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Data-driven Neuroanatomical Subtypes in Various Stages of Schizophrenia: Linking cortical thickness, glutamate, and language functioning

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Abstract

The considerable variation in the spatial distribution of cortical thickness changes has been used to parse heterogeneity in schizophrenia. We aimed to recover a ‘cortical impoverishment’ subgroup with widespread cortical thinning. We applied hierarchical cluster analysis to cortical thickness data of three datasets in different stages of psychosis and studied the cognitive, functional, neurochemical, language and symptom profiles of the observed subgroups. Our consensus-based clustering procedure consistently produced a subgroup characterized by significantly lower cortical thickness. This ‘cortical impoverishment’ subgroup was associated with a higher symptom burden in a clinically stable sample and higher glutamate levels with language impairments in the first-episode sample. Overall, cortical thinning is more prevalent among patients, especially those with glutamate excess and speech dysfunctions in the early stages and higher residual symptom burden at later stages.

Keywords

Hierarchical cluster analysis, Schizophrenia, Neurocognition, Cortical thickness, Magnetic resonance spectroscopy, Heterogeneity, First-episode psychosis, Language impairment

Summary for Lay Audience

Schizophrenia is one of the most disabling and chronic mental illnesses. Patients, despite having the same diagnosis, can have very different clinical histories, symptom profiles and treatment responses. This has posed challenges for clinicians to provide personalized treatment plans. Therefore, researchers have made efforts to classify patients into subtypes, so that this illness can be better understood and characterized. The current thesis pursued this line of effort and aimed to find patient subtypes based on brain features. Compared to clinical features that could be subjective and fluctuate over time, brain features are a more stable and objective indicator of cognitive and mental health status. For example, cortical thickness, the thickness of the outer layer of the brain, is found to be abnormal in some patients with schizophrenia. It may be an important first step to differentiate patients with a healthy cortical thickness profile from patients with lower cortical thickness, because these two patient subgroups may represent distinct origins of the same illness.

Cluster analysis is a useful mathematical tool to identify patient subgroup(s) with different brain profiles. It can assign patients with similar profiles to the same group, and then we can determine when the subgroups are too distant to belong to one. In our study, we found that there were two subgroups of patients in both chronic and first-episode schizophrenia. One subgroup showed no difference in cortical thickness patterns from healthy controls, while the other displayed cortical thinning in multiple regions of the brain. In chronic and stable schizophrenia, patients with extensive cortical thinning experienced a higher residual symptom burden. In first-episode schizophrenia, this subgroup showed an abnormal level of glutamate. Glutamate is a molecule in our brain that sends signals to excite brain cells. This subgroup also had impaired speech production such as simplicity in the structures of the sentences, and reduced cohesion between sentences.

To conclude, a patient subgroup with widespread cortical thinning may represent a distinct subtype which is stable across various stages of schizophrenia with dysregulated neurochemical levels and abnormal language production. It may be important to customize mental health care strategies for this subgroup of patients.

Co-Authorship Statement

This thesis was adapted from two manuscripts, “Cortical impoverishment in a stable subgroup of schizophrenia: Validation across various stages of psychosis”, published in May 2022 on Schizophrenia Research; and “Widespread Cortical Thinning, Excessive Glutamate and Impaired Linguistic Functioning in Schizophrenia: A Cluster Analytic Approach”, published in August 2022 on Frontiers in Human Neuroscience. Walter Heinrichs, Lena Palaniyappan and Peter Francis Liddle supervised the individual study data collection and analysis. Jean Theberge designed spectroscopy protocol and supervised Peter Jeon for MRS data acquisition and analysis. Sabrina Danielle Ford and Michael MacKinley recruited patients and collected clinical and speech data. Angelica M. Silva analyzed the speech data. Liangbing Liang performed MRI data analysis and statistical analysis, designed the figures, authored Chapters 1, 2 & 4, and co-authored Chapter 3 with Angelica M. Silva under the supervision of Lena Palaniyappan.

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Chapter 1 Introduction

Chapter 1 Introduction provides an overview of symptoms, course, outcome, treatment, etiology, and neurobiological basis of schizophrenia. This chapter will discuss and emphasize schizophrenia as a thought disorder (with language dysfunctions) as well as a brain disorder (neuroanatomical and neurochemical abnormality), with a focus on data-driven approaches to investigate its heterogeneous nature.

1.1 Symptoms of Schizophrenia

Schizophrenia is a severe and chronic mental illness that affects the patients' perception, cognition, emotion, language production and thought processes (Ross et al., 2006). According to the most recent edition, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), key symptomatic characteristics of schizophrenia include delusions, hallucinations, disorganized speech/behaviours, and negative symptoms (Tandon et al., 2013b). Psychotic symptoms such as hallucination (sensations without external stimuli), and delusion (false and rigid beliefs), are also described as positive symptoms, whereas negative symptoms describe the absence of healthy emotions and behaviours, such as lack of emotional expression, social withdrawal, inattention to environmental inputs, and poverty of speech (American Psychiatric Association, 2013). Furthermore, there is a third group of symptoms, termed cognitive symptoms. Compared to healthy populations, patients diagnosed with schizophrenia have impaired cognitive abilities in multiple domains including working memory, processing speed, social cognition, attention/vigilance and executive functioning (Ross et al., 2006).

1.2 Treatment, Outcome and Course of Schizophrenia

Schizophrenia affects around 1% of the population (McGrath et al., 2008) and typically develops around late adolescence and early adulthood (Kirkbride et al., 2012). Before illness onset, patients in the prodromal phase may start to perform poorly in academic, employment or social settings (Møller & Husby, 2000) as well as experiencing brief psychotic-like symptoms (Fusar-Poli, Borgwardt, et al., 2013). Psychotic symptoms are

often episodic and can be effectively alleviated by antipsychotic medications in around 70% of patients (Elkis, 2007), but the response to treatment varies greatly (Case et al., 2011). In contrast, negative symptoms and cognitive impairments tend to persist in chronic schizophrenia despite medications (Jauhar et al., 2022). Due to the presence of psychotic, negative and cognitive symptoms, patients often have difficulties in occupational functioning, personal relationships or self-care (Bowie & Harvey, 2006; Tandon et al., 2013b) and only around 15%-40% of patients have good functional outcome according to a few meta-analyses (Jauhar et al., 2022). Early intervention has been found to be beneficial for both clinical and functional recovery (Correll et al., 2018).

1.3 Schizophrenia as a Thought Disorder

Formal Thought Disorder (FTD) describes impairments in organizing thoughts logically and purposefully, and expresses frequently in schizophrenia (Ayer et al., 2016; Jerónimo et al., 2018). In general, FTD is commonly characterized by impoverishment (e.g., slow thinking) and disorganization (e.g., thought interference) of thoughts. FTD can manifest itself as overt communication difficulties and language dysfunctions (Kircher et al., 2018b; Liddle, Ngan, Caissie, et al., 2002a). Impoverishment of speech describes reduced quantity in speech contents, conceptualized as negative FTD; while disorganization of speech is characterized by incoherence and looseness of language use, conceptualized as positive FTD (Kircher et al., 2018b; Palaniyappan, 2021a). The most affected domains of linguistic functioning included semantic, syntactic and pragmatic levels of language use (Covington et al., 2005; Kircher et al., 2018b).

Thought disorder and speech production impairment can be measured clinically or computationally. Clinical rating scales such as the Thought and Language Disorder scale (Kircher et al., 2014) or the Thought and Language Index (Liddle, Ngan, Caissie, et al., 2002a) capture a variety of FTD symptoms. Additionally, thought and speech production deficits can be objectively quantified using novel computational approaches combined with linguistic analyses. For example, natural language processing (NLP) uses computer algorithms to extract linguistic features (e.g. syntactic complexity, word type usage), and has been found to capture subtle language disturbances in schizophrenia (Tang et al., 2021). Specifically, patients with schizophrenia tend to have lower similarity within

neighbouring sentences, reduced semantic density, shorter sentence length and lack of referential word use (Corcoran et al., 2020).

1.4 Schizophrenia as a Brain Disorder

The etiology of the illness is not yet known, but it is widely agreed that a wide range of genetic and environmental factors lead to changes in neurochemistry, structure or functions of the brain, which lead to the onset of psychotic symptoms (Tsuang, 2000). According to large-scale genome-wide association studies (GWAS), schizophrenia is heritable, with hundreds of common genetic variants that increase the risk for psychosis by a very small proportion, and a few rare genetic variants that have large effect sizes (Smeland et al., 2020). As for environmental vulnerability factors, it has been reported that birth complications, immigration, exposure to viruses during the prenatal period, and stressful life events can increase the risk for schizophrenia (Tsuang, 2000). The genetic and environmental risk factors leading to the condition vary across patients and this has complicated etiologic research that aims to pinpoint risk factors and the neurobiological causes of the illness.

As various brain imaging tools and analytic methods become readily available, we are now able to measure the molecules, structures, functions, and physiology of the brain, a large amount of evidence shows that schizophrenia is associated with abnormality in the brain (Ross et al., 2006) and is a biologically based brain disease. One of the brain imaging tools used constructs 3-dimensional images of the brain to uncover the brain structures including grey matter, white matter, ventricles, and subcortex. For example, computerized tomography (CT) and magnetic resonance imaging (MRI) can both inform us of neuroanatomical features, including gyrification, cortical thickness and brain volumes. Another brain imaging tool is magnetic resonance spectroscopy (MRS) which can be used to determine the concentrations of biochemicals in a certain location of the brain.

Although many studies have shown a difference in neurobiology between healthy controls and patients diagnosed with schizophrenia, a common biomarker that lies in the pathway to schizophrenia has not yet been identified. The lack of clear neuropathogenesis of schizophrenia after years of research has prompted many researchers to look for

multiple pathophysiological pathways. There have been multiple hypotheses on the neurobiological pathogenic pathways to schizophrenia (Smeland et al., 2020). The most influential theories postulate that the dysregulation of neurotransmitters including dopamine, glutamate and/or GABA in the striatum, hippocampus, prefrontal cortex, and midbrain leads to psychosis. Another model describes psychosis as a neurodevelopmental disorder (Smeland et al., 2020). The neurodevelopmental model of psychosis theorizes that abnormal development of the brain, specifically structure, connectivity and physiology, results in aberrant information processing (Smeland et al., 2020). In general, patients with schizophrenia, compared to healthy controls, have initial and progressive loss of grey and white matter volume and an increase in ventricular volume (Fusar-Poli, Smieskova, et al., 2013; Haijma et al., 2013; Olabi et al., 2011; Vita et al., 2012). Patients also have widespread cortical thickness reduction that progresses more quickly with age, illness duration and higher antipsychotic medication exposure (van Erp et al., 2018).

1.5 Heterogeneity of Schizophrenia

The various pathogenic models of schizophrenia further support the polygenetic and multifactorial architecture of schizophrenia. These models are not mutually exclusive, but instead, they can co-manifest to different degrees in patients. This suggests that patients could have divergent abnormalities in multiple neural systems at varied impaired levels that contributed to different subtypes of schizophrenia or converged to a dimension that cut across the schizophrenia spectrum (Ruan et al., 2020). The wide range and variations of brain abnormalities that we observed in schizophrenia are discussed as neurobiological heterogeneity. Neurobiological heterogeneity in schizophrenia can be demonstrated by the great variations of measurements obtained from patients, and the lack of high effect-size differences in patients as a single group, compared to the unaffected, apparently healthy population.

It is not surprising to expect heterogeneity in the underlying biological mechanisms of schizophrenia, because the diagnosis of schizophrenia itself is solely based on symptoms without assisting biological tests, and has naturally brought in a level of clinical heterogeneity based on the diagnostic criteria. Based on the DSM-5 (American Psychiatric Association, 2013), out of the five major symptom categories (e.g.

hallucinations, delusions, disorganized speaking, disorganized movements and negative symptoms), the presence of two symptoms meets the diagnostic criteria, alongside social or occupational dysfunctions. In other words, two patients with the same diagnosis can share no symptoms in common.

Heterogeneity of schizophrenia can become problematic when we try to discover biologically guided treatment options in relation to disease mechanisms, because great variances can produce inconsistent results with small effect sizes which masks us from identifying meaningful biomarkers that can be used for diagnosis, prognosis, and outcome prediction (Marquand et al., 2016).

1.6 Parsing Heterogeneity of Schizophrenia

Research into the diagnosis, prognosis and treatment of schizophrenia could be better informed if the heterogeneity of schizophrenia can be parsed to identify meaningful subgroups of patients. One way to achieve this is by applying typologies to organize patients with unsupervised machine learning approaches (Jablensky, 2010). Such subtyping strategies have been summarized in a systematic review (Habtewold et al., 2020), based on symptoms and cognitive performance. The data analyzed were generally collected from patient self-reports, clinical interviews or observations of symptoms, or scores from psychiatric rating scales or neuropsychological tests, but this approach has three major problems: (I) patients' symptoms are rated via subjective clinical judgments; these are prone to multiple sources of measurement bias (Everitt et al., 1971; Tandon et al., 2013a); (II) the assumption that patients with similar clinical or cognitive profiles share common underlying pathophysiological mechanisms is an untested one. In other words, symptoms- or cognitive ability-based patient subtypes may not be biologically homogeneous; this will continue to impede our ability to develop mechanistically informed diagnosis, treatment and prediction; (III) Symptom severity and cognitive performance measurements are time-varying parameters; they change throughout the course of the illness (Dollfus & Petit, 1995; Miles et al., 2014), which may lead to temporal instability in symptom- or cognition-based subtypes. Stable and accurate classification systems are important because they would help explain disease mechanisms and inform clinical decisions, especially the development of tailored treatment.

1.7 Project Overview

Data-driven subtypes of schizophrenia have focused primarily on symptoms and cognitive performance (Habtewold et al., 2020; Schnack, 2019) and Clementz et al. were one of the research groups to investigate biotypes in schizophrenia (Clementz et al., 2016, 2020, 2021), and also multiple other studies make efforts in discovering neuroanatomical or physiological subtypes of schizophrenia (Dwyer et al., 2018a; Honnorat et al., 2019a; Pan et al., 2020a; Sugihara et al., 2017a). Brain-based patient subtyping may facilitate the transition from subjective clinical judgment to objective biology-grounded clinical practice, which aligns with the goals of The National Institute of Mental Health's Research Domain Criteria (RDoC) (Insel et al., 2010). This study continued the efforts of brain-based patient subtyping and was conducted with three schizophrenia patient samples of different clinical statuses, which were independently recruited across different geographical locations, and scanned with different MRI scanners.

Our primary aim was to confirm the existence of a cortical impoverishment subgroup of schizophrenia by capturing the variation in cortical thickness across patients and healthy controls matched for IQ. Second, we aimed to test the validity of cortical thickness-based subtypes across various clinical stages, antipsychotic exposure rates, and functional stability in 2 other samples with patients at different stages of schizophrenia. We predicted that a constant ‘cortical impoverishment’ subgroup would emerge irrespective of early vs. late stages of schizophrenia, acute vs. chronic symptom status, and minimal vs. chronic exposure to antipsychotics. Third, we leveraged the multimodal ultra-high field MRS and MRI data available from one of the 3 samples to investigate if patients with pronounced cortical impoverishment also showed glutamatergic excess. Given that the spectral resolution for precise quantification of glutamate in vivo is currently only feasible at ultra-high field strengths, this method provides robust evidence linking glutamatergic excess to cortical impoverishment in schizophrenia.

Chapter 2 Cortical Impoverishment Subgroup in Chronic Schizophrenia

Cortical thinning is a well-known feature in schizophrenia. The considerable variation in the spatial distribution of thickness changes has been used to parse heterogeneity. A 'cortical impoverishment' subgroup with a generalized reduction in thickness has been reported. However, it is unclear if this subgroup is recoverable in chronic schizophrenia. Chapter 2 aimed to replicate the cortical thinning subgroup in chronic schizophrenia and validate the finding in a second chronic sample. We found that cortical thinning does not vary with functioning or cognitive impairment, but it is more prevalent among patients, especially those with higher residual symptom burden at stable stages. This chapter was adapted from the manuscript published on *Schizophrenia Research* [1].

2.1 Background

2.1.1 Dissecting Heterogeneity in schizophrenia

Schizophrenia spectrum disorders are characterized by individual differences in clinical trajectory, symptom burden, and cognitive performance (Andreasen, 1999; Carpenter & Kirkpatrick, 1988). The source of this heterogeneity is unknown, but suspected to arise from etiological and neurobiological variations (Lv et al., 2020; Alnæs et al., 2019; Brugger & Howes, 2017), possibly reflecting multiple neuropathological pathways to the disorder (Seaton et al., 2001). To dissect this heterogeneity, several attempts have been made using cluster analysis, a multivariate technique to discover subgroups with minimal within-group variance for a variable of interest (Everitt et al., 2011). Cluster analytic strategies have been applied to cognitive (Cobia et al., 2011; Geisler et al., 2015; Heinrichs & Awad, 1993; Van Rheenen et al., 2017; Weinberg et al., 2016), clinical (Dickinson et al., 2018; Dollfus & Brazo, 1997; Talpalaru et al., 2019), physiological (Clementz et al., 2015), and neurobiological (Chand et al., 2020b; Dwyer et al., 2018b;

[1] A version of this chapter has been published on *Schizophrenia Research* (Liang, Heinrichs, et al., 2022).

Honnorat et al., 2019b; Pan et al., 2020b; Planchuelo-Gómez et al., 2020; Sugihara et al., 2017b) variables to delineate subtypes in schizophrenia. Subgrouping patients based on neuroanatomy has a particular appeal. First, it is advantageous to look directly at the underlying neurobiological substrate of psychosis instead of the downstream emergent clinical features (e.g., symptoms or functioning), as highly similar clinical profiles can emerge from varying mechanistic processes. Second, neuroanatomical data are relatively stable metrics that are accessible from 7-10 minutes of non-invasive structural magnetic resonance imaging (MRI) scanning. Finally, in contrast to the use of symptom measures for clustering, neuroanatomical data allow us to pool both patients and healthy controls into one sample for analysis. Although differences in multiple neurobiological variables between patients with schizophrenia and healthy controls have been reported (Gong et al., 2020; van Erp et al., 2018), treating patients and controls as completely distinct groups in case-control neuroimaging studies ignores the shared variance (Voineskos et al., 2020) and also assumes that there is no useful subgrouping information within the healthy samples. Deriving neurobiological subgroups without considering diagnostic statuses allows us to leverage 'healthy variations' in addition to pathological inter-individual differences and investigate how patients and controls naturally aggregate and separate in the biological feature space.

