we have appended a reading list below.

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Appendices

Appendix A: Research Ethics Board Approval for "Tracking Outcomes In Psychosis

Western Research

Date: 4 July 2022

To: Dr. Hooman Ganjavi

Project ID: 108268

Review Reference: 2022-108268-68325

Study Title: The Pathophysiology of Thought Disorder in Psychosis (TOPSY)

Study Sponsor: Lawson HRI

Application Type: HSREB Amendment Form

Review Type: Delegated

Meeting Date / Full Board Reporting Date: 26/Jul/2022

Date Approval Issued: 04/Jul/2022 17:19

REB Approval Expiry Date: 24/Oct/2022

Dear Dr. Hooman Ganjavi ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date
Western Protocol TOPSY 4_Jul_2022	Protocol	04/Jul/2022

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Electronically signed by:

Patricia Sargeant, Ethics Office [redacted] on behalf of Dr. Philip Jones, HSREB Chair, 04/Jul/2022 17:19

Reason: I am approving this document.

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

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Expected presentation date	Dec 2022
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Appendix C: Curriculum Vitae

Curriculum Vitae: Michael MacKinley

Education

Western University
Neuroscience, Schulich School of Medicine and Dentistry, 2022
University of Waterloo
MSc. School of Public Health and Health Systems, 2017
Kings University College at Western University
B.A. (Honors), Psychology
Graduation with Distinction

Awards & Honors

2022 - Canada Health Student Research Forum
National Poster Competition, Award of Excellence (Silver)
2022 - Top Cited Author, 2020-2021
Wiley, Early Intervention in Psychiatry
2021 - Jonathan and Joshua Memorial Scholarship
Value: $25,000.00
2020 - Jonathan and Joshua Memorial Scholarship
Value: $25,000.00
2019 - Parkwood Institute Research – Student Endowment
Value: $10,500
2015- Canadian Evaluation Society Student Case Competition
National Finalist (Top 3 Finisher)
2015 - Three Minute Thesis, University of Waterloo
Applied Health Sciences Faculty, 1st place
2014 - Canadian Evaluation Society Student Case Competition
National Finalist (Top 3 Finisher)
2010-2013 - Deans Honor List
Kings University College, UWO

Productivity

Manuscripts:

Mackinley, M., Ford, F., Jeon, P., Theberge, J., & Palaniyappan, L. (2022). Central Oxidative Stress and Early Vocational Outcomes In First Episode Psychosis: A 7-Tesla Magnetic Resonance Spectroscopy Study of Glutathione. Scz. Bulletin. *Accepted Manuscript.* **Impact Factor: 9.30**. My role: recruitment, cognitive assessment, clinical assessment, longitudinal outcome tracking and analysis of data, writing of manuscript draft and responses to reviewers.

Mackinley, M., Chan, J., Ke, H., Dempster, K., & Palaniyappan, L. (2019). Linguistic determinants of formal thought disorder in first episode psychosis. Early Intervention in Psychiatry. Impact Factor: 3.32 My role: recruitment, cognitive assessment, and analysis ofdata, writing of manuscript.

MacKinley, M., Sabesan, P., & Palaniyappan, L. (2020). Deviant cortical sulcation related to schizophrenia, but not cognitive deficits,likely predate brain development in the second trimester. Translational Neuroscience, 11(1):236-240. Impact Factor: 1.56. My role: analysis of data, writing of manuscript.

Alonso-Sánchez, M.F., Ford, S.D**., MacKinley, M.** *et al.* (2022). Progressive changes in descriptive discourse in First Episode Schizophrenia: a longitudinal computational semantics study. *Schizophr* **8,** 36

Liang L, Silva AM, Jeon P, Ford SD, **MacKinley M,** Théberge J and Palaniyappan L (2022) Widespread cortical thinning, excessive glutamate and impaired linguistic functioning in schizophrenia: A cluster analytic approach. Front. Hum. Neurosci. 16:954898. doi: 10.3389/fnhum.2022.954898

Silva, A., Limongi, R., **MacKinley, M.,** Ford, S.D., Alonso-Sanchez, MF., Palaniyappan, L. (2022). Syntactic complexity of spoken language in the diagnosis of Schizophrenia: A probabilistic Bayes Network Model. *Schiz. Res.* 22:S0920-9964(22)00245-6. Impact Factor 4.8. My Role: Data collection, assisted with data analysis, writing of methods section, contribution to discussion section, editing of manuscript.

Dempster, K., Jeon, P., **MacKinley, M**., Williamson, P., Théberge, J., & Palaniyappan, L. (2020). Early treatment response in first episode psychosis: a 7-T magnetic resonance spectroscopic study of glutathione and glutamate. Molecular Psychiatry, 1-11. ImpactFactor: 11.973 My role: recruitment, cognitive assessment, and analysis of demographic data, contributed to writing of manuscript methods section.