2.1.2 Thickness-based Clustering

Cortical thickness is useful as a variable to aggregate patients in subgroups alongside healthy controls. Several studies have documented deviations in cortical thickness patterns in patients in relation to symptom severity, but the spatial distribution of thickness changes is heterogeneous with effect sizes being small to moderate (Kuperberg et al., 2003; Narr et al., 2005; Schultz et al., 2010; van Erp et al., 2018; van Haren et al., 2011; Goldman et al., 2009), indicating the possible existence of subgroups with varying locations and degree of thickness change. Furthermore, region-specific cortical deficits associate with more severe positive and negative symptoms (Walton et al., 2018; Xiao et al., 2015), cognitive dysfunction (Hartberg et al., 2011), and treatment resistance (Zugman et al., 2013). While the mechanistic pathways influencing the diffuse reduction in cortical thickness are yet unclear, some studies that combine structural imaging and

magnetic resonance spectroscopy (MRS) suggest glutamate-mediated excitotoxicity as one of the mechanisms underlying thickness changes in schizophrenia (Plitman et al., 2016; Shah et al., 2020). These findings highlight the utility of profiling patients based on cortical thickness when attempting to uncover mechanistically homogeneous subgroups of schizophrenia.

A distinct subgroup has emerged in previous cortical thickness-based clustering of schizophrenia patients and healthy subjects (Pan et al., 2020b; Sugihara et al., 2017b). This subgroup predominantly comprised patients with significantly reduced cortical thickness compared to other subgroups. It parallels with clustering based on cognitive measures (especially IQ) across diagnostic boundaries (Van Rheenen et al., 2017), which has also identified a broadly compromised subgroup. Studies have linked cortical thickness to IQ in both healthy subjects (Deary et al., 2010) and patients with schizophrenia (Cobia et al., 2011). In prior thickness-based clustering studies (Pan et al., 2020b; Sugihara et al., 2017b), patients had notable cognitive deficits compared to healthy subjects; as a result, it is unclear if the patient-dominant 'cortical impoverishment' subgroup occurs independently of cognitive heterogeneity among the individuals under consideration. A recent study (Xiao et al., 2021) reported a subgroup of established cases of schizophrenia to have cortical impoverishment and higher cognitive deficits. However, this study clustered only patients, without leveraging the variability among healthy subjects. Taken together, the evidence does not clearly indicate whether cortical impoverishment subgroups are simply patients with general intellectual impairment (Carruthers et al., 2019). Furthermore, we do not know whether the presence of the cortical impoverishment subgroup is related to ageing effects (Y. Lin et al., 2019) or could be the result of exposure to higher doses of antipsychotic medications rather than a distinct disease process in a subset of patients (Fusar-Poli, Smieskova, et al., 2013; Ho et al., 2011).

2.1.3 Aims of Study

Our primary aim was to confirm the existence of a cortical impoverishment subgroup of schizophrenia by capturing the variation in cortical thickness across patients and healthy controls matched for cognitive ability. To this end, we recruited 136 subjects; 73 with

established schizophrenia and 63 with age, sex, years of education, and IQ-matched healthy controls. Second, we aimed to test the validity of cortical thickness-based subtypes across various clinical stages, and functional stability. We predicted that a constant ‘cortical impoverishment’ subgroup would emerge irrespective of illness duration and illness stability. To this end, we validated the stability of our clustering solution in the IQ-matched ‘discovery’ dataset in another sample with patients (n=41).

2.2 Material and Methods

2.2.1 Participants

Data used in the present study were obtained from two previously reported patient samples, with each sample in different clinical stages, antipsychotic exposure rates, and functional stability. Written informed consent was obtained from all participants.

The primary dataset for the ‘discovery’ approach (NeuroCog Dataset) was composed of 63 healthy controls and 73 patients with a DSM-IV diagnosis (First et al., 1996) of schizophrenia or schizoaffective disorder recruited through outpatient programs in Hamilton, Ontario, Canada. Most of the patients were taking antipsychotics and had chronic schizophrenia. To enable cognitively matching patients and controls, controls were oversampled from communities with lower employment and education levels, while patients with near-normal cognition were specifically sought, eventually capturing both cognitively normal patients and sub-normal healthy controls. Details on participant recruitment have been previously reported (Heinrichs et al., 2017; Hanford et al., 2019). This study was approved by York University (#2010-107), St. Joseph's Healthcare, Hamilton, and McMaster University (#10-3315) review boards.

The validation dataset (CONN Dataset) was composed of 40 healthy controls (group-matched for sex, age and parental socioeconomic status measured using National Statistics Socio-Economic Classification (NS-SEC; Rose et al., 2005), to reduce confounding due to psychosocial differences during early development) and 41 patients with a DSM-IV diagnosis (First et al., 1996) of schizophrenia or schizoaffective disorder, recruited through community-based services in Nottinghamshire, United Kingdom. Unlike the ‘discovery’ sample, CONN patients were recruited only if they satisfied

‘stable illness phase’ criteria, which were that patients needed to have no change in medication over the prior 6 weeks and no more than 10 points change in their Global Assessment of Function [DSM-IV] score, assessed 6 weeks prior and immediately before study participation. Recruitment of participants and data collection has been described previously (Palaniyappan & Liddle, 2014) and was approved by National Research Ethics Committee, Nottinghamshire (NHS REC Ref: 10/H0406/49).

2.2.2 Measures

In the NeuroCog project, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) was administered to all participants to measure abilities in seven different cognitive domains, including working memory, attention or vigilance, verbal memory and learning, processing speed, problem-solving, visual learning, and social cognition (Kern et al., 2008; Nuechterlein et al., 2008). IQ scores of all participants were measured with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The patients’ symptom severity was assessed with the 30-item Positive and Negative Syndrome Scale (PANSS-30) to index positive, negative, and general psychopathology (Kay et al., 1987). The Canadian Objective Assessment of Life Skills (COALS) was administered to index functional competence (McDermid Vaz et al., 2013).

The validation sample was acquired in the CONN studies. In the CONN study, we used the Signs and Symptoms of Psychotic Illness (SSPI) (Liddle, Ngan, Duffield, et al., 2002) to measure symptom severity and the Social and Occupational Functional Assessment Scale (SOFAS) to measure the overall functioning (Morosini et al., 2000a) of patients. This sample did not have a detailed cognitive characterization that was available for the discovery dataset.

2.2.3 MRI and MRS Data Acquisition and Processing

The details of data acquisition in the NeuroCog and CONN projects (3.0-Tesla MRI) have been reported previously (Heinrichs et al., 2017; Palaniyappan & Liddle, 2014) and are summarized here. In the NeuroCog ‘Discovery’ Dataset, a 3.0-Tesla whole-body

short bore General Electric System MRI scanner equipped with an 8-channel parallel receiver head coil was used to scan participants at the Imaging Research Centre at St. Joseph's Healthcare Hamilton. Anatomical images of 152 slices (2 mm thick with 1 mm overlap) were generated. The scanning parameters of T1-weighted 3-dimensional fast spoiled gradient recalled echo sequence with inversion recovery preparation were as follows: repetition time (TR)/echo time (TE) = 7.5/2.1 ms, TI = 450 ms, field of view (FOV) = 24 cm, matrix = 512 × 512, flip angle = 12°, receiver bandwidth (rBW) = +/−62.5 kHz, and number of excitations (NEX) = 1. In the CONN 'Validation' Dataset, MR scans were collected with Philips 3.0-Tesla imaging systems which were equipped with an 8-channel phased array head coil in the University of Nottingham. The scanning protocol included a single high-resolution three-dimensional T1-weighted MPRAGE volume of isotropic voxel size 1 × 1 × 1 mm^3, TR/TE = 8.1/3.7 ms, flip angle 8°, field of view 256 × 256 × 160 mm^3, 160 slices of 1 mm thickness each were collected in an acquisition matrix 256 mm × 256 mm and in-plane resolution 1 × 1 mm^2.

The obtained images underwent FreeSurfer automated image analysis for alignment of cortical regions and segmentation of the brain (version 5.1.0; http://surfer.nmr.mgh.harvard.edu/) (Fischl et al., 1999). Preprocessing of these images included the removal of non-brain tissues as well as spatial and intensity normalizations. Cortical thickness was defined as the Euclidean distance between the pial surface to the grey/white matter boundary across 160,000 vertices in both cerebral hemispheres. Cortical regions were assorted according to the gyral and sulcal structures in both hemispheres defined by Destrieux et al. (2010).

2.2.4 Statistical Analysis

This study applied agglomerative hierarchical cluster analysis to age-corrected cortical thickness values among 148 brain regions with the *hclust* function in R (R Core Team, 2020). Thickness values of 148 cortical regions of interest were adjusted for age with linear regression, and the residuals were input as variables for clustering. Ward's method with Euclidean distance was used. We visually inspected the dendrogram to determine the possible stratification solutions.

The *NbClust* function in R statistical software was used to determine the optimal number of clusters. The *NbClust* function in *R* packages (Charrad et al., 2014) offers multiple clustering validity indices and outputs the recommended number of clusters for each validity index. In the current study, 16 validity indices in the *NbClust* package were selected to evaluate the clustering results ("ch", "cindex", "kl", "hartigan", "db", "silhouette", "ratkowsky", "ball", "ptbiserial", "gap", "mcclain", "gamma", "gplus", "tau", "dunn", "sdindex"). These validity indices either regard the elbow point as optimal, or attempt to reach the maximum ratio of inter-cluster separation over intra-cluster compactness. The optimal number of clusters was determined by the consensus of the 16 validity indices.

To assess external validity, key characteristics of each cluster were compared across clusters, including illness prevalence, antipsychotic exposure, cortical thinning patterns, socio-demographic, clinical, and cognitive information as well as neurometabolic levels. Clinical information included duration of illness (years) and symptom severity measured by PANSS or SSPI. MCCB composite scores were converted into T scores (mean = 50, SD = 10). Antipsychotic medication dose equivalents were calculated based on Defined Daily Doses (DDDs) according to the World Health Organization (WHO) guidelines (http://www.whocc.no). Multiple Student or bootstrapped t-tests (two-tailed, $\alpha<0.05$) were used for comparison of continuous variables, while chi-square tests (two-tailed, $\alpha<0.05$) were used for comparisons of non-categorical variables between participants in each cluster.

In the ‘discovery’ dataset, Pearson correlation coefficients between medication exposure, symptom severity, and cognitive performance were calculated tested for significance for patients in each subgroup, respectively. The correlation magnitudes retrieved from the two subgroups of patients were tested against each other with a two-tailed z-test using Fisher’s z transformation of correlations.

2.3 Results

2.3.1 Demographic and Clinical Characteristics of Participants

Demographic and clinical details were summarized in Table 1. The patient sample in NeuroCog (average illness duration = ~17 years) and CONN (average illness duration = ~7 years) consisted of patients with chronic schizophrenia or schizoaffective disorder, with 85% of the NeuroCog sample and 88% of the CONN sample taking antipsychotic medications at the time of scanning (Table 2).

Table 1 Demographic, cognitive and clinical information of 'Discovery' and 'Validation' dataset.

		NeuroCog Study 'Discovery' Dataset		**CONN Study** 'Validation' Dataset	
		Patients	**Controls**	**Patients**	**Controls**
Demographics	N	73	63	41	40
	Age	41.42 ± 10.48	38.87 ± 11.46	33.63 ± 9.24	33.40 ± 9.10
	Female/male	29/44	24/39	10/31	11/29
	Education, years	12.90 ± 2.20	12.48 ± 2.24	-	-
Cognitive Measurements	MCCB total T score	29.26 ± 13.13	41.38 ± 14.31	-	-
	WASI	96.42 ± 21.16	101.19 ± 20.38	-	-
Functional Outcome	COALS	35.66 ± 10.83	-	-	-
	SOFAS	-	-	54.63 ± 13.11	-
MRI data	Global CT, mm	2.45 ± 0.37	2.53 ± 0.37	2.43 ± 0.38	2.44 ± 0.38
		Patients Only		**Patients Only**	
Symptom Severity	PANSS or SSPI *(Median [IQR])*	PANSS-30: 61[51, 70]		SSPI: 11[5, 18]	
	Min-max normalized score	0.20 ± 0.087		0.15 ± 0.093	

Clinical Information	Duration of Illness *(Median [IQR])*	17 [9.75, 25], in years			6 [4, 14], in years		
Antipsychotic Medication	DDD	Median	Mean	IQR	Median	Mean	IQR
		1.00	1.30	[0.73, 1.66]	1.25	2.03	[0.42, 2.84]

Note: Means and standard deviations are reported unless specified otherwise. IQR: interquartile range is the first and third quartile. T scores are standardized scores with a mean of 50 and standard deviation of 10. MCCB: MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; WASI: Wechsler Abbreviated Scale of Intelligence; COALS: Canadian Objective Assessment of Life Skills; SOFAS: Social and Occupational Functioning Assessment Scale; Global CT: average cortical thickness across the whole brain (measured in millimetres); PANSS: Positive and Negative Syndrome Scale; SSPI: Signs and Symptoms of Psychotic Illness; DDD: defined daily dose calculated according to World Health Organization (http://www.whocc.no). Symptom severity scores were normalized into values of a range of 0-1 using min-max normalization using equation (1):

$$Normalized\ score = \frac{x - \min(x)}{\max(x) - \min(x)} \qquad (1)$$

where x is a patient's total score while $\min(x)\ and\ \max(x)$ are the minimum and maximum scores of the scales.

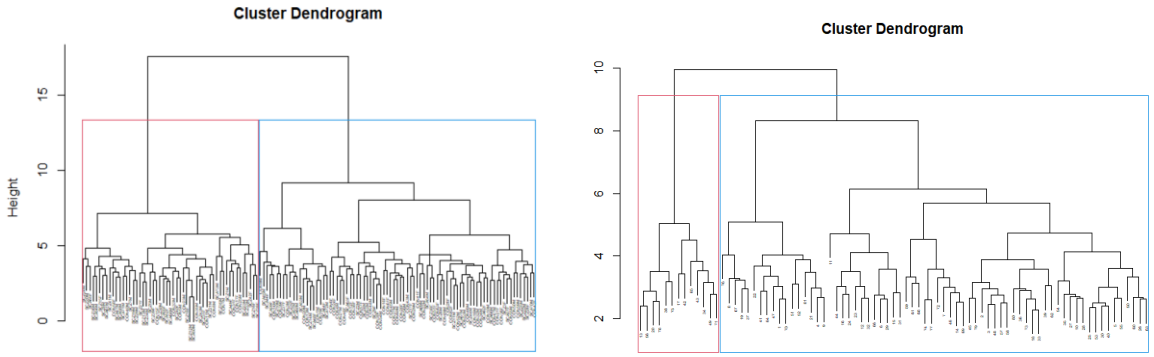
Table 2 Medication information of patients in the NeuroCog study

	Schizophrenia (n = 44)	Schizoaffective (n = 29)	Patients (n = 73)
Antipsychotic DDDs (mean ± SD)	1.33 ± 0.92	1.24 ± 0.79	1.30 ± 0.87
Received antipsychotics or not	Yes: 36 No: 2	Yes: 26 No: 0	Yes: 62 (85%) No: 2 (3%)
1st Generation	6	5	11 (15%)
Trifluoperazine	1	1	2
Zuclopenthixol	1	0	1
Flupentixol	2	0	2
Haloperidol	0	1	1
Fluphenazine	1	1	2
Perphenazine	1	1	2
Aripiprazole	0	1	1

	Schizophrenia (n = 44)	Schizoaffective (n = 29)	Patients (n = 73)
2nd Generation	22	14	36 (49%)
Risperidone	5	4	9
Olanzapine	4	4	8
Clozapine	10	4	14
Quetiapine	2	0	2
Ziprasidone	1	2	3
Combination	8	7	15 (21%)
Received depot injection	5	9	14 (19%)
Received antidepressants	Yes: 18 No: 20	Yes: 15 No: 11	Yes: 33 (45%) No: 31
Received Benzodiazepine	Yes: 15 No: 23	Yes: 12 No: 14	Yes: 27 (37%) No: 37
Unknown medication history	6	3	9 (12%)

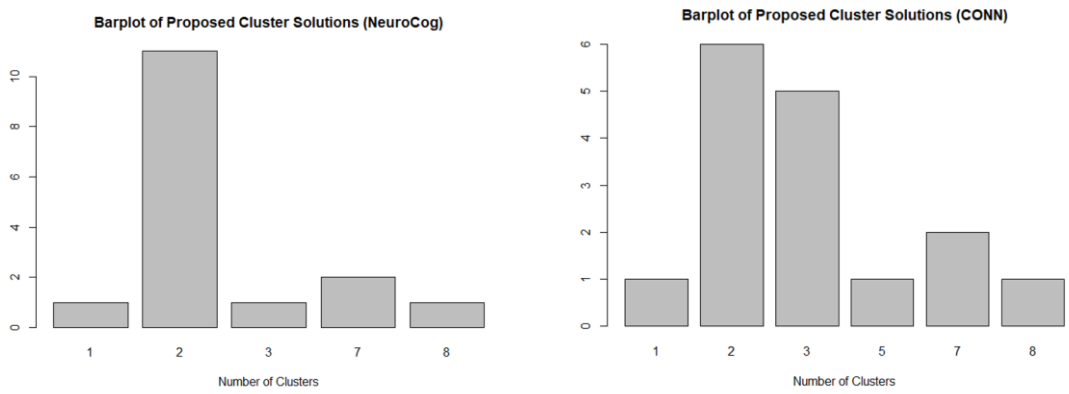
2.3.2 Clustering Solution and Composition

A visual inspection of the agglomerative hierarchical cluster analysis dendrograms (Figures 1A-1B) suggested that subtyping solutions of 2 to 8 clusters could be meaningful. Subsequently, the *NbClust* function in R (Charrad et al., 2014) was used to compute 16 external validity indices for two- to eight-cluster solutions, respectively. The output showed that a two-cluster consistently received the highest number of votes (Neurocog: 10/16; CONN: 6/16; Figures 2A-2B). The same clustering procedure was re-applied to the patient samples only, and a two-cluster solution was again the most favoured solution (Figure 3A-3B). Out of the 53 patients identified as cortically impoverished with whole-sample approach, 48 patients were correctly identified with patient-only approach, providing a subgroup-level accuracy of 90% (Table 3). A two-cluster solution was chosen based on the majority consensus.



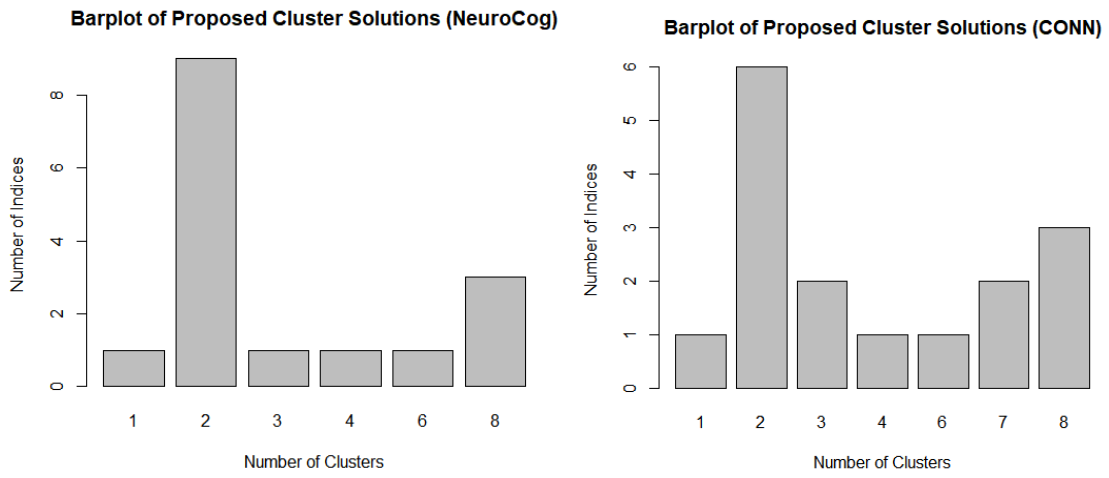
(A) NeuroCog 'Discovery' Dataset (B) CONN 'Validation' Dataset

Figure 1 Hierarchical cluster dendrogram of the 'Discovery' and 'Validation' samples



(A) NeuroCog 'Discovery' Dataset (B) CONN 'Validation' Dataset

Figure 2 Bar plots of the frequency of proposed cluster solutions, when clustering with patients and healthy controls.



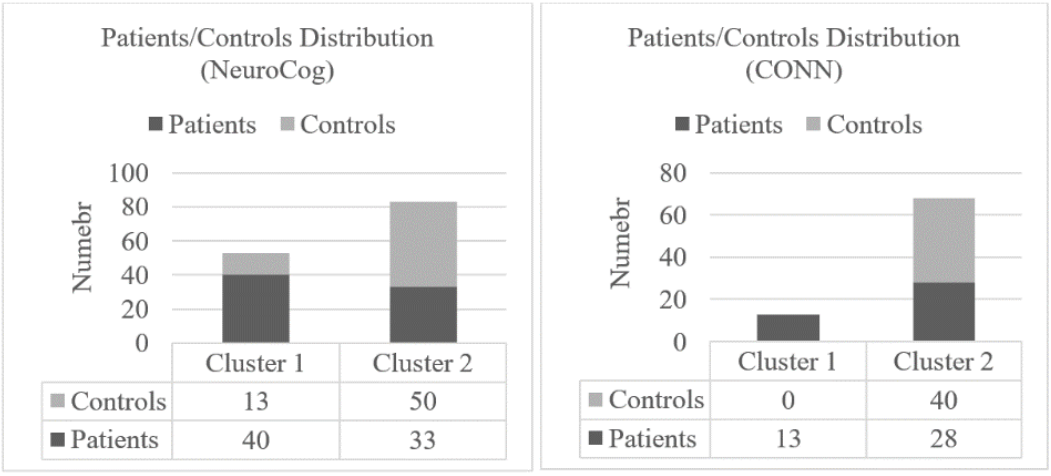
(A) NeuroCog 'Discovery' Dataset (B) CONN 'Validation' Dataset

Figure 3 Bar plots of the frequency of proposed cluster solutions, when clustering with patients only.

Table 3 'Cortical impoverishment' subgroup membership when clustering is carried out with or without the data from healthy controls.

NeuroCog 'Discovery' Dataset Patients only		SCZ-only clustering	
		Cortical Impoverishment	Non-impoverished
Whole sample clustering	Cortical Impoverishment	35	5
	Non-impoverished	3	30
CONN 'Validation' Dataset Patients only		SCZ-only clustering	
		Cortical Impoverishment	Non-impoverished
Whole sample clustering	Cortical Impoverishment	13	0
	Non-impoverished	16	12

With a two-cluster solution, the proportion of patients (Figures 4A-4B) varied significantly across clusters [NeuroCog: χ^2 (N = 136) = 15.186, $p < 0.0001$; CONN: χ^2 (N = 81) = 20.128, $p < 0.0001$], revealing a subgroup (Cluster 1) with mostly patients. The proportion of patients relative to healthy controls within Cluster 1 was 75.5% and 100% in NeuroCog and CONN samples, respectively. A larger second cluster comprised a relatively balanced ratio of patients and controls, with patients accounting for 40% and 41% in the two datasets.



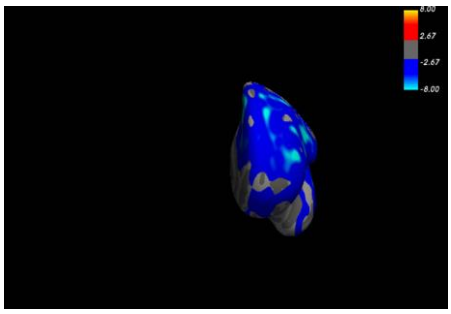
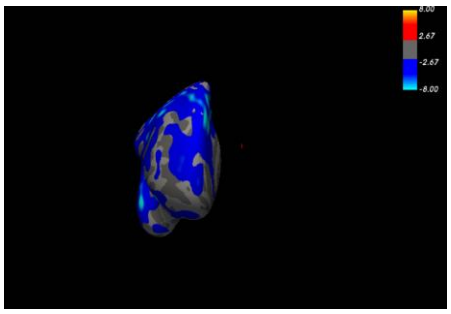
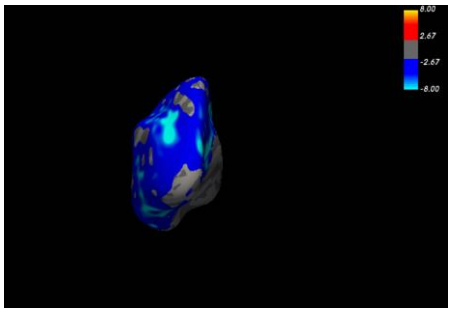
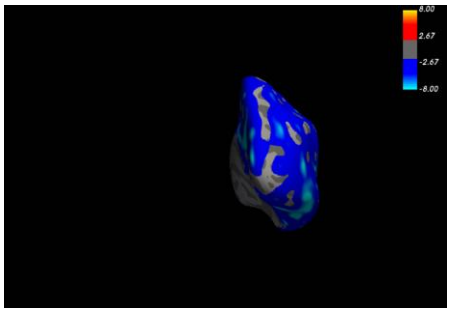
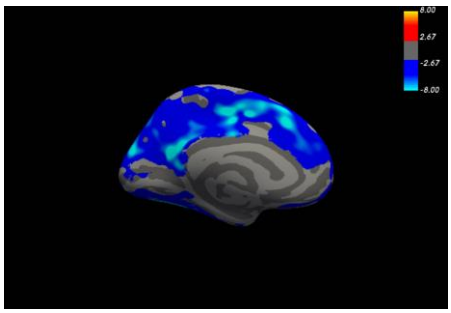
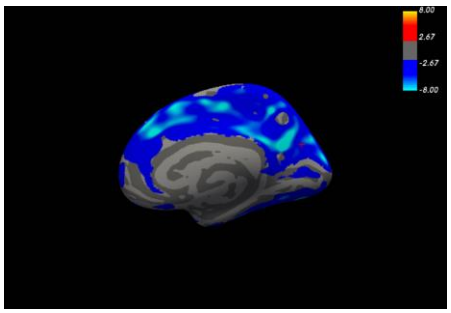
(A) NeuroCog Study (B) CONN Study

Figure 4 Distribution of patients and healthy controls in the two thickness-based clusters in the two studies.

2.3.3 Neuroanatomical Differences Between Clusters

Multiple t tests with Bonferroni correction were conducted to examine differences between clusters. A consistent pattern of cortical thinning was observed in Cluster 1 (see vertex-wise comparison in Figure 5); Number of cortical regions that were significantly thinner in Cluster 1 after correction: 100/148 in NeuroCog and 11/148 in CONN). When examining patients only, 44/148 regions in NeuroCog and 7/148 regions in CONN showed significantly thinner cortex among Cluster 1 patients ($p < 0.01$ after Bonferroni correction; See Table 4 for the top 5 cortical regions and cortical thickness maps that showed significant differences in each sample), with none of the cortical regions showing a significantly higher thickness among cluster 1 patients. To investigate whether patients

and controls clustered together indeed had similar thickness patterns, we also compared patients and controls in terms of cortical thickness values in Cluster 2 which had a relatively balanced patient/control ratio. The results showed no significant differences in any of the anatomical regions after multiple-testing corrections across all three samples.

	'NeuroCog' Discovery Dataset (Cluster 1 N = 49; Cluster 2 N = 67)	
	Left Hemisphere	Right Hemisphere
Anterior View		
Posterior View		
Medial View		

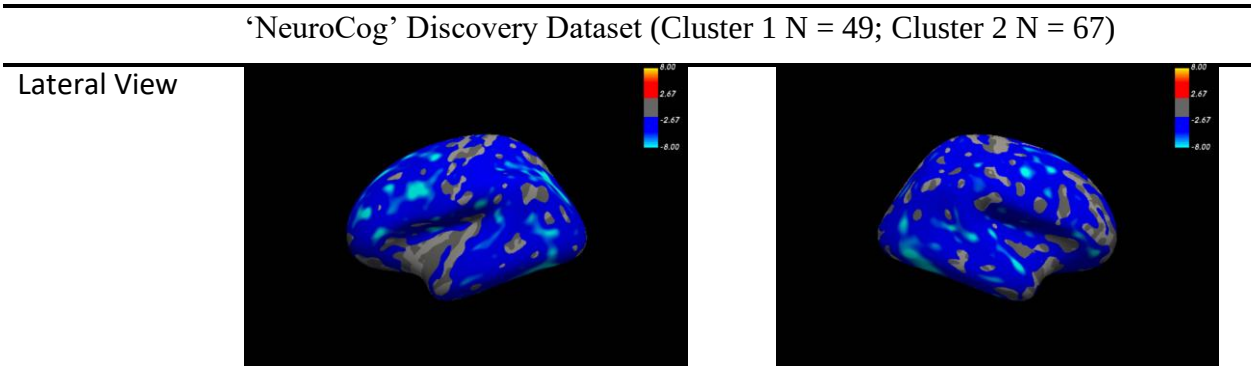


Figure 5 Cortical thickness maps of differences between members of the two clusters in the discovery dataset.

Note: **The cluster membership is irrespective of diagnostic status (i.e, both patients and control subjects are included). Only the cortical surfaces generated by FreeSurfer (regressing out age effect with general linear model, uncorrected) without any need for manual editing are included in this vertexwise analysis. Scale indicates log10 of p-values and cortical regions with p-values > 0.01 were highlighted. Blue/cyan colours indicate Cluster 1 < Cluster 2 while red/yellow colour indicate Cluster 2 < Cluster 1. Cluster 1 is the 'cortical impoverishment' group that shows a globally distributed thickness reduction compared to Cluster 2.**

Table 4 Top 5 cortical parcellations that showed largest effect sizes in thickness between patients of the two clusters.

NeuroCog sample	CONN sample
R superior frontal gyrus	R planum temporale or temporal plane of the superior temporal gyrus
R middle posterior cingulate gyrus and sulcus	L planum temporale or temporal plane of the superior temporal gyrus
L superior frontal gyrus	L superior temporal sulcus
R paracentral gyrus and sulcus	L supramarginal gyrus
R middle frontal gyrus	L precentral gyrus

2.3.4 Characteristics of Participants in Each Cluster

2.3.4.1 Cognitive Characteristics

In the NeuroCog Sample, there was no significant difference between patients in the two clusters in WASI IQ estimate and MCCB composite scores, but healthy controls of the two subgroups differed significantly on these two cognitive measures (Figure 6A-6B). Results from examining differences between patients and controls within the clusters showed that patients were cognitively indistinguishable from the controls in Cluster 1 (MCCB: patients M[SD]= 29.18[14.1] vs. controls M[SD]= 33.46[13.3]; p = 0.33), while patients in Cluster 2 were more cognitive impaired than controls in the same subgroup

(MCCB: patients M[SD] = 29.36[11.69] vs. controls M [SD]= 43.44[13.95]; p < 0.0001). The seven cognitive domains were separately examined (see Figure 6C).

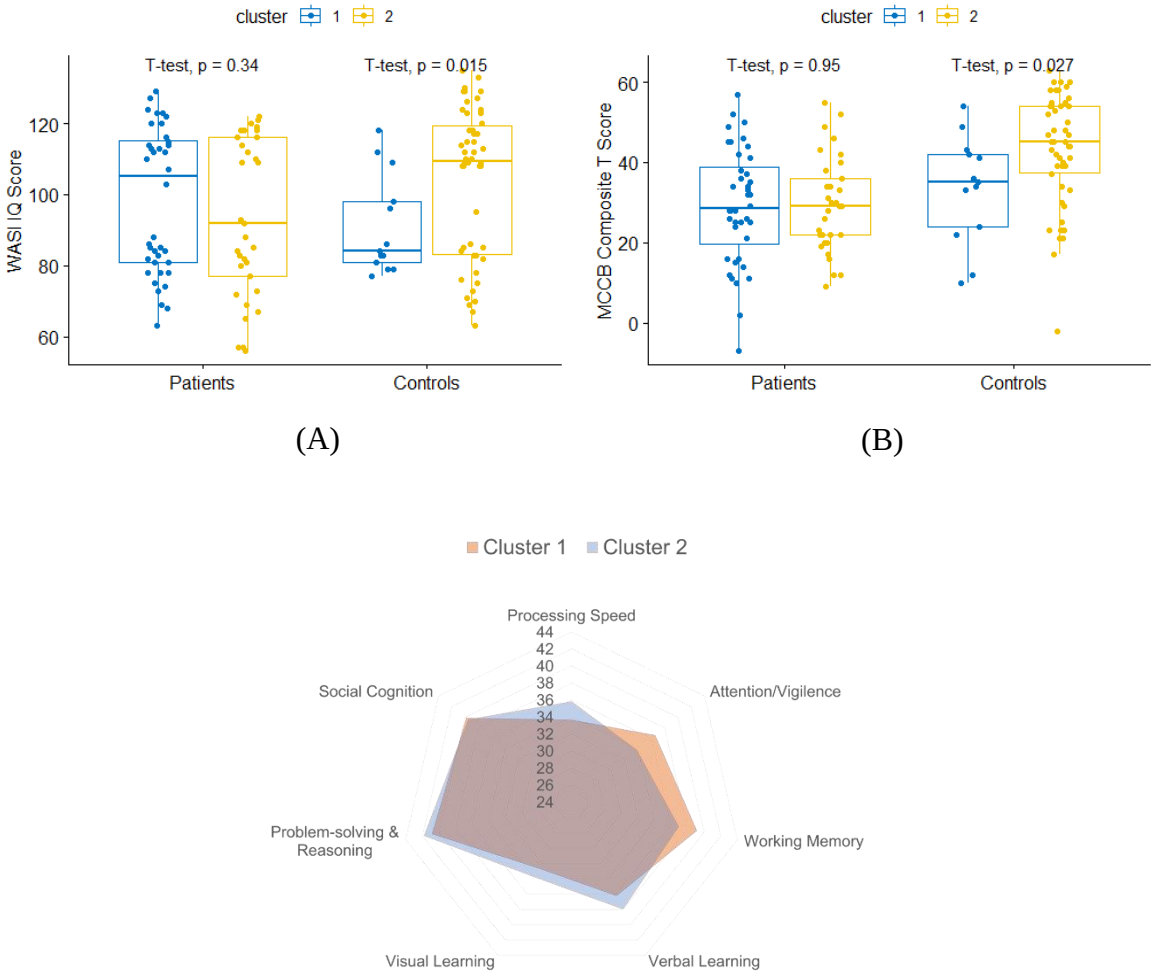
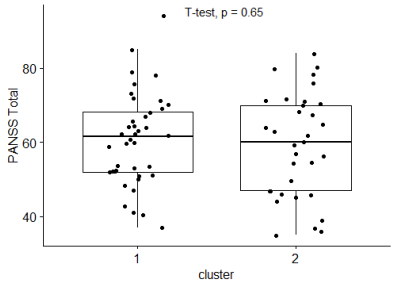
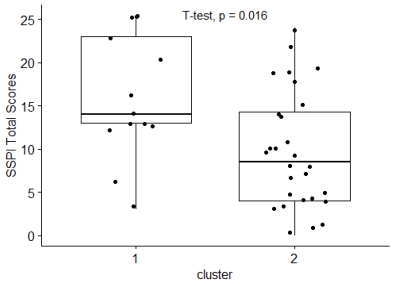
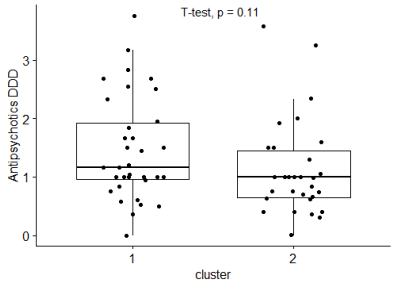
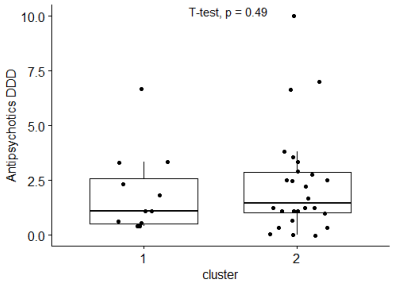
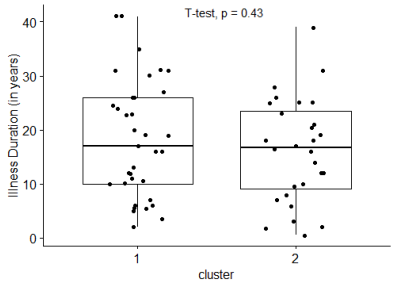
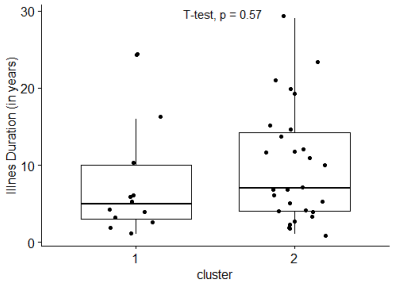


Figure 6 Comparisons of cognitive characteristics of members in each cluster in the NeuroCog 'Discovery' Sample.

Note: (A) WASI: Wechsler Abbreviated Scale of Intelligence; (B) MCCB: MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; (C) Seven cognitive domain scores from MCCB of patients in each cluster. MCCB Composite and domain scores are standardized as T-scores with a mean of 50 and a standard deviation of 10.

2.3.4.2 Clinical Characteristics

Comparison of patients between clusters showed no significant difference in overall symptom severity measured by PANSS in the NeuroCog (Figure 7A), but in the CONN study, there was a significant difference between the two clusters in the severity of symptoms measured by SSPI (Cluster 1 > Cluster 2; p = 0.016; Figure 7B). There was no significant difference in antipsychotic medication (Figures 7C-7D) or duration of illness (Figures 7E-7F) in both the discovery and the CONN validation dataset. There was no significant difference in functioning between patients of the two clusters, which was measured by COALS or SOFAS (Figures 7G-7H).