Dey, A., Dempster, K**., MacKinley, M**., Jeon, P., Das, T., Khan, A., Gati, J., & Palaniyappan, L. (2021). Conceptual disorganization andredistribution of resting-state cortical hubs in untreated first-episode psychosis: A 7T study. Npj Schizophrenia, 7(1), 1–9. https://doi.org/10.1038/s41537-020-00130-3. Impact Factor:4.3 My role: recruitment, cognitive assessment and clinical assessment, development of clinical and cognitive database and analysis of demographic data. Contributed to editing and preparation of manuscript

Jeon P, **Mackinley M**, Théberge J, Palaniyappan L. The trajectory of putative astroglial dysfunction in first episode schizophrenia: A longitudinal 7-Tesla MRS study. Scientific Reports, 2021 Nov 16; 11 (1): 22333, Data collection and clinical assessment, DOI: 1038/s41598-021-01773-7.

Jeon P, Limongi R, Ford SD, Branco C, Mackinley M, Gupta M, Powe L, Théberge J, **Palaniyappan L**. Glutathione as a molecular marker of functional impairment in patients with at-risk mental state: 7-Tesla 1H-MRS study. Brain Science, 2021 Jul 17; 11 (7): 941, Data collection, clinical assessment, editing of manuscript, DOI: 10.3390/brainsci11070941.

Jeon, P., Limongi, R., Ford, S. D., **Mackinley, M**., Dempster, K., Théberge, J., & Palaniyappan, L. (2021). Progressive Changes in Glutamate Concentration in Early Stages of Schizophrenia: A Longitudinal 7-Tesla MRS Study. Schizophrenia Bulletin Open, 2(sgaa072). https://doi.org/10.1093/schizbullopen/sgaa072 Impact factor: 7.57. My role: recruitment, cognitive assessment, and analysisof demographic data, contributed to writing of manuscript methods section.

Limongi, R., Jeon, P., **Mackinley, M.,** Das, T., Dempster, K., Théberge, J., ... & Palaniyappan, L. (2020). Glutamate and Dysconnectionin the Salience Network: Neurochemical, Effective-connectivity, and Computational Evidence in Schizophrenia. Biological Psychiatry. Impact Factor: 11.5 My role: recruitment, cognitive assessment, and analysis of demographic data, contributed to writing of method section, edited first manuscript draft.

Limongi, R., **Mackinley, M**., Dempster, K., Khan, A. R., Gati, J. S., & Palaniyappan, L. (2020). Understanding the Effect of Left PrefrontalStimulation on Positive Symptoms of Schizophrenia: A Dynamic Causal Modeling Study of Ultra-high field (7-Tesla) Resting-state fMRI. bioRxiv. My role: recruitment, cognitive assessment, and analysis of demographic data, contribution to writing of method section, editingof manuscript drafts.

Limongi, R**., Mackinley, M**., Dempster, K., Khan, A. R., Gati, J. S., & Palaniyappan, L. (2021). Frontal–striatal connectivity and positivesymptoms of schizophrenia: Implications for the mechanistic basis of prefrontal rTMS. European Archives of Psychiatry and Clinical Neuroscience, 271(1), 3–15. https://doi.org/10.1007/s00406-020-01163-6 Impact Factor: 3.42m My Role: collection of all imaging, clinical and cognitive data, edit and preparation of manuscript.

Pan, Y., Pu, W., Chen, X., Huang, X., Cai, Y**., MacKinley M**., ... & Palaniyappan, L. (2020). Morphological Profiling of Schizophrenia: Cluster Analysis of MRI-Based Cortical Thickness Data. Schizophrenia bulletin, 46(3), 623-632. Impact Factor: 7.575. My role: Assistedwith methods development and analysis, contributed significantly to editing of initial manuscript.

Park, M. T. M., Jeon, P., Khan, A. R., Dempster, K., Chakravarty, M. M., Lerch, J. P**., MacKinley, M**., Théberge, J., & Palaniyappan, L. (2021). Hippocampal neuroanatomy in first episode psychosis: A putative role for glutamate and serotonin receptors. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 110, 110297. https://doi.org/10.1016/j.pnpbp.2021.110297 Impact Factor:4.3. My role: recruitment, cognitive assessment, and analysis of demographic data, contributed to writing of manuscript methods section.

Penner, J., Jeon, P**., Mackinley, M**., Das, T., Dempster, K., Théberge, J., & Palaniyappan, L. (2020). Glutamate Levels Correlate WithAnomalous Brain Functional Networks in First-Episode Psychosis Participants. Biological Psychiatry, 87, S399. https://doi.org/10.1016/j.biopsych.2020.02.1019 Impact Factor:12. My role: recruitment, cognitive assessment, and analysis of demographic data, Assisted with manuscript preparation.

Silva, A., Limongi, R., **MacKinley, M**., & Palaniyappan, L. (2020). Small Words That Matter: Linguistic Style and Conceptual Disorganisation in Untreated First Episode Schizophrenia. Schizophrenia Bulletin Open.2(1). My Role: involved in the collection andanalysis of linguistic and demographic variables.