	NeuroCog 'Discovery' Dataset	CONN 'Validation' Dataset
Symptom Measures	 (A)	 (B)
Antipsychotic Medication Dose	 (C)	 (D)
Illness Duration	 (E)	 (F)

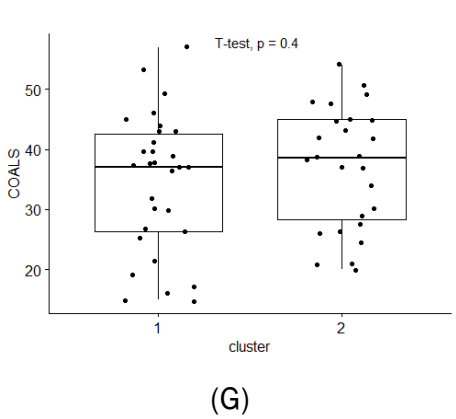
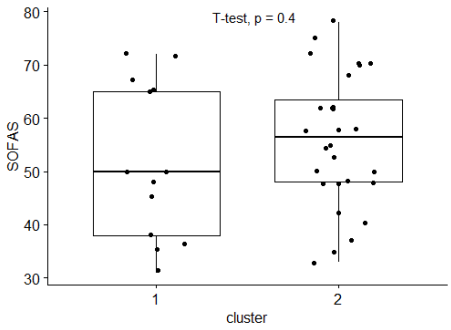
	NeuroCog 'Discovery' Dataset	CONN 'Validation' Dataset
Functional Outcome	 (G)	 (H)

Figure 7 Comparisons of clinical characteristics of patients in each cluster.

Note: **(A) 30-items Symptom severity of patients in NeuroCog sample measured by Positive and Negative Syndrome Scale (PANSS); (B) Symptom severity of patients in CONN sample measured by Signs and Symptoms of Psychotic Illness (SSPI); (C-D) Antipsychotic medication defined daily dose (DDD) calculated according to World Health Organization. (E-F) Duration of illness measured in years. (G) Independent living skills measured by Canadian Objective Assessment of Life Skills (COALS) in the NeuroCog sample; (H) General functioning measured by SOFAS in the CONN sample.**

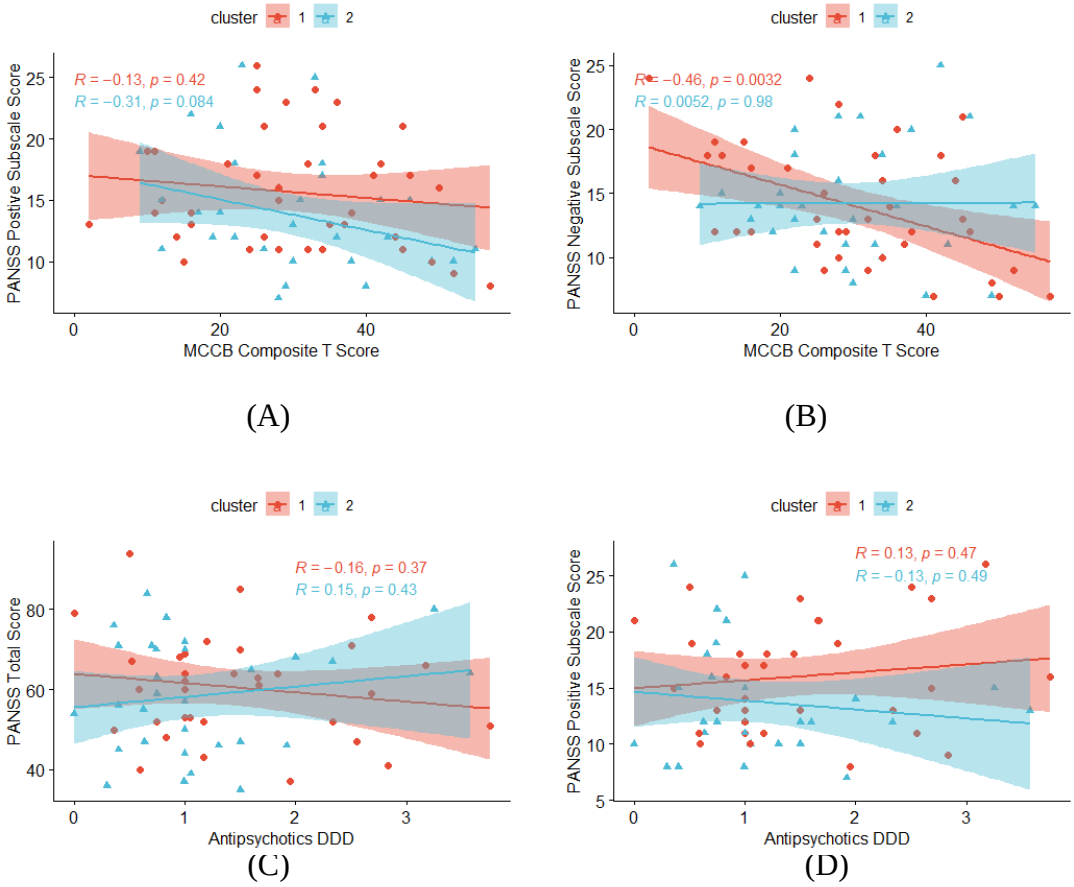
2.3.5 Exploratory Analysis of Symptoms, Cognition and Medication

In the Discovery Dataset, cognitive deficits did not show a significant relationship with positive symptom severity in either subgroup (Figure 8A). However, cognitive performance was significantly reduced in patients with more severe negative symptoms in Cluster 1 (r = -0.46, p = 0.0032), but not in Cluster 2 (Figure 8B). Negative symptom-cognition correlation coefficients were significantly different between subgroups (z = -2.234, p = 0.013).

Both illness severity and antipsychotic medication dose have been implicated in cortical thickness changes in schizophrenia (Andreasen et al., 2013; Lepage et al., 2020). We examined whether both thickness-based subgroups of patients had the same relationship between higher doses of antipsychotics and higher symptom severity. There was no

correlation between antipsychotic exposure and overall or positive symptom burden in Cluster 1 or Cluster 2 (Figure 8C-8F), but an increase in antipsychotic exposure was associated with different directions of change in negative symptom severity in Cluster 1 and Cluster 2 (z = -1.987, p = 0.023; Figure 8E).

Additionally, antipsychotic exposure and cognitive abilities were not significantly associated (Figure 8G), and the two subgroups did not show a difference in this relationship (z = -0.687, p = 0.246).



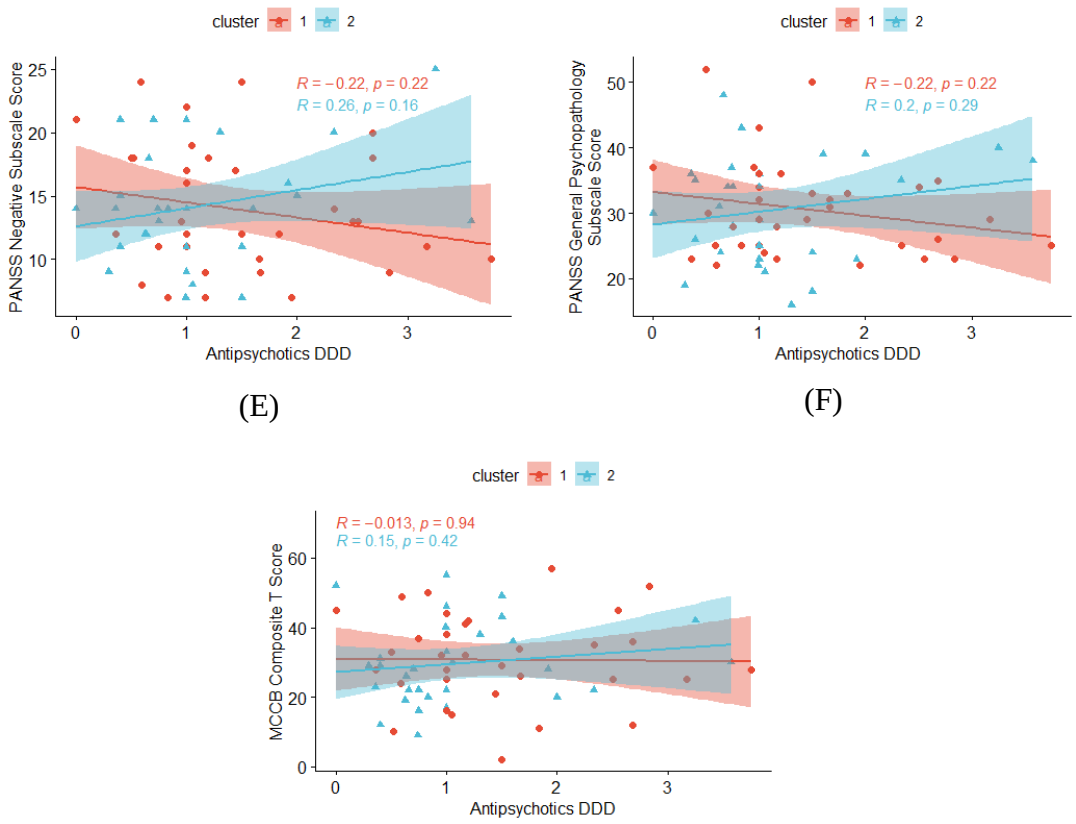


Figure 8 Relationships between cognitive test scores, symptoms severity measurements and antipsychotics defined daily dose in Cluster 1 and Cluster 2 patients, respectively in the NeuroCog 'Discovery' Sample.

Note: **MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; PANSS: Positive and Negative Syndrome Scale; DDD, defined daily dose calculated according to World Health Organization.**

2.4 Discussion

2.4.1 Discovery and Validation of Two thickness-based subgroups

We identified two subgroups based on cortical thickness profiles across the whole brain. The two subgroups differed in the proportion of 'cortical normality' indicated by the amount of variance shared with healthy controls. One subgroup displayed reduced thickness or impoverishment and the majority of the members in this subgroup were patients with schizophrenia. The remaining patients had more typical or spared thickness patterns. The neuroanatomical differences between the two clusters varied across the two samples, possibly due to differences in recruitment criteria as well as the sample size differences, which combined with our stringent correction for multiple testing, reduced the likelihood of demonstrating significant regional differences in validation sample. Furthermore, the presence of stage-specific differences in the location of grey matter differences (i.e., the duration of illness effect) from age- and sex-matched healthy cohorts is a well-established finding in schizophrenia (M. Li et al., 2022; Palaniyappan, 2017). While scanning parameters varied across the two studies, it is important to note that both patients and healthy controls were scanned using the same acquisition parameters within each study. Further, we did not see any notable variations in the global estimates of cortical thickness across the two studies.

Previous cluster analytic studies based on cortical thickness generally selected one clustering validation method to determine the optimal number of clusters (Pan et al., 2020b; Sugihara et al., 2017b). However, we demonstrated that the number of clusters depends on the selection of validity indices. A variety of cluster solutions were deemed meaningful in our three datasets, which could partially explain the inconsistency in the number of clusters reported in the literature (see *Figure 2 and 3*). Instead of cluster selection based on a single validity measure, the application of multiple validation indices allows for convergence to a final and consensual cluster solution.

Our two-cluster solution resembles Type I and Type II schizophrenia proposed by Crow (Crow, 1980). Crow anticipated pronounced brain structural abnormalities in one group (in line with our cortical impoverishment subgroup), referred to as Type II of schizophrenia, but not the other (Crow, 1980). However, in a later version, Crow

admitted the possibility that the two subtypes he proposed may indeed be two distinguishable dimensions of illness that might coexist in an individual case (Crow, 1985). More recently, Chand and colleagues uncovered a strikingly similar two-cluster solution by clustering on the grey matter volume of patients. Despite the differences in the statistical approach and variable selection (thickness vs. volume), they also reported a lack of clinical and demographic differences between the two subgroups (Chand et al., 2020b).

2.4.2 Aggregation of patients and controls

A sizeable number of IQ-matched healthy controls (nearly one-fifth) in the discovery dataset were part of the subgroup with thinner cortex. Thus, the differences among healthy individuals may contribute, in part, to the reported variability in effect sizes from case-control studies, reducing the ability to discriminate a patient from a non-patient based on the brain structure (Greenstein et al., 2012; Takayanagi et al., 2011).
It is worth noting that around half of patients had thickness patterns that were indistinguishable from the majority of healthy participants, indicating that processes that disrupt cortical morphology do not operate across all patients with schizophrenia. This pattern argues against the presence of a detectable anatomical signature across the whole brain to describe the neurodevelopmental or neurodegenerative nature of schizophrenia. Crow also argued that the lack of structural brain changes in the ‘Type I’ syndrome of schizophrenia is reflective of a hyperdopaminergic process, producing reversible features of an acute, positive-symptom-dominated profile with intact cognition (Crow, 1985). A lack of prominent structural changes in a majority of patients may also result from compensatory processes that lead to structural reorganization in the post-onset period (Palaniyappan, 2019). If cortical reorganization with time is a relevant process, it raises a question regarding the stability of subgroup membership. Longitudinal studies are required to parse this issue.

2.4.3 Similarities between the two thickness-based subgroups

Irrespective of brain structural differences between the subgroups, a feature that is conspicuous by its absence is the lack of significant clinical and cognitive differences

between the patients of the two subgroups. This lack of clinical differences among structural MRI-based subgroups has been reported in several other studies (Chand et al., 2020b; Dwyer et al., 2018b; Pan et al., 2020b; Planchuelo-Gómez et al., 2020). Although some studies have related a longer illness duration (Dwyer et al., 2018b; Pan et al., 2020b; Planchuelo-Gómez et al., 2020) and higher medication exposure (Pan et al., 2020b; Sugihara et al., 2017b) to more extensive cortical thinning, we did not find these associations in our data. Age differences between subgroups likely accounted for these differences in those previous studies (Dwyer et al., 2018b; Pan et al., 2020b; Planchuelo-Gómez et al., 2020).

In our discovery dataset, cognitive differences were found among healthy controls between the 2 subgroups, in line with prior data (Deary et al., 2010), but between the two subgroups, patients did not differ on their IQ or MCCB test scores. This implies that although poor cognitive performance is associated with cortical thinning in healthy people, developmental influences that result in impaired cognition in schizophrenia are unrelated to processes associated with impoverished cortex. This result is discrepant with studies that report cognitive impairment as a correlate of compromised cortical structural integrity in schizophrenia (Hartberg et al., 2011; Alkan et al., 2021). Cluster analytics studies that dissected heterogeneity in the cognitive feature space generally found subtypespecific neuroanatomical signatures (Cobia et al., 2011; Geisler et al., 2015; Ivleva et al., 2017; Weinberg et al., 2016). Similarly, in a cluster analysis based on cortical thickness, surface area and subcortical volume, Xiao et al. (2021) found that the cluster with widespread grey matter and subcortex deficits exhibited a significant impairment in cognition compared with patients with minimal or no significant brain alterations. The cognitive similarity between the two thickness-based subgroups of patients in our study does not negate the discriminative ability of other brain features (for example, white matter or subcortical volume, or connectivity (Kelly et al., 2019; Wexler et al., 2009) in identifying cognition-based clusters. However, our finding is in line with recent proposals that several disease-associated factors (i.e., psychological, symptomatic and social factors) likely contribute to cognitive dysfunction (Moritz et al., 2017, 2020), and it is possible that among patients, these factors are not differentially distributed on the basis of grey matter thickness alone.

Overall, our results suggest that the illness duration and cognitive deficits do not vary with cortical thickness across the whole brain in schizophrenia. If cortical impoverishment lies on the causal mechanistic pathways to schizophrenia, then the lack of notable clinical differences supports the argument that similar 'phenocopies' may emerge from distinct mechanisms.

2.4.4 Differences between the two thickness-based subgroups

The only group-level difference in clinical features between the 2 clusters in our analysis came from the CONN 'Validation' dataset where patients with 'cortical impoverishment' displayed a more severe total symptom burden than other patients. In essence, this meant that the variation in SSPI total score across the patients in CONN sample represented the variability in symptoms that persisted despite treatment that provided a degree of clinical stability. Thus, cortical impoverishment may determine symptom persistence, rather than the acute severity. This is consistent with indistinguishable acute presentations, despite diverging inter-episode clinical patterns in schizophrenia (Jablensky, 2006a). Other phenotypic information such as the degree of treatment resistance and the time taken to respond to the treatment were not available to us, but these may be of interest in future studies of thickness.

Another difference between the two patient subgroups involved the correlations between negative symptom severity, cognitive deficits, and medication dosage. The relationship between cognitive deficits and negative symptoms is considered a central feature of schizophrenia that influences poor long-term functioning (Strassnig et al., 2015; Ventura et al., 2009). Our results indicated a relationship between negative symptom severity and cognitive impairment in patients with cortical thinning, but not in patients with near-normal thickness. Patients with cortical impoverishment displayed a co-occurring pattern of cognitive deficits and negative symptoms. In contrast, the cortically spared group had a notable dissociation between cognitive deficits and negative symptoms. The shared variance between negative symptoms and cognitive deficits is a well-established feature of schizophrenia (Harvey et al., 2006); our findings indicate that structural deficits may influence this reported relationship. Thus, structural heterogeneity may affect the covariance among symptom domains (negative/cognitive), rather than simply changing

the overall severity of clinical features. We also noted a dissociation between negative symptom severity and the prescribed doses of antipsychotics in the 2 clusters, although the antipsychotic dose had no significant relationship with symptoms or cognitive deficits in either cluster. To ascertain if the treatment response of the 2 subgroups differs, especially in the domain of negative symptom severity, larger samples with data on cumulative antipsychotic exposure are required.

2.4.5 Limitations

Our study has several strengths, including the recruitment of an IQ-matched patient and control group, and validation of the initial cluster solution in a validation sample with different illness duration. While the healthy subjects in our discovery sample (group matched for IQ with patients) likely differed from their peers in the validation sample, majority of healthy controls in each of the 2 samples aggregated within the structurally unimpaired subgroup. This indicates that over-sampling cognitively underperforming healthy subjects has not introduced systematic errors in the retrieved cluster structure and composition. Some limitations also require consideration. First, the multivariate patterns that separated the two subgroups in one dataset cannot be re-applied to other samples. Second, we lacked prospective data to confirm the stability of the reported clusters. Third, we are not able to conclude with certainty that the number of thickness-based clusters is limited to two, as increasing the sample size may capture more sources of variance that are missing in our current sample, but may yield further partitions within the patient group. Finally, despite our best efforts, the proportion of female participants remained lower than optimal. We urge caution when readers attempt to generalize our findings to mixed samples.

Chapter 3 Cortical Impoverishment Subgroup in First-episode Psychosis

Symptoms of schizophrenia are closely related to aberrant language comprehension and production. In this Chapter, we aimed to first seek patient subgroups with different neurobiological signatures and then quantify linguistic indices that capture the symptoms of "negative formal thought disorder" (i.e., fluency, cohesion, and complexity of language production). We characterized a patient subgroup with thinner cortex in first-episode psychosis. This subgroup, identifiable through macroscopic changes, is also distinguishable in terms of neurochemistry (frontal glutamate) and language behavior (complexity and cohesion of speech). This study supports the hypothesis that glutamate-mediated cortical thinning may contribute to a phenotype that is detectable using the tools of computational linguistics in schizophrenia. This chapter was adapted from the manuscript published on *Frontiers in Human Neuroscience* [2].

3.1 Introduction

3.1.1 Language Deficits in Schizophrenia

Schizophrenia is a disorder that affects how language is employed in everyday use during social interactions (Covington et al., 2005; Kuperberg, 2010; Wible, 2012). Based on the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) (American Psychiatric Association, 2013), all of the 5 symptom criteria for diagnosing schizophrenia involve speech and language in one form or another (American Psychiatric Association, 2013). For example, hallucinations are often voices that speak (Alderson-Day et al., 2021); negative symptoms are characterized by 'alogia' or reduced speech fluency; thought disorder is expressed as deviations in speech; catatonic features often include mutism (lack of speech production) (*Sims' Symptoms in the Mind: Textbook of*

[2] A version of this chapter has been published on *Frontiers in Human Neuroscience* (Liang, Silva, et al., 2022)

Descriptive Psychopathology - 7th Edition, n.d.); delusions often include an element of misinterpretation of social conversations or deficits in the use of propositional language (Zimmerer et al., 2017). Despite this strong linguistic dependency of the construct of schizophrenia, not every patient diagnosed with this illness displays a detectable speech disturbance (Kircher et al., 2018a; Oomen et al., 2022; Roche et al., 2015). It is important to identify patients who are most likely to be afflicted in the language domain, as speech disturbances directly affect the educational and occupational success (Palaniyappan et al., 2019), interpersonal (Tan et al., 2014) and social functioning (Marggraf et al., 2020) and endured stigma (Penn et al., 2000). Identification of this subgroup may assist in prognostication in schizophrenia, as well as making early and targeted interventions for a group that may have higher educational and vocational needs possible, before they manifest significant deficits in these domains.

3.1.1.1 Computational Measures of Language Deficits

The heterogeneity of linguistic deficits may stem from the presence of a subgroup of patients who do not display the expected language anomalies (Oomen et al., 2022). Alternatively, conventional measures of 'formal thought disorder (FTD)' that seek to examine overt communication difficulties may miss the subtle aspects of this deficit, thus introducing an apparent heterogeneity (Mikesell & Bromley, 2016). We need sensitive and objective measures of language indices to study this issue in detail (See Elvevag et al. (Elvevåg et al., 2010; Holmlund et al., 2020) and Foltz et al. (Foltz et al., 2016) for more explanations). One of these tools is natural language processing (NLP) in computational linguistics (Corcoran et al., 2020; Corcoran & Cecchi, 2020; Hitczenko et al., 2021; Ratana et al., 2019). NLP tools use computer algorithms to understand and analyze written text or speech. NLP is a branch of artificial intelligence that uses real-world language as input, processes it using linguistic rules or patterns identified through statistics, to allow machines to make sense of our language. Such NLP tools do not rely on a clinician's inferential skill to assess the cognitive-linguistic health status (Voleti et al., 2020) of patients from early stages of psychosis (Delvecchio et al., 2019) and are able to predict psychosis onset in individuals at clinical high-risk (CHR) (Bedi et al., 2015).

These approaches have broadly focused on syntactic (Covington et al., 2005; Delvecchio et al., 2019; Thomas, 1996; Thomas et al., 1990) and semantic indices (Alonso-Sánchez et al., 2022; Bar et al., 2019; Corcoran et al., 2018; Parola et al., 2022) as the affected domains in psychosis.

Prior studies that focused on quantitative analysis of language have established the following dysfunctions in patients with schizophrenia. First, patients display syntactic simplification (Bilgrami et al., 2022; DeLisi, 2001; Fraser et al., 1986; King et al., 1990; R. D. Morice & Ingram, 1982, 1983; R. Morice & McNicol, 1986) i.e., they use simple constructions with minimal clause dependencies and also with a limited richness of content. Secondly, patients show patterns of reduced cohesion (Crider, 1997), for example, lacking prior reference when invoking a description (Chaika & Lambe, 1989) or insufficient lexical repetitions (Gupta et al., 2018) needed to generate cohesion during a discursive discourse (Crossley et al., 2016). Reduced syntactic complexity and cohesion can lead to aberrant word graphs (Mota et al., 2012) and a reduction in number of words spoken (reduced fluency) (Allen et al., 1993; DeLisi, 2001; Morgan et al., 2021).

3.1.2 Detecting Subgroups with Language Dysfunctions

While some of these features have been linked to the presence of clinically detected FTD, the rating-scale measures of FTD have been poor predictors of linguistic dysfunction per se (Mackinley et al., 2021; Tang et al., 2021). Furthermore, as symptom measures fluctuate over time (state-like), they have limited utility in identifying stable subgroups (Jablensky, 2006b). Even among speech characteristics, those that relate to 'positive symptoms' appear to be more state-related, while those relating to negative symptoms (or Impoverishment of Thinking (Liddle, Ngan, Caissie, et al., 2002b)) appear to be more pervasive. More trait-like measures, e.g., those derived from brain anatomy or genetic composition, that map on to emerging biological insights (e.g., implicating the glutamatergic synapses (Iyegbe & O'Reilly, 2022; Trubetskoy et al., 2022)), may be required to see if specific subgroups of patients have linguistic deficits. Furthermore, as antipsychotics themselves can induce language impairment (de Boer et al., 2020), recruitment of patients with first-episode psychosis with minimal exposure to

antipsychotic medications is necessary to identify subgroups with language dysfunction from illness onset.

3.1.2.1 Cortical thickness-based Subgroups

In the current study, we first identify subgroups of patients with first-episode schizophrenia using the neuroanatomical measure of MRI-derived cortical thickness. Structural neuroanatomical features are considered to be more stable than symptom rating and physiological recordings, which can vary on a day-to-day basis. In addition, MRI-derived thickness is quantified objectively in an automatized manner with minimal manual intervention in the quantification process. Thus, brain structure can provide more stable and reliable clustering solutions. Further, aberrant cortical thickness has been reported in various illness stages of schizophrenia (Zhao et al., 2022), and has been also found to relate to track the inter-individual differences in psychotic symptoms (Oertel-Knöchel et al., 2013) and Thought and Language Disorder scores in schizophrenia (Palaniyappan et al., 2020). Prior cluster analytic studies have uncovered a consistent cluster of patients with generalised reduction in cortical thickness (Chand et al., 2020a; Dwyer et al., 2018a; Liang, Heinrichs, et al., 2022). We use similar methods in this study.

3.1.3 Cortical thickness and Glutamate

After deriving thickness-based subgroups, we examined if these subgroups have a meaningful neurochemical basis for their differences, by examining the MRS-derived glutamate levels measured from their frontal cortex, extending our recent work (Liang, Heinrichs, et al., 2022) to a larger sample.

Abnormal cortical thickness in schizophrenia has been previously linked to dysregulated glutamate levels (Plitman et al., 2014, 2016; Shah et al., 2020) and glutamatergic dysfunction had been considered to contribute to the ‘formal thought disorder’ burden in schizophrenia (Kircher et al., 2018a). We select dACC as our region of interest for glutamate measurement as it constitutes the core hub of the large-scale brain network called the Salience Network that appears to play a key role in the neurocognitive dysfunction in schizophrenia (Palaniyappan, 2021b).

3.1.4 Negative FTD-related Language Features

Finally, we used a picture description task to study computational linguistic measures that are reflective of a "negative" formal thought disorder, first described by Fish (Casey & Kelly, 2019) and later reported by Andreasen (Andreasen, 1979) and others (Kircher et al., 2018a) as being more characteristic of established schizophrenia. Negative FTD is characterized by reduced quantity and quality of speech output; in a linguistically impoverished subgroup, this will be reflected in (i) reduced fluency (number of words spoken), (ii) reduced cohesion (measured by counting instances of content with prior reference, i.e. repeat content lemmas, e.g., run, running and ran), and (iii) reduced syntactic complexity (mean length of sentences, clauses and minimal terminable units [T-units, the smallest word group that could be considered a grammatical sentence, often composed of a main clause and subordinate clauses attached to it (Hunt, 1970)]).
While there are numerous quantitative linguistic measures reported to be different in case-control comparisons, we chose items that predominantly map onto the negative symptom domain of schizophrenia (Bilgrami et al., 2022; Tan et al., 2021), independent of corpus-based distributional probabilities (which has limitations in understanding compositionality (Lenci, 2018) - a crucial locus of dysfunction in schizophrenia (Chaika, 1974)) and are readily interpretable (e.g. we did not use referential cohesion measure which is conflated in the presence of perseveration (Lundin et al., 2020)). The features we selected are also intuitive in their link to known clinical features (reduce word count relates to alogia; lack of cohesion and simplified syntax relates to the poverty of content (Bedi et al., 2015; Corcoran et al., 2018; Minor et al., 2019)). Furthermore, compared to other aspects of communication disturbances, the features of reduced fluency and richness of content (negative factor) selectively relate to poor response to treatment (Peralta et al., 1992). A neuroanatomically-defined subgroup high in these 'negative FTD type' linguistic features can be expected to be of prognostic relevance in schizophrenia.

3.1.5 Hypotheses

Considering previous structural imaging-based cluster analytic studies, our primary hypothesis is that patient subgroups with distinct cortical thickness patterns can be

identified in first-episode schizophrenia. In particular, a subgroup with widespread cortical thinning would emerge. Considering the association between cortical thinning, dysregulated glutamate levels and formal thought disorder burden, our secondary hypotheses are as follows: (i) The subgroup with deviant cortical thickness patterns also has abnormal glutamate levels measured in dACC; (ii) This subgroup displays impairments (negative FTD-type) in language production features, such as syntactic simplicity, reduced speech output and lower speech cohesion.

3.2 Methods

3.2.1 Participants

We recruited 76 patients with first-episode psychosis from the Prevention and Early Intervention for Psychosis Program at the London Health Sciences Centre in London, Ontario, Canada from 2017 to 2021. Since 10 patients were unable to go through magnetic resonance imaging (MRI) scanning, we included data collected for 66 patients in this study. Inclusion criteria for patients include (1) having less than 14 days of lifetime exposure to antipsychotic medications, and (2) being at their first clinical presentation of psychotic symptoms. We followed up with patients for over 6 months to determine the validity of a diagnosis of first-episode schizophrenia prospectively. We also recruited 36 healthy volunteers, group-matched for age, sex, and parental socioeconomic status, who had no personal history of mental illnesses and no family history of psychotic disorders. All participants had no significant head injury, drug/alcohol dependence or major medical illnesses, were fluent in English, and provided written informed consent to participate in the study. The work reported here is part of a longitudinal study registered on clinicaltrials.gov (Identifier: NCT02882204) and approved by the Western University Health Sciences Research Ethics Board, London, Ontario, Canada.

3.2.2 Measures and instruments

3.2.2.1 Psychiatric Symptoms

Symptom severity was measured by the 8-item Positive and Negative Syndrome Scale (PANSS) (C.-H. Lin et al., 2018) through interviews conducted by two research psychiatrists. Functional outcome was indexed by the Social and Occupational Functional Assessment Scale (SOFAS) (Morosini et al., 2000b). The duration of untreated psychosis was calculated using the first report of positive symptoms as the starting point. We also obtained patients' NEET (Not in Education, Employment and Training) status. We converted participants' level of education into an ordinal scale (1: incomplete high school diploma; 2: completed high school diploma; 3: some post-secondary study; 4: completed post-secondary study or higher). Lifetime antipsychotic medication exposure was calculated by multiplying the number of days taking antipsychotics and prescribed Defined Daily Dose (DDD) values according to the World Health Organization (*Defined Daily Dose (DDD)*, n.d.).

3.2.2.2 Thought and Language Index (TLI)

Data was collected using TLI (Liddle, Ngan, Caissie, et al., 2002b) to reflect the two dimensions of language disorders in schizophrenia, impoverishment and disorganization. We used a picture-speech task that induced participants to elaborate 1-min spontaneous speech (oral soliloquies) in response to three images from the Thematic Apperception Test (Murray, 1943) after hearing specific instructions: "I am going to show you some pictures, one at a time. When I put each picture in front of you, I want you to describe the picture to me, as fully as you can. Tell me what you see in the picture, describe what you see in this image, and what you think might be happening." Responses were recorded, transcribed, and scored. Impoverishment score was the sum of scores for these 3 dimensions: poverty of speech, weakening of goal and preservation of ideas, while disorganization score was indexed by 5 dimensions: looseness, peculiar use of words, peculiar sentences, peculiar logic, and distractibility.

3.2.2.3 Language assessment

The same transcribed speech samples also underwent automatic analysis to measure both syntactic complexity and cohesion at the semantic level.

3.2.2.3.1 Tool for the automatic analysis of syntactic complexity and sophistication (TAASSC)

TAASSC is an open-source (https://www.linguisticanalysistools.org/taassc.html) used in wide-ranging languages and grammatical frameworks with recent improvements in machine-learning approaches and Natural Language Processing (NLP). This tool is complemented by a syntactic complexity analyzer (SCA)—a package with an accuracy of around 90% in part of speech (POS) tagging. The package includes a traditional and large measure of syntactic complexity following the taxonomy in Lu (2010) (Lu, 2010): mean length of sentences (MLS), mean length of T-units (MLT) and mean length of clauses (MLC), word counts, and Terminal Units (T-unit) defined as the main clause with its attached subordinate clause(s) indicating speech cohesion as well as logical flow in the given information (See Supplementary Material for more detailed descriptions).

3.2.2.3.2 Tool for the Automatic Analysis of Cohesion (TAACO 2.0)

TAACO 2.0 (https://www.linguisticanalysistools.org/taaco.html) (Crossley et al., 2016) is a freely available text analysis tool which incorporates a wide-ranging of global indices— over 150 classic and recently developed indices related to text cohesion—local, global, and overall text cohesion can significantly predict both text cohesion and speaking quality whether the speaking samples show greater semantic overlap incorporating automated semantic analysis (Crossley et al., 2019). TAACO includes 194 indices of cohesion in seven main categories: Type token ratio (TTR) and density, lexical overlap (sentences), lexical overlap (paragraphs), semantic overlap, connectives, givenness, and source text similarity. Of this, we focus on the givenness index as we analyze speech rather than written text. Givenness, as opposed to newness in a discourse transcript, indicates whether information occurring in a segment has already occurred in an earlier segment. Repeat content words or lemmas (e.g., nouns, verbs, adjectives, etc.)

are calculated as a proportion of the total number of words spoken within each 1-minute picture description.

3.2.3 MRI and MRS Acquisition and Processing

A total of 66 participants underwent neuroanatomy and spectroscopy scanning with an ultra-high-resolution 7-Tesla MRI scanner (8-channel transmit and 32-channel receive head-only coil) at Centre for Functional and Metabolic Mapping (CFMM), Western University, London, Canada. Structural images were obtained by a T1-weighted 0.75 mm isotropic MP2RAGE sequence with the following parameters: Repetition Time (TR) = 6000 ms, Time to Echo (TE) = 2.83 ms, Inversion Time $(TI)_1$ = 800 ms, TI_2 = 2700 ms, flip-angle 1 (α_1) = 4°, flip-angle 2 (α_2) = 5°, Field of View (FOV) = 350 mm × 263 mm × 350 mm, T_{acq} = 9 min 38 s, $iPAT_{PE}$ = 3 and 6/8 partial k-space, slice thickness = 0.75mm. Freesurfer (version 6.0.0) (*FreeSurfer*, n.d.) was used to preprocess the obtained T1-weighted images. FreeSurfer provides automated brain image processing steps including intensity normalization, tissue segmentation and cortical parcellation (*Recon-All - Free Surfer Wiki*, n.d.). Visual inspections of errors such as surface location misplacement were carried out according to the troubleshooting guide provided by FreeSurfer team (*FsTutorial/TroubleshootingData - Free Surfer Wiki*, n.d.). We acquired the cortical thickness values based on the Destrieux parcellation atlas (Destrieux et al., 2010b). Magnetic resonance spectroscopy (MRS) signal was measured on a voxel placed in the dorsal anterior cingulate cortex (dACC; MNI coordinates: 1, 16, 38). The details of MRS acquisition and analysis have been previously described (See Supplementary Material) and a subset of this sample has been reported in prior works (Jeon et al., 2021; Liang, Heinrichs, et al., 2022).

3.2.4 Statistical Analyses

We applied agglomerative hierarchical clustering with Ward's method and Euclidean distance to 148 cortical thickness values (based on Destrieux parcellation atlas (Destrieux et al., 2010b) output using FreeSurfer) of all 102 participants including 66 patients and 36 healthy controls. Agglomerative hierarchical clustering starts with calculating the distance (e.g., Euclidean distance) between all pairs of data objects and putting the most

similar data objects into the same cluster. The newly formed clusters are then again grouped with one another based on a linkage function (e.g., Ward's method), until all data objects merge into one single cluster. The optimal number of clusters was determined by the consensus votes from 16 clustering validity indices using NbClust (Charrad et al., 2014) in R (version 4.0.3). Pearson's chi-squared tests (with Yate's continuity correction) were used to compare categorical variables, while Welch t-tests were used to compare continuous variables. If the obtained subgroups showed difference(s) in confounding variables (e.g., age or gender), ANCOVA was used to show effects between subgroups while accounting for effects of the covariates. We used FreeSurfer to find (1) between-cluster differences in vertex-by-vertex cortical thickness while regressing out the effect of age using a general linear model, and to locate (2) cortical regionals that correlated with glutamatergic metabolic levels. The thickness values at each vertex were mapped to the surface of an average brain template, and the cortical map was smoothed with a Gaussian kernel of 10mm full width at half-maximum. We used Monte Carlo simulations with 1000 permutations and a cluster-forming threshold of P = 0.05 (two-tailed) to correct for multiple comparisons as implemented in FreeSurfer.

3.2.5 Sensitivity Analyses

To examine the effects of chosen types of participants, clustering methods and cortical parcellations on the findings, we performed the following sensitivity analyses (Parpia et al., 2022) and assessed the robustness of the conclusions.

1) To examine how changing participant type affects the clustering solution: Since we included both patients and healthy controls in our clustering procedure, there were naturally two categories of participants and hence a 2-cluster solution could emerge as a dominant effect. To rule out this possibility, we included only patients and performed the same clustering procedure.

2) To examine how clustering methods affect the clustering solution: We replaced the agglomerative hierarchical clustering method with K-means clustering. Compared to hierarchical clustering that computes pairwise similarity between

datapoints, K-means clustering holds the assumption that each cluster has a representative center point, called “centroid”. K-means clustering starts with randomly selecting a pre-defined number of centroids, and then assigned every datapoint to its nearest centroids to form clusters. New centroids are then re-calculated for the newly formed clusters. This process is iterated until the centroids do not change. While hierarchical clustering assumes a nested tree-like data structure, K-means clustering divides datapoints into non-overlapping subgroups. Participant subgroup assignments from these two different clustering methods were compared to investigate the effects of chosen clustering method on results.

3) To examine how cortical parcellation atlas affects the clustering solution: The cortical parcellation system developed by Destrieux at al. was developed based on classical neuroanatomical nomenclature (Destrieux et al., 2010b). In contrast to this brain atlas based on structurally distinct regions, we selected another brain parcellation system based on functionally distinct regions (Schaefer et al., 2018; Thomas Yeo et al., 2011). This approach segments the brain into large-scale brain networks based on functional MRI resting-state functional connectivity (RSFC) and further maps cortical region boundaries based on homogeneous RSFC patterns. We used the 7-network (Visual, Somatomotor, Dorsal Attention, Ventral Attention, Limbic, Default, Frontoparietal Network) atlas with 200 cortical regions of interest (ROIs), compared to 148 ROIs in the Destrieux atlas (See Appendix E for cortical parcellation maps).