Conference Presentations:

Mackinley, M., Ford, F., Jeon, P., Theberge, J., & Palaniyappan, L. (2022). Central Oxidative Stress and Early Vocational Outcomes In First Episode Psychosis. Accepted Poster Presentation: Canadian Health Student Research Forum, National Poster competition (Award of Excellence). CHSRF is a national competition to present health research open to the top 5% of Canadian PhD students presenting work from across the CIHR portfolio.

Mackinley, M., Ford, F., Jeon, P., Theberge, J., & Palaniyappan, L. (2022). Central Oxidative Stress and Early Vocational Outcomes In First Episode Psychosis. Accepted Oral Presentation at the Schizophrenia International Research Society (SIRS) 2022; 2022.

Mackinley M, Yunzhi, P., Jeon, P., Palaniyappan L. Association between Aberrant Gyrification, Symptom Severity and Social and Vocational Functioning in Drug-Naive First Episode Psychosis. Accepted poster presentation at the Schizophrenia International Research Society (SIRS) 2022; 2022

Mackinley M, Chan J, Ke H, Dempster K, Palaniyappan L. Linguistic determinants of formal thought disorder in first episode psychosis.Schizophrenia International Research Society (SIRS) 2019; 2019

MacKinley, M.L., Ijaz, M., Iranipirast, M., Tang, G., Costa, S., & Tyas, S.L. (2015). The impact of education and apolipoprotein E oncognitive reserve is modified by late life cortical atrophy. Poster presented at the annual Canadian Society for Epidemiology and Biostatistics Conference, Mississauga, Ontario.

MacKinley, M.L., Ijaz, M., Iranipirast, M., Tang, G., Costa, S., & Tyas, S.L. (2015). The impact of education and apolipoprotein E oncognitive reserve is modified by late life cortical atrophy. Poster presented at the annual Canadian Society for Epidemiology and Biostatistics Conference, Mississauga, Ontario.

Swan-Merrison J, McCauley K**, MacKinley M**, Barden C, Khan Hu, Khan Ha, Palaniyappan L. What the (?!@#) happened? Creativestrategies to engage youth in a first episode program: interactive psychosis workbook. 11th International Conference on Early Intervention in Mental Health; 2018.

Limongi R, Jeon P, Dempster K, **Mackinley M**, Theberge J, Palaniyappan L. Aberrant sensory precision in firstepisode psychosis: A 7-Tesla resting-state fMRI and stroop-task study. Schizophrenia International Research Society (SIRS) 2019; 2019.

Dey A, Das T, Dempster K, **Mackinley M**, Jeon P, Gati J, Khan A, Palaniyappan L. Early stages of conceptual disorganisation and redistribution of cortical hubs in untreated first episode psychosis; A 7T fMRI study. Schizophrenia International Research Society (SIRS)2019; 2019

Pan Y, Das T, Khan A, Dempster K**, Mackinley M**, Palaniyappan L. Acute conceptual disorganization in untreated first-episodepsychosis: A 7T Dti study of cingulum trac. Schizophrenia International Research Society (SIRS) 2019; 2019.

Das, T. Dempster, K., **Mackinley, M.L**., Jeon, P., Theberge, J., Gati, J., Khan, A., Palaniyappan, L. (2018). Ultra-High Field Morphometryin Drug-Naïve First Episode Psychosis. Poster accepted for presentation at the Schizophrenia International Research Society Biennial Conference, Florence, Italy.

Park MT, Das T, Khan A, Dempster K, Chakravarty MM**, Mackinley M**, Palaniyappan L. Hippocampal subfield morphology and myelination in untreated first episode psychosis: A 7T MRI study. Schizophrenia International Research Society (SIRS) 2019; 2019

Das, T. Dempster, K., **Mackinley, M.**L., Jeon, P., Theberge, J., Gati, J., Khan, A., Palaniyappan, L.(2018). Structural Covariance in Drug-Naïve First Episode Psychosis: An Ultra-High Field MRI Study. Poster accepted for presentation at the Schizophrenia InternationalResearch Society Biennial Conference, Florence, Italy.

Iranipirast, M., Ijaz M., **MacKinley, M.L.**, Costa, S., Tyas, S.L. (2015). Is educational attainment or high school performance a better predictor of dementia? Poster presented at the annual Canadian society for Epidemiology and Biostatistics Conference, Mississauga,Ontario.

Ijaz, M., Dubin, J., Iranipirast, M., **MacKinley, M.L**., Costa, S., Tyas, S.L. (2015). Does high educational attainment and academic performance contribute to shorter survival in individuals with Alzheimer pathology? A test of the cerebral reserve hypothesis. Posterpresented at the annual Canadian society for Epidemiology and Biostatistics Conference, Mississauga, Ontario.

Research and Teaching Employment:

2016-2022 - Research Coordinator, PEPP-London, London Health Science Centre
2021-2022 - Teacher's Assistant, Western University, Neuro3000
2018-2021 - Teachers Assistant, Western University, Neuro4000
2016-2016 - Student Researcher, Elgin-St Thomas Public Health
2014-2015 - Teacher's Assistant, University of Waterloo, Intro to Gerontology
2014-2015 - Research Assistant, University of Waterloo, The Nun Study