3.3 Results

3.3.1 Subgroup Characteristics

Demographic, clinical, linguistic, and neurobiological measurements of first-episode psychosis patients and healthy controls are provided in Table 5.

The cluster validity procedure of hierarchical clustering of 148 cortical thickness values of 66 patients with first-episode psychosis and 36 healthy controls suggested that a two-

cluster solution is optimal (9/16 cluster validity indices). Proceeding with a two-cluster solution, around 70% of patients (n = 46) with first-episode psychosis were clustered with the majority of the healthy controls (n = 33) in Cluster 1, while the remaining 30% of patients (n = 20) were in Cluster 2 which only included 3 healthy individuals. Demographic, clinical, neurometabolite and language functioning information of the three subgroups (Cluster 1 patients, Cluster 2 patients and Cluster 1 healthy controls) is summarized in Table 6, and patient subgroups comparisons of key variables are shown in Figure 9. Overall, compared to Cluster 1 patients, Cluster 2 patients have significantly older age, lower mean cortical thickens (non-significant age effect), higher glutamate concentration in dACC (non-significant age effect) as well as lower mean length of T-units (complexity) and repeated contents lemmas (cohesion) despite a preserved number of words within the given time frame (fluency). There is no significant difference between the two clusters in duration of untreated psychosis, lifetime exposure to antipsychotics, PANSS and SOFAS scores.

Comparisons of cortical thickness between patients from the two subgroups (adjusted for age) are shown in Figure 10. After multiple testing corrections, patients in Cluster 1 had significantly lower thickness in 8 clusters (average area size = 410.44 mm^2) in the left hemisphere and right hemisphere respectively (Figure 11 and Table 7). Comparisons of cortical thickness between the patients and controls from Cluster 1 (adjusted for age and corrected for multiple comparisons) revealed no regional differences in thickness values, indicating that this subgroup of patients had a 'healthy' cortical morphological pattern. Multiple cortical regions were correlated with dACC glutamate levels in patients (Figure 12), but these correlations were not significant after multiple testing corrections. Correlation matrices of other variables of interest are presented in Supplementary Material.

In summary, patients from Cluster 1 had similar neuroanatomical patterns to healthy controls, while patients from Cluster 2 were a distinct subgroup with widespread cortical thinning, higher glutamate concentration, and exhibited and reduced syntactic complexity and cohesion. This subgroup was thus impoverished in cortical structure as well as linguistic features.

Table 5 Demographic, clinical, neurobiological, and linguistic data of patients with first-episode psychosis and healthy controls

	FEP	HC	Pearson's Chi-squared test or Welch T-tests	
N	66	36	-	
Demographics				
Age (years)	22.82 (4.77)	21.53 (3.32)	t (94.043) = 1.6005, p-value = 0.1128	
Female/Male	12/54	12/24	X-squared (1) = 2.1896, p-value = 0.1389	
Education Scale (1/2/3/4)	15/18/20/13	5/3/14/13	X-squared (3) = 8.0131, p-value = 0.04574	*
Clinical				
PANSS-8 (Total)	25.18 (6.72)	-	-	
PANSS-8 Positive	11.62 (3.48)	-	-	
PANSS-8 Negative	6.97 (4.41)	-	-	
PANSS-8 General	5.18 (2.46)			
DUP (weeks) (median [IQR])	11.0 [4, 24]	-	-	
DDD lifetime exposure (median [IQR])	0.5 [0, 2.99]	-	-	
Antipsychotic naïve (%)	42%			
Functional				
SOFAS	40.96 (12.40)	-		
NEET status: Yes/No	24/29	0/31	X-squared (1) = 17.497, p-value < 0.0001	***
Neurobiological				
Glutamate (mM)	6.79 (1.16)	6.51 (1.35)	t (53.766) = 0.99493, p-value = 0.3242	
Mean cortical thickness (mm)	2.45 (0.12)	2.48 (0.096)	t (94) = 1.90350, p-value = 0.0600	
Language Variables				
TLI (Total)	1.48 (1.41)	0.29 (0.39)	t (81.668) = 6.4188, p-value < 0.00001	***
TLI Impoverishment	0.57 (0.72)	0.14 (0.25)	t (87.397) = 4.3669, p-value < 0.0001	***
TLI Disorganization	0.91 (1.21)	0.15 (0.26)	t (75.114) = 4.9033, p-value < 0.00001	***
Average total number of words	119.18 (38.85)	141.34 (29.83)	t (88.706) = -3.1775, p-value = 0.002045	***

MLS	14.37 (4.58)	14.21 (2.74)	t (96.753) = 0.20899, p-value = 0.8349	
MLT	12.21 (3.00)	12.49 (2.08)	t (93.295) = -0.56025, p-value = 0.5767	
MLC	7.73 (1.20)	8.19 (1.18)	t (73.659) = -1.8858, p-value = 0.06327	
Repeated contents lemmas	0.229 (0.047)	0.247 (0.033)	t (89.792) = -2.1269, p-value = 0.03617	*

Note: Values are reported as "Mean (SD)" unless specified otherwise. IQR: Interquartile range. FEP: first episode psychosis; HC: healthy controls. PANSS: Positive and Negative Symptoms Scale; DUP: duration of untreated psychosis; DDD: Defined Daily Dose; SOFAS: Social and Occupational Functioning Assessment Scale; NEET: not in employment, education and training; TLI: Thought and Language Index; MLS: mean length of sentences, MLT: mean length of T-units, MLC: mean length of clauses.
* p values < 0.05
** p values < 0.01
*** p values < 0.001

Table 6 Demographic, clinical, neurobiological, and linguistic data of subgroups.

	Subgroup 1 Patients	**Subgroup 2 Patients**	**Patient Subgroup Comparison**	**Subgroup 1 Healthy Controls**
N	46	20		33
Demographics			**Pearson's Chi-squared test or Welch T-tests**	
Age (years)	21.37 (3.72)	26.15 (5.31)	t (27.433) = -3.6527, p-value = 0.001081 *	21.15 (3.08)
Female/Male	10/36	2/18	X-squared (1) = 0.62274, p-value = 0.43	12/21
Education Scale (1/2/3/4)	9/14/16/7	6/4/4/6	X-squared (3) = 3.7761, p-value = 0.2867	5/3/14/10
Clinical			**Welch T-tests**	
PANSS-8 (Total)	25.76 (7.02)	23.85 (5.91)	t (42.677) = 1.1376, p-value = 0.2616	-
PANSS-8 Positive	11.67 (3.46)	11.50 (3.64)	t (34.519) = 0.18146, p-value = 0.8571	-

PANSS-8 Negative	7.48 (4.46)	5.80 (4.15)	t (38.757) = 1.4755, p-value = 0.1481	-
PANSS-8 General	5.22 (2.41)	5.10 (2.63)	t (33.503) = 0.17063, p-value = 0.8655	
DUP (weeks) (median [IQR])	13 [4, 26]	8.5 [5.75, 16.5]	t (23.362) = -0.53167, p-value = 0.6027	-
DDD lifetime exposure (median [IQR])	0 [0, 2.54]	1.25 [0, 3.9]	t (20.156) = -1.6477, p-value = 0.1149	-
Functional			**Welch T-tests**	
SOFAS	40.98 (13.19)	40.90 (10.67)	t (44.354) = 0.025424, p-value = 0.9798	-
NEET status: Yes/No	19/19	5/10	X-squared (1) = 0.62686, p-value = 0.4285	-
Neurobiological			**ANOVA with age as a covariate**	
Glutamate (mM)	6.57 (1.03)	7.28 (1.30)	F(1)=5.10, p = 0.028 * Age effect: p = 0.13	6.50 (1.40)
Mean cortical thickness (mm)	2.50 (0.068)	2.32 (0.057)	F(1)=126.225, p < 0.000 *** Age effect: p = 0.12	2.49 (0.061)
Language Variables			**Welch T-tests**	
TLI (Total)	1.28 (1.28)	1.93 (1.64)	t (29.517) = -1.5629, p-value = 0.1287	0.28 (0.40)
TLI Impoverishment	0.48 (0.61)	0.79 (0.92)	t (26.725) = -1.3843, p-value = 0.1777	0.13 (0.23)
TLI Disorganization	0.82 (1.14)	1.14 (1.37)	t (30.974) = -0.92366, p-value = 0.3628	0.16 (0.26)
Average total number of words	119.47 (35.45)	118.43 (47.46)	t (24.954) = 0.084721, p-value = 0.9332	141.53 (31.15)
MLS	14.58 (4.01)	13.91 (5.89)	t (23.59) = 0.4227, p-value = 0.6763	14.03 (2.67)

MLT	12.79 (3.09)	10.75 (2.20)	t (43.928) = 2.9509, p-value = 0.005066 **	12.45 (2.13)
MLC	7.90 (1.25)	7.30 (0.96)	t (40.658) = 2.0284, p-value = 0.04911 *	8.24 (1.21)
Repeated contents lemmas	0.240 (0.044)	0.204 (0.047)	t (28.741) = 2.6991, p-value = 0.01152 *	0.249 (0.034)
			ANOVA with age as a covariate	
TLI (Total)			F(1)=2.96, p = 0.090 Age effect: p = 0.39	
TLI Impoverishment			F(1)=2.61, p = 0.11 Age effect: p = 0.29	
TLI Disorganization			F(1)=1.00, p = 0.32 Age effect: p = 0.15	
Average total number of words			F(1)=0.009, p = 0.92 Age effect: p = 0.126	
MLS			F(1)=0.25, p = 0.62 Age effect: p = 0.25	
MLT			F(1)=6.46, p = 0.014 * Age effect: p = 0.57	
MLC			F(1)=3.30, p = 0.074 Age effect: p = 0.126	
Repeated contents lemmas			F(1)=7.56, p = 0.0081 ** Age effect: p = 0.515	

Note: Values are reported as "Mean (SD)" unless specified otherwise. IQR: Interquartile range. FEP: first episode psychosis; HC: healthy controls. PANSS: Positive and Negative Symptoms Scale; DUP: duration of untreated psychosis; DDD: Defined Daily Dose; SOFAS: Social and Occupational Functioning Assessment Scale; NEET: not in employment, education and training; TLI: Thought and Language Index; MLS: mean length of sentences, MLT: mean length of T-units, MLC: mean length of clauses.

* p values < 0.05

** p values < 0.01

*** p values < 0.001

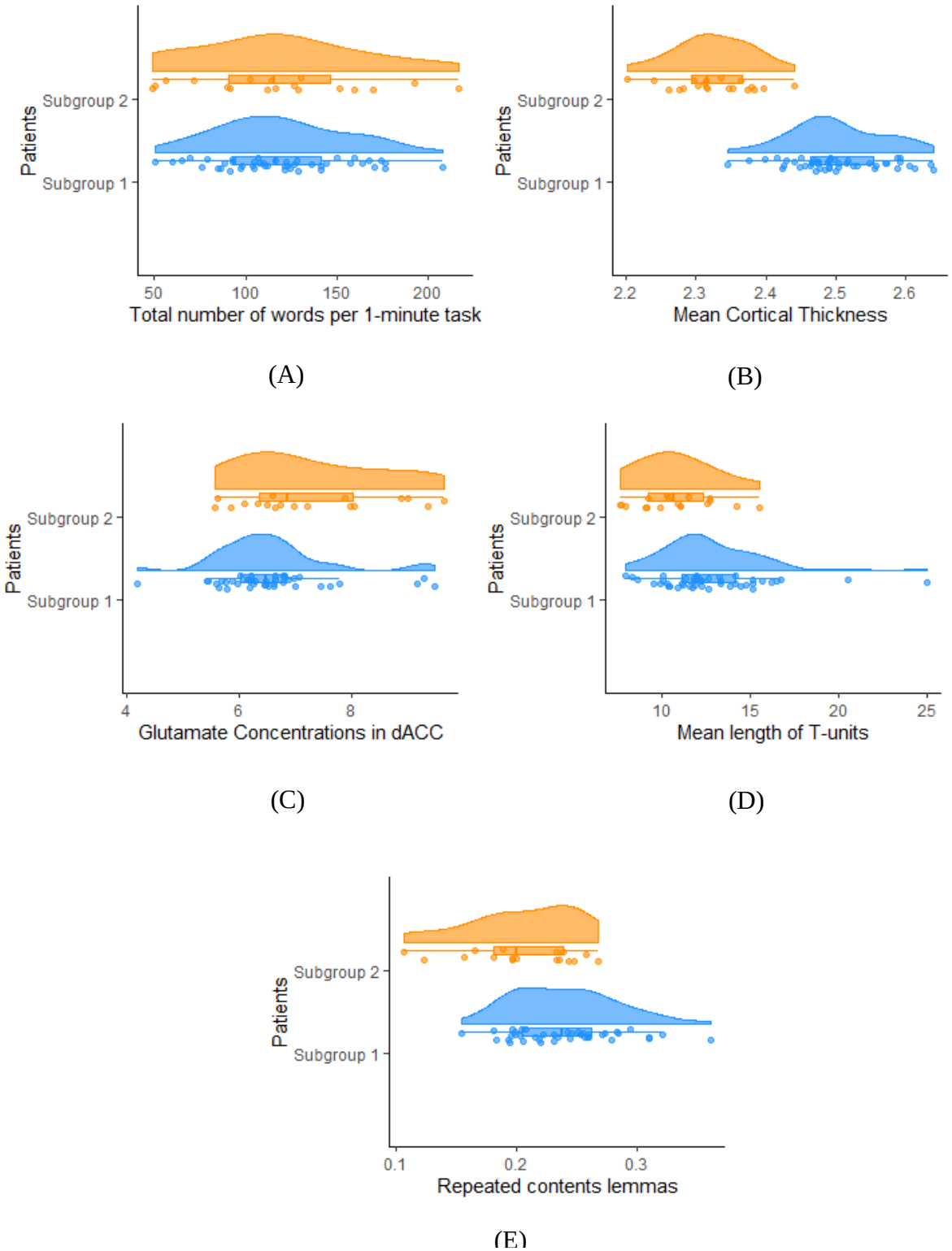


Figure 9 Raincloud plots depicting the comparisons of distributions between the two patient subgroups.

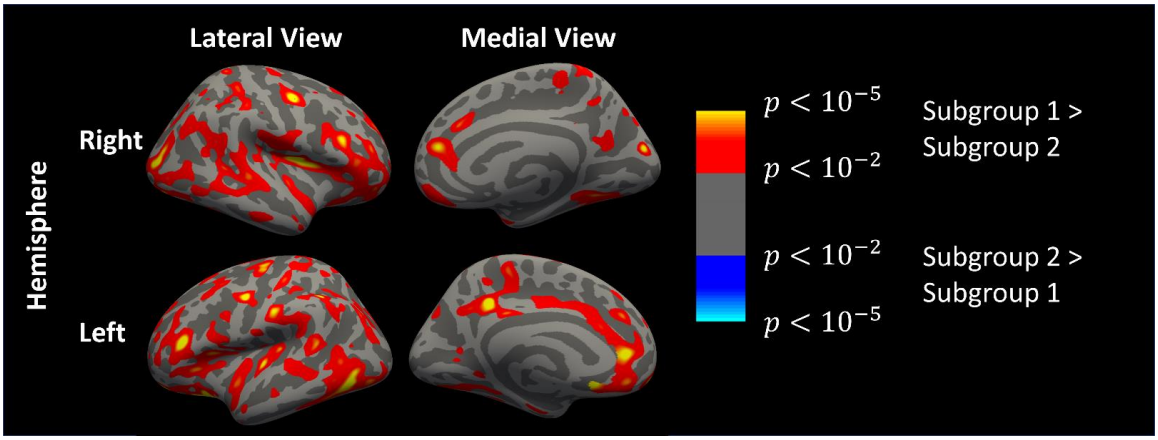


Figure 10 Cortical thickness map of differences between patients from Subgroup 1 and Subgroup 2 generated by FreeSurfer (regressing out age effect with a general linear model, uncorrected). Left hemisphere and right hemisphere in lateral and medial view respectively.

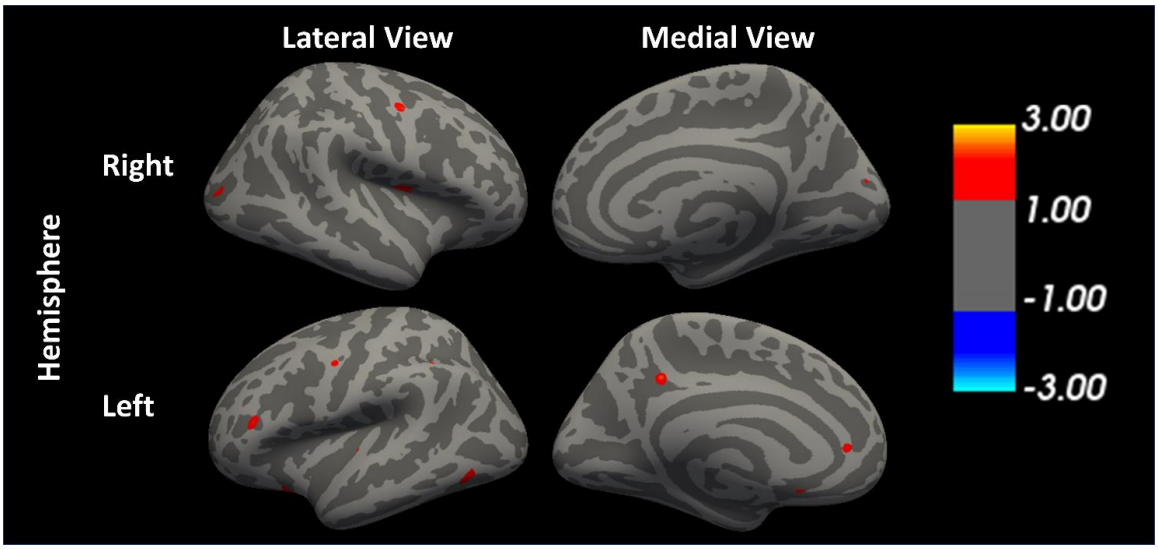


Figure 11 Cortical thickness map of differences between patients from Subgroup 1 and Subgroup 2 generated by FreeSurfer.

***Note*: Regressing out age effect with a general linear model, multiple comparison corrections using Monte Carlo simulations of 1000 permutations with 1000 permutations with a cluster-wise threshold of 0.05). Left hemisphere and right hemisphere in lateral and medial view respectively. The scale indicates log10 of p-**

values. Red and yellow represent higher cortical thickness in patients from Subgroup 1.

Table 7 Cortical regions with their area size (mm2) showed significant differences after Monte Carlo simulation correction between patients from the two subgroups, in the left and right hemispheres respectively.

	Left Hemisphere	Right Hemisphere
Inferior temporal	1) 1082.27	
Lateral orbitofrontal	2) 579.75 3) 530.65	
Rostral middle frontal	4) 462.95	1) 560.93 2) 260.59
Precentral	5) 389.09	3) 420.84 4) 247.97
Precuneus	6) 289.00	
Rostral anterior cingulate	7) 234.62	
Postcentral	8) 182.27	
Lateral occipital		5) 437.17 6) 333.73 7) 266.67
Lingual		8) 258.06

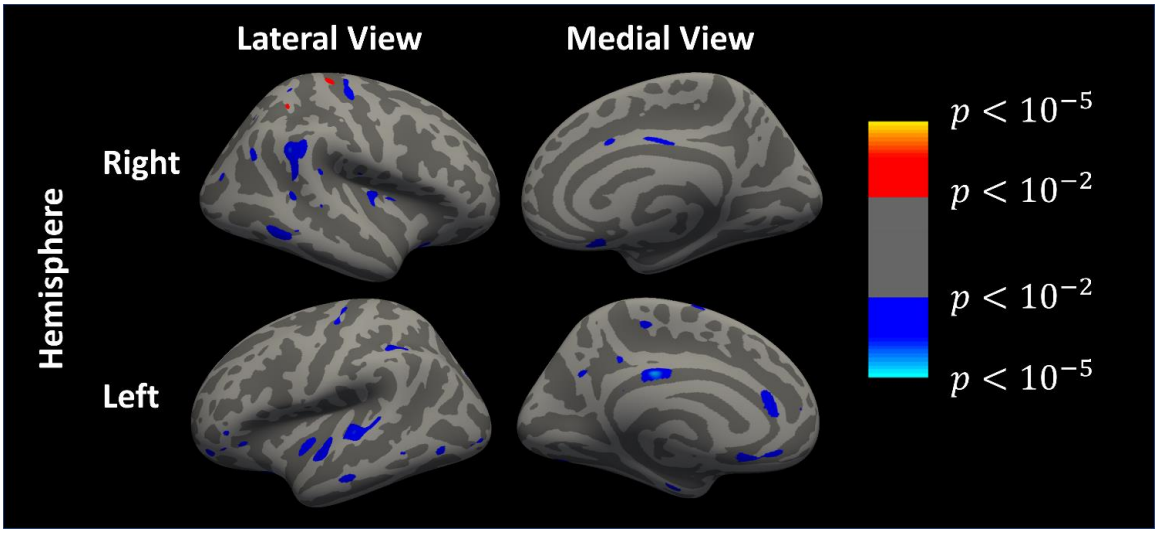


Figure 12 Cortical regions that are correlated with dACC glutamate levels (uncorrected) generated by FreeSurfer.

***Note*: Left and right hemispheres in lateral and medial view respectively. Blue/cyan colours indicate negative correlations while red/yellow colours indicate positive correlations.**

3.3.2 Cluster Solution Consistency

The variations of the same clustering procedure are summarized Table 8. Overall, the two-cluster solution was consistently the most favoured. Out of the 66 patients, 37 patients (56%) were consistently classified in the 'cortically healthy' subgroup while 14 patients (21%) were consistently classified in the 'cortically impoverished' subgroup, adding up to 77% of patients classified concurrently in all scenarios.

Table 8. Sensitivity analyses to examine the effects of different methods on findings.

Variations		1	2 (original)	3	4	5
(1) Types of participants	Patients only	✓				
	Patients and healthy controls together		✓	✓	✓	✓

(2) Clustering Methods	Hierarchical clustering	✓	✓	✓		
	K-means clustering				✓	✓
(3) Parcellation atlas	Destrieux	✓	✓		✓	
	Schaefer			✓		✓
Dataset dimension		66 x 148	102 x 148	102 x 200	102 x 148	102 x 200
Number of validity indices that suggested a 2-cluster solution		9/16	9/16	11/16	9/16	11/16
Number of patients classified to be in the 'cortical impoverished' subgroup		27	20	19	27	27
% Misclassified, referencing to the original analysis		10.6%	-	16.7%	13.6%	13.6%

3.4 Discussion

3.4.1 'Cortical Impoverishment' Subgroup

In the current study, we identified a subgroup of 30% of patients with first-episode schizophrenia who are distinguishable on the basis of their MRI-derived cortical thickness profiles – displaying a generalized reduction in thickness (referred to as "Subgroup 2") compared to the other group (70%) who have an unimpaired thickness profile similar to most healthy control subjects (referred to as "Subgroup 1"). Subgroup 2 is older in age at the time of the first presentation, has higher MRS-derived glutamate levels in the dorsal ACC and showed a pattern of linguistic impoverishment characterized by reduced fluency, syntactic simplicity, and repetitiveness. Taken together, these observations indicate a distinct subtype of schizophrenia that shows a pattern of cortical impoverishment along with linguistic impoverishment in the presence of higher prefrontal (dACC) glutamate levels at first presentation.

The emergence of a cortical impoverishment group showing a distributed reduction in cortical thickness compared to the other subgroup of patients and healthy controls is now a well-established feature of cluster analytical studies in schizophrenia. In a prior work where we studied two independent groups of patients with established schizophrenia as well as a part of the sample reported here, we observed a reliably identifiable subgroup of patients with cortical impoverishment (Liang, Heinrichs, et al., 2022), who did not differ from other patients in the cognitive or clinical severity. Similar findings also reported a 'cortical impoverishment subgroup' at various illness stages (Chand et al., 2020a; Dwyer et al., 2018a; Pan et al., 2020b; Sugihara et al., 2017b), supporting the stability of this subtype.

3.4.2 Cortical Thinning and Glutamate Excess

While the mechanistic processes underlying this structural deviation are still circumspect, the finding that the impoverished cortical thickness profile is associated with higher glutamate levels in dACC provided robust evidence for the hypothesis that glutamate-induced toxicity relates to structural compromise in schizophrenia (Kritis et al., 2015; Plitman et al., 2014). The relationship between structural impoverishment and glutamate

dysregulations is supported by findings reporting that they appear to share similar risk gene variants (Schultz et al., 2011), and are both associated with treatment resistance (Egerton et al., 2018; J. Li et al., 2020; Shah et al., 2020; Zugman et al., 2013), negative symptom severity (Reid et al., 2019; Walton et al., 2018; Wijtenburg et al., 2021) and cognitive impairment (Godlewska et al., 2021; Hartberg et al., 2011; Wijtenburg et al., 2021). According to the NMDA hypofunction or glutamatergic dysregulation models of schizophrenia, higher glutamate transmission may relate to excitation-inhibition imbalance (Limongi et al., 2020) and if unchecked, may result in synaptic and neuronal loss (Wang & Qin, 2010). These cellular mechanisms have been hypothesized to underlie structural deficits in schizophrenia (Plitman et al., 2014). Multilevel genetic and physiological studies are needed to further pursue this observation. We now provide an important lead in this pursuit by identifying language dysfunction in this subgroup of schizophrenia.

However, one caveat to our observation is that we measured glutamate levels only from the dACC, while cortical thickness reduction is more generalized. Prior results showing a regional correspondence of glutamate levels and structure (Plitman et al., 2016; Shah et al., 2020) indicate that this relationship is likely to be generalized across the brain. Further, other groups have focused on glutamatergic excitotoxicity in the hippocampal circuits (Lieberman et al., 2018). Taken together, our observations indicate that glutamatergic dysregulation in one brain region (dorsal ACC in our case) may influence the structure of other connected brain regions, either via distributed networks or through a generalised glutamatergic dysfunction. This hypothesis can be tested using multi-voxel MRS data (for example, see Kumar et al., 2020).

3.4.3 Cortical Thinning and Language Deficits

3.4.3.1 Syntactic Simplicity in ‘Cortical Impoverishment’ Subgroup

Through a parts-of-speech (POS) tagging approach in NLP, we studied “poverty of content” at 3 components of grammatical structures: mean length of sentences, clauses and T-units. All are large syntactic complexity indices used as a proxy of cognitive parameters because producing a T-unit is a more complex process than producing

coordinated clauses (Szmrecsanyi, 20040101). T-units serve as an informative index to distinguish the amount of independent clausal coordination in the expressed idea. Moreover, T-units provided the rule-based identification process considering the selecting word for subordination (e.g., using ‘because’) or coordination (e.g., using ‘and ’) (Beaman, 1984). Therefore, a reduction in coordinated T-units demonstrates notable syntactic simplicity in our Subgroup 2. These results are congruent with Bilgrami and colleagues’ works (Bilgrami et al., 2022) who also reported lower POS syntactic complexity in those patients who had negative symptoms. The authors found that reduced sentence length and decreased use of words that introduce dependent clauses (e.g., using complementizer or determiner pronouns such as “that” and “which”) are associated with negative thought disorder (Bilgrami et al., 2022). Additionally, our observations raise the question of whether patients with higher developmental disruption form the subgroup with cortical and linguistic impoverishment since syntactic complexity is a phenomenon that develops during childhood (Frizelle et al., 2018; Givon, n.d.) and reaches a plateau around the age of 20 (Nippold et al., 2014). If developmental disturbances during childhood and adolescence lie in the pathogenesis of schizophrenia and can be detected using NLP tools (via progressive aberrations in syntactic complexity; see Silva et al. (Silva et al., 2022)), this may provide a promising avenue for early identification.

3.4.3.2 Impaired Cohesion in ‘Cortical Impoverishment’ Subgroup

We observed a reduction of repeated content lemma (e.g., nouns, verbs, adjectives) in our Subgroup 2. This index traditionally characterizes the systematic relationship – explicit or implicit – between lexical items, i.e., cohesive cues, placed at the text surface (Sanders & Maat, 1976). For example, if two adjacent ideas (sentence-to-sentence, clause-to-clause) comprise the same noun (e.g., woman), the lexical repetition will explicitly help connect both ideas. However, if the first clause contains the word “bridge” and the second contains the word “iron”, the connection weakens even though it is logical. Therefore, in this work, we quantify cohesion (Graesser et al., 2004; Halliday & Hasan, 1976) through a lexical approach applied to how speech has been produced, without any assumption about how it is understood by listeners or readers (i.e., lexical cohesion as distinct from semantic coherence) (Just et al., 2020).

The linguistic phenomenon of reduced content word-lemmas relating to cortical thinning can be understood in several ways (Crossley et al., 2016). Firstly, reduced repetition of content-lemmas directly negatively influences the givenness of the generated speech. Givenness refers to the distribution of the given/known information or ideas as opposed to the new/unknown information. A 'cortically impoverished' patient may build ideas as small clauses with little relationship between them. Secondly, a decline in the use of repeated content lemma makes it difficult to recover the meaningful information from the preceding passage, generating a sense of empty speech (i.e., poverty of content) with reduced informative value to the listener.

3.4.4 Strengths

Our study has several strengths: We were able to overcome the difficulty of collecting speech data in an acute, untreated state of psychosis, and determine their diagnosis of first-episode schizophrenia. Furthermore, we ensured transcribers, as well as speech analysts, were blind to diagnosis. We employed ultra-high field strength MRS whereby the glutamate quantification from MS-spectra had a high specificity. Third, we used multiple clustering procedures and derived a two-cluster solution based on a majority-based consensus, adding to the stability of the observed subtype. Finally, in clinical settings, linguistic dysfunction in schizophrenia traditionally relies on a standardized rating scale (PANSS and TLI) to define speech impairment as one sign of formal thought disorder (FTD) (Elvevåg et al., 2007; Iter et al., 2018). Instead, we used automated quantitative processes to parse the subtler aspects of language dysfunction, and our results speak to the ability of using NLP tools to detect minor language impairments that cannot be detected with subjective clinical rating scales (Corcoran & Cecchi, 2020; Hitczenko et al., 2021).

3.4.5 Limitations

Nevertheless, several limitations need consideration. We had a limited number of female participants which limits generalizability; we did not see a statistical effect of sex between the groups, but our small numbers preclude a stratified analysis. Second, thickness-based clustering resulted in age differences between the subgroups; however,

we included age as a covariate in downstream analyses for glutamate and regional thickness to ensure this confound did not affect the inferences we make. Nevertheless, the non-linear influence of age on these variables cannot be ruled out. Third, we did not assess IQ formally. In our recent study where we examined the influence of cognition on thickness-based clustering in greater detail, the effect of individual differences in cognitive performance in the thickness profile was minimal among patients (Liang, Heinrichs, et al., 2022). Thus, while we can be confident that the reported thickness reduction and language dysfunction in a subgroup is not due to low extreme distributions of IQ as a result, we cannot exclude that an undetermined proportion of variance in these variables could be explained by cognitive differences. Finally, our speech samples were restricted to one language (English) and were based on a single discursive discourse (picture description) and single modality (oral soliloquies-monologue) elicited in the context of a research interview. The effect of contextual differences, language as well as types and duration of elicitation task on our linguistic observations needs further examination.

Chapter 4 Conclusions

Neuroanatomical heterogeneity exists in schizophrenia, but such variations are not restricted to the illness per se because we can also see it in healthy populations. Leveraging the variances of cortical thickness data of patients and healthy controls, we identified two subgroups based on cortical thickness profiles across the whole brain. Despite displaying similar symptom severity and social functioning, the two patient subgroups have distinct neurobiological underpinnings, and may represent different pathophysiological pathways of developing schizophrenia. The cortical thickness-based data-driven two-cluster solution presented here emerges as an invariant feature across illness stages, acute symptom severity, functional status, and treatment exposure. The two-cluster typology remains robust when reproducing it across different patient samples and varying the choices of brain parcellation atlases or clustering algorithms.

A ‘cortical impoverished’ subgroup was consistently seen across the 3 samples irrespective of illness duration, stage, or state, and the strength of the scanners used. We can link the putative excitotoxicity (glutamate excess) to reduced grey matter thickness (cortical impoverishment) and the objectively computed negative phenomenology of language (or linguistic impoverishment) in first-episode schizophrenia. Connecting the cellular/synaptic processes (glutamate) with objectively quantified language behaviours through macroscopic brain changes (thickness) may facilitate more consistent brain-behaviours mapping in schizophrenia. While cortical thinning is neither necessary nor sufficient for clinical expression, a specific mechanistic pathway operating via glutamate excess and resulting in language production impairment in the early stage of schizophrenia as well as a higher residual symptom burden in chronic schizophrenia may present with cortical impoverishment in schizophrenia.

4.1 Future Directions

The current study validated and characterized a ‘cortical impoverishment’ subgroup of schizophrenia in terms of symptom, cognition, functional outcome, language and neurometabolite. Further investigations into the genetic makeup and other biological

features (e.g., functional brain activities, inflammatory markers), as well as the longitudinal outcome and stability of this subgroup, could be of interest for future studies.

The ultimate goal of finding meaningful patient subtypes is to assist biomarkers-guided clinical decisions and improve treatment outcomes for patients. To find the most clinically relevant cluster solutions, future studies that pursue the efforts in uncovering patients subtypes in schizophrenia can consider the followings:

1) Extensive external validation to facilitate brain-behaviours mapping across various patient samples. To consider a subgroup generated from cluster analytic algorithms to be a meaningful subtype, it is important to externally validate the clusters extensively across various features including genetics, symptoms, outcome, course, neurobiology, and cognition (Seaton et al., 2001; Tamminga et al., 2017). Patient subtypes only become clinically meaningful when they are validated, reproducible and carefully characterized.

2) Investigation of the longitudinal outcome and stability of the subgroups. The diagnostic construct of schizophrenia lacks corresponding neurobiological features observable in all patients. Instead, multiple abnormalities have been reported that nest variably within portions of the patient distribution. In this context, one of the key questions in the pursuit of subtypes of this illness is the longitudinal stability of any typology identified.

3) Consistency across various cluster solutions. In the investigation of the heterogeneity of schizophrenia, the cluster solutions were highly dependent on the choice of variables and clustering algorithms (Marquand et al., 2016). A challenging but necessary step before biomarkers-guided clinical decisions is to compare and evaluate the different subtyping solutions reported in the cluster analytic studies. This effort has been lacking in the literature (Schnack, 2019). Evaluations of different subtyping solutions will be informative when we need to decide which one is the most clinically relevant. The most ideal theoretical framework(s) would be to find consistency between these subtyping solutions, as well as use it to predict the course and outcome of schizophrenia [see a model for

heterogeneity proposed by Seaton et al. (2001)]. The redundancy, agreement, and lack thereof among various data-driven subtyping solutions require further examination of multiple biological and symptomatic correlates before clinically feasible recommendations can be made.

4) Parsing heterogeneity in multimodal cross-domain features. Most subtyping studies so far account for heterogeneity in only one of these characteristics – symptom, cognition, neurobiology or genetics. Very few studies have attempted to parse heterogeneity across different feature spaces, for example, by combining biological and clinical data (Schnack, 2019).

Luxburg and colleagues raised the question of whether clustering is an art or science, highlighting the difficulty with unsupervised clustering as it throws a huge number of possibilities regarding how it is administered and what its implications are (Luxburg et al., 2012). Cluster algorithms will always provide us with a cluster solution, and whether it is deemed useful or useless depends on how and when it can be used for inference. It is sensible to conclude the work presented here with the same sentiment: cortical impoverishment cluster, if mapped successfully onto treatment selection, adjustment, or tailoring, will be immensely helpful in developing personalized patient care and advancing precision psychiatry. With such clinically meaningful utility, morphological clustering may advance us beyond the impasse in the treatment of schizophrenia.

Appendices

Appendix A. Language Metrics

Measures	Dimensions	Detailed Descriptions
Thought and Language Index		
Impoverishment	Poverty of speech	Speech productions lack details and elaboration
	Weakening of goal	Lack of ideas and meaningful information
	Preservation of ideas	Repetitive contents, even if given different stimuli
Disorganization	Looseness	Lack of logical flow or connection of ideas
	Peculiar use of words	Invented or rarely used words
	Peculiar sentences	Unusual sentence structures that impede speech comprehension
	Peculiar logic	Reaching conclusions without enough evidence
	Distractibility	Distracted by external stimulus
Syntactic Complexity (Production)	Mean length of sentences (MLS)	Average number of words per sentence.
	Mean length of T-units (MLT)	Average number of words per T-unit. T-unit is defined as the main clause with its attached subordinate clause(s).
	Mean length of clauses (MLC)	Average number of words per clause.
Cohesion	Repeated contents lemmas	Average number of content words that are repeated at least once divided by the total number of words in the text

Appendix B. Patient Speech Data Examples

Example output of syntactic complexity. Traditional indices from Tool for the automatic analysis of syntactic complexity and sophistication (TAASSC)

ID	Picture	Transcribe speech	MeanMLS	MeanMLT	MeanMLC
FEPxxx	2	Uh there is a black and white sun seen in all the building all the big painted building It is wood there is three windows there is a girl that is looking down from the balcony there is water down on the water there is another an abandoned building there is a guy in a canoe there is lots of workers maybe gathering up some fish and that is it that is all I can get uh it is black and white pencil sketched	7.417	7.639	6.078

Example output of Textual cohesion based upon the givenness index. Tool for the Automatic Analysis of Cohesion (TAACO) 2.0.4

ID	Picture	Transcribe speech	Repeated contents lemmas (Givenness)	Repeated_content_and_pronoun_lemmas (Givenness)
FEPxxx	1	Um he is looking at an enemy who is done wrong to him and she is trying to console him they are both of uh decent socioeconomic status they have nice clothing nicely cropped hair and uh he is probably he is probably under the influence of alcohol and uh I think he like there is something going on underneath the surface for him that she does not know about but she is still there trying to, trying to face things for him there is a woman in the background so that probably suggests that um I do not know	0.160	0.320

Note. MLS: mean length of sentences; MLT: mean length of T-units; MLC: mean length of clauses. Givenness: It is an average number of content words that are repeated at least once divided by the total number of words in the text.

Appendix C. Tissue volume fractions in the voxel placed in dorsal anterior cingulate cortex.

	First-episode psychosis (N = 66)	Healthy controls (N = 36)	Total (N = 102)
Grey matter	0.5590 ± 0.0620	0.5911 ± 0.0502	0.5701 ± 0.0599
White matter	0.2041 ± 0.0706	0.1961 ± 0.0379	0.2014 ± 0.0612
Cerebrospinal fluid	0.2367 ± 0.0740	0.2128 ± 0.0591	0.2285 ± 0.0698

Note: Values are reported as mean ± standard deviation of tissue proportion in the voxel.

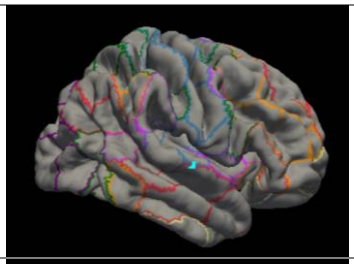
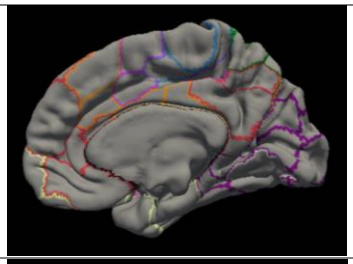
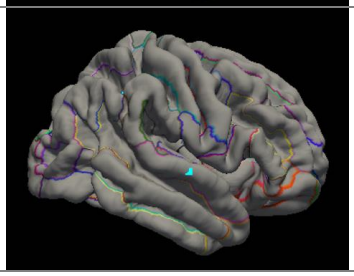
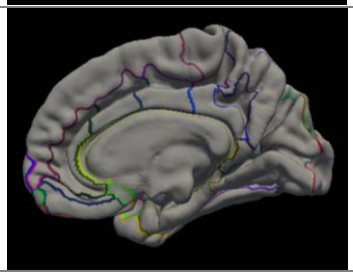
Appendix D. Description of single voxel 1H-MRS of MRS hardware, data acquisition, analysis, and quality assessment details.

1. Hardware	
a. Field strength [T]	7-Tesla
b. Manufacturer	Siemens
c. Model (software version if available)	VB17
d. RF coils: nuclei (transmit/receive), number of channels, type, body part	32 channel head coil (8-channel Tx, 32-channel Rx)
e. Additional hardware	N/A
2. Acquisition	
a. Pulse sequence	semi-LASER
b. Volume of Interest (VOI) locations	Bilateral dorsal anterior cingulate cortex
c. Nominal VOI size [cm^3, mm^3]	2 x 2 x 2 cm^3
d. Repetition Time (TR), Echo Time (TE) [ms,s]	TR = 7500ms, TE = 100ms
e. Total number of excitations or acquisitions per spectrum	32 averages, 1 measurement
f. Additional sequence parameters (spectral width in Hz, number of spectral points, frequency offsets)	2048 points
g. Water Suppression Method	VAPOR
h. Shimming Method, reference peak, and thresholds for “acceptance of shim” chosen	FASTESTMAP
i. Triggering or motion correction method	N/A
3. Data analysis methods and outputs	
a. Analysis software	MATLAB, fitMAN, Barstool

b. Processing steps deviating from quoted reference or product	N/A
c. Output measure (e.g. absolute concentration, institutional units, ratio)	Absolute concentration
d. Quantification references and assumptions, fitting model assumptions	Each spectrum was phase and frequency corrected to the first spectral acquisition before being averaged into a single spectrum for further post-processing. 17 brain metabolites (described in Methods) were included our fitting template and quantification analysis.
4. Data Quality	
a. Reported variables (SNR, Linewidth (with reference peaks))	SNR
b. Data exclusion criteria	No subjects excluded
c. Quality measures of postprocessing Model fitting (e.g. CRLB, goodness of fit, SD of residual)	CRLB
d. Sample Spectrum	See Supplementary Figure 4

Note: This table was based on a MRS reporting standardized template provided by Lin et al. (2021)

Appendix E. Two different cortical parcellation maps

	Lateral View	Medial View
Schaefer Parcellation ROI = 200		
Destrieux Parcellation ROI = 148		

Appendix F. Bash Scripts and R Codes

Bash script to reconstruct brain surfaces and calculate vertex-wise thickness values in FreeSurfer	#!/usr/bin/env bash export SUBJECTS_DIR=/media/sf_subjects/recon for subj in `ls ./nifti` do recon-all -s $subj -i ./nifti/$subj/*.nii -all -qcache done

Bash script to extract thickness values based on Destrieux parcellation (Destrieux et al., 2010b)	# define subjects data directory path
	export SUBJECTS_DIR=/home/charlotte/Desktop/recon
	
	# output stats from recon-all
	aparcstats2table --hemi lh \
	  --meas thickness \
	  --parc aparc.a2009s \
	  --tablefile 211108_lh_thicknes_destrieux.txt \
	  --subjects
	
	aparcstats2table --hemi rh \
	  --meas thickness \
	  --parc aparc.a2009s \
	  --tablefile 211108_rh_thicknes_destrieux.txt \
	--subjects

Bash script to output cortical thickness map of differences between two subgroups (regressing out age effect with a general linear model, multiple comparison corrections using Monte Carlo simulations of 1000 permutations with a cluster-wise threshold of 0.05)	export SUBJECTS_DIR=/home/charlotte/Desktop/recon cat group_diff.fsgd | sed 's/\r/\n/g' > new.group_diff.fsgd # Resampling subjects data into a common space; spatial soothing mris_preproc --fsgd new.group_diff.fsgd --target fsaverage --hemi lh --meas thickness --out lh_group_diff.mgh mris_preproc --fsgd new.group_diff.fsgd --target fsaverage --hemi rh --meas thickness --out rh_group_diff.mgh # GLM model fit mri_glmfit --y lh_group_diff.mgh --fsgd new.group_diff.fsgd --C group_diff.mtx --glmdir group.age_10sm.lh --fwhm 10 --surface fsaverage lh --eres-save mri_glmfit --y rh_group_diff.mgh --fsgd new.group_diff.fsgd --C group_diff.mtx --glmdir group.age_10sm.rh --fwhm 10 --surface fsaverage rh --eres-save

	# Multiple testing correction mri_glmfit-sim --glmdir group.age_10sm.lh --2spaces --cwp 0.05 --perm 1000 3 abs mri_glmfit-sim --glmdir group.age_10sm.rh --2spaces --cwp 0.05 --perm 1000 3 abs

R codes to run clustering procedure and other statistical analyses	#Import dataset generated by FreeSurfer----
	TOPSY <- read_excel("E:/subjects/Bash Scripts/TOPSY_destrieux_thickness_211108_66FEP36HC.xlsx")
	TOPSY_thickness <- as.data.frame(TOPSY[c(37:184)])
	rownames(TOPSY_thickness) <- TOPSY$ID
	
	# Use original thickness values for clustering ----
	# Hierarchical Cluster Analysis
	TOPSY_dist <- dist(TOPSY_thickness, method = "euclidean")
	TOPSY_hc_ward <- hclust(TOPSY_dist, method = "ward.D2")
	TOPSY_cluster_solution <- matrix(rep(0, len=length(selected)),nrow = length(selected))
	for (i in 1:length(selected)){
	  TOPSY_cluster_solution[i,] <- unname(NbClust::NbClust(TOPSY_thickness, min.nc=1, max.nc=8, method="ward.D2", index=selected[i])$Best.nc)[1]
	}
	barplot(table(TOPSY_cluster_solution), main = "Barplot of Proposed Cluster Solutions",xlab="Number of Clusters")
	plot(TOPSY_hc_ward)
	rect.hclust(TOPSY_hc_ward, k = 2)
	TOPSY_2clusters <- cutree(TOPSY_hc_ward, k=2)
	
	# Subgroups Statistics
	TOPSY$cluster = TOPSY_2clusters
	
	# Explore two-cluster solution
	TOPSY_TypeCluster <- table(data.frame(TOPSY$Type,TOPSY$cluster))
	barplot(TOPSY_TypeCluster,xlab="cluster assignment", ylab="patient or control",
	  main="Patient & control in each cluster",legend=rownames(TOPSY_TypeCluster))
	chisq.test(TOPSY_TypeCluster)
	write.csv(TOPSY_FEP,"E:/TOPSY/TOPSY_FEP_FULL.csv")
	
	# Use original thickness and clustering with FEP only ----
	# Hierarchical Cluster Analysis

	TOPSY_FEP_thickness <- as.data.frame(TOPSY_FEP[c(37:184)])
	TOPSY_dist <- dist(TOPSY_FEP_thickness, method = "euclidean")
	TOPSY_hc_ward <- hclust(TOPSY_dist, method = "ward.D2")
	TOPSY_cluster_solution <- matrix(rep(0,
	len=length(selected)),nrow = length(selected))
	for (i in 1:length(selected)){
	TOPSY_cluster_solution[i,] <-
	unname(NbClust::NbClust(TOPSY_thickness, min.nc=1,
	max.nc=8, method="ward.D2", index=selected[i])$Best.nc)[1]
	}
	barplot(table(TOPSY_cluster_solution), main = "Barplot of
	Proposed Cluster Solutions",xlab="Number of Clusters")
	plot(TOPSY_hc_ward)
	rect.hclust(TOPSY_hc_ward, k = 2)
	TOPSY_2clusters <- cutree(TOPSY_hc_ward, k=2)
	
	# Subgroups Statistics
	TOPSY_FEP$cluster_FEP = TOPSY_2clusters
	
	# Check cluster consistency
	cluster_consistency_table <-
	table(data.frame(TOPSY_FEP$cluster,TOPSY_FEP$cluster_FEP))
	barplot(cluster_consistency_table, xlab="x", ylab="y",
	main="Cluster Consistency")

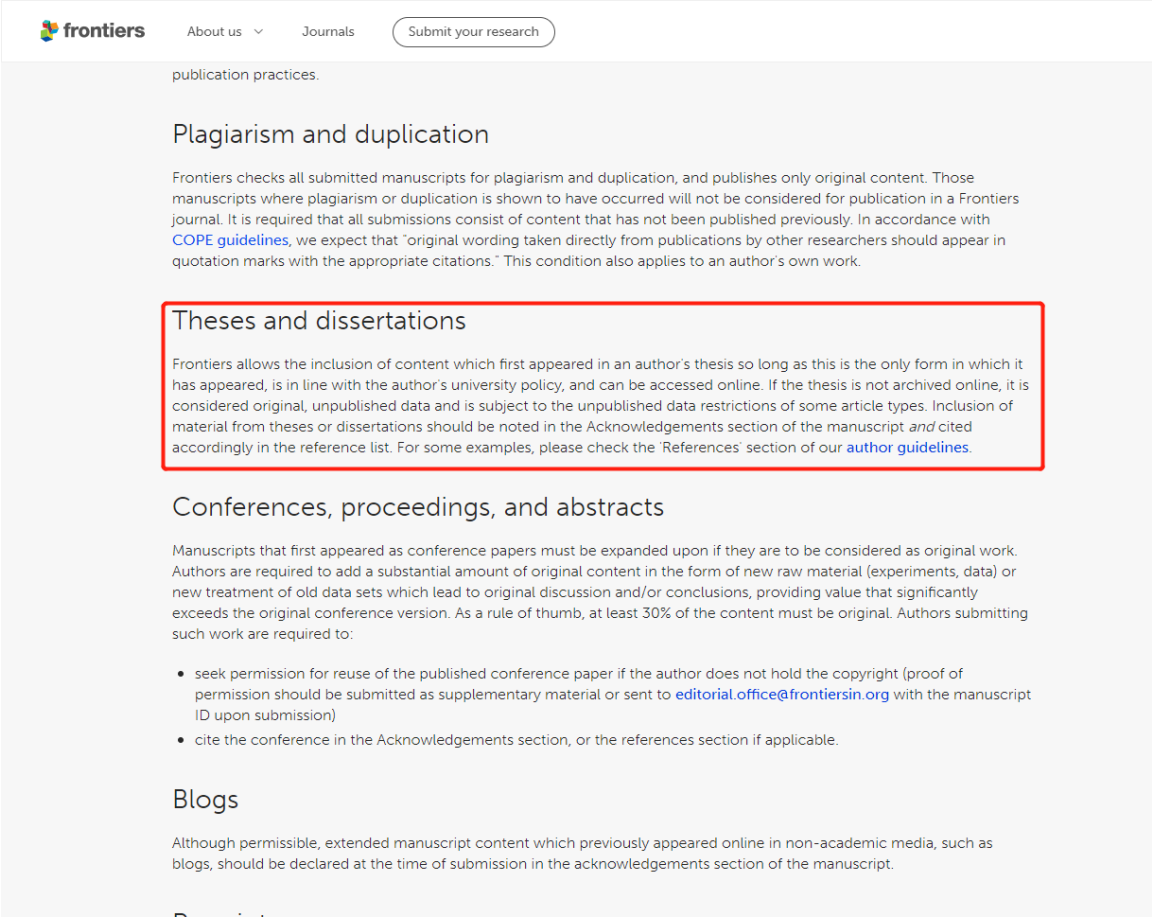
R codes to run correlation matrices and draw raincloud plots	# Correlations between symptom and language scores ---- TOPSY_Language2$MeanThickness <- TOPSY$meanThickness CorMatrix <- TOPSY_Language2[,c(3,7:8,18,24,30,40:43,60,62)] #variables of all participants corrplot.mixed(cor(CorMatrix, method = "pearson", use = "pairwise.complete.obs")) corrplot(cor(CorMatrix, method = "pearson", use = "pairwise.complete.obs"),addCoef.col = 'black',type = 'lower',diag = FALSE) CorMatrix_FEP <- subset(TOPSY_Language2, Type =="FEP")[,c(3,7:8,18,24,30,40:43,60,62)] #variables of FEP only colnames(CorMatrix_FEP) = c("Age", "PANSS Positive", "PANSS Negative","SOFAS","Glutamate","TLI","Number of Words", "MLS","MLT","MLC","Repeated content lemmas", "Mean Cortical Thickness")

```
corrplot(cor(CorMatrix_FEP, method = "pearson", use =
"pairwise.complete.obs"),addCoef.col = 'black',type =
'lower',diag = FALSE,tl.srt = 30)

CorMatrix_FEP1 <- subset(subset(TOPSY_Language2, Type
=="FEP"),cluster==1)[c(3,7:8,18,24,30,40:43,60,62)] #variables
of FEP1 only
colnames(CorMatrix_FEP1) = c("Age", "PANSS Positive", "PANSS
Negative","SOFAS","Glutamate","TLI","Number of Words",
                    "MLS","MLT","MLC","Repeated content
lemmas", "Mean Cortical Thickness")
corrplot(cor(CorMatrix_FEP1, method = "pearson", use =
"pairwise.complete.obs"),addCoef.col = 'black',type =
'lower',diag = FALSE,tl.srt = 30)

CorMatrix_FEP2 <- subset(subset(TOPSY_Language2, Type
=="FEP"),cluster==2)[c(3,7:8,18,24,30,40:43,60,62)] #variables
of FEP2 only
colnames(CorMatrix_FEP2) = c("Age", "PANSS Positive", "PANSS
Negative","SOFAS","Glutamate","TLI","Number of Words",
                    "MLS","MLT","MLC","Repeated content
lemmas", "Mean Cortical Thickness")
corrplot(cor(CorMatrix_FEP2, method = "pearson", use =
"pairwise.complete.obs"),addCoef.col = 'black',type =
'lower',diag = FALSE,tl.srt = 30)

CorMatrix_HC <- subset(TOPSY_Language2, Type
=="HC")[c(3,24,30,40:43,60,62)] #variables of HC only
colnames(CorMatrix_HC) = c("Age", "Glutamate","TLI","Number
of Words",
                    "MLS","MLT","MLC","Repeated content
lemmas", "Mean Cortical Thickness")
corrplot(cor(CorMatrix_HC, method = "pearson", use =
"pairwise.complete.obs"),addCoef.col = 'black',type =
'lower',diag = FALSE,tl.srt = 30)

# Raincloud plots for variables ----
remotes::install_github('jorvlan/raincloudplots')
library(raincloudplots)

#Define plotting raincloud plot function
Plot_raincloud <- function(variable){
```

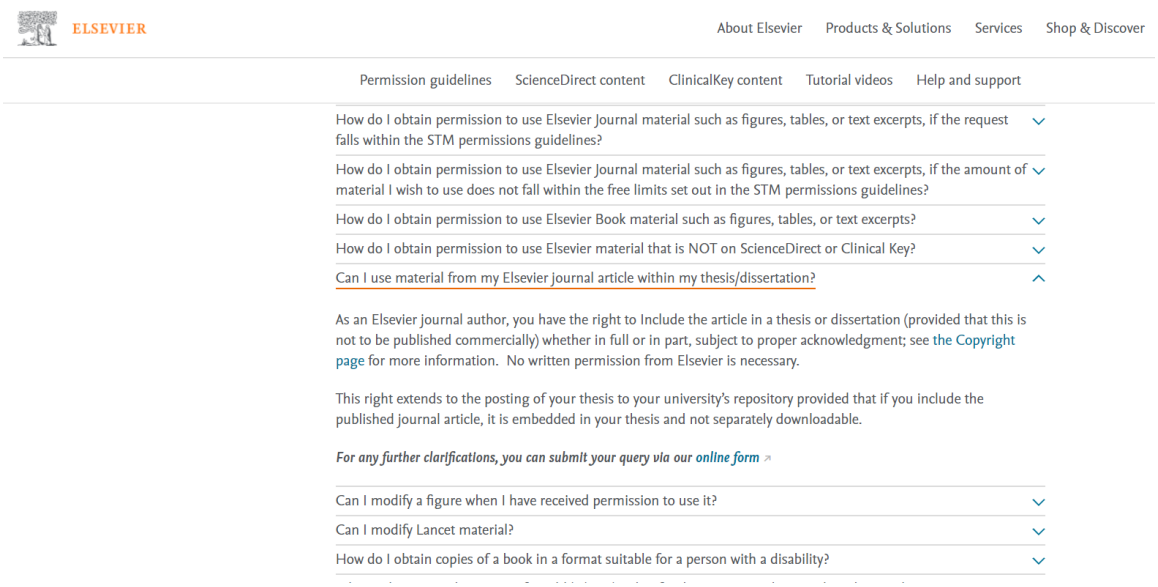
```
  variable_rain <- data_1x1(array_1 =
subset(subset(TOPSY_Language2,
cluster==1),Type=="FEP")[[variable]],
                      array_2 = subset(subset(TOPSY_Language2,
cluster==2),Type=="FEP")[[variable]],
                      jit_distance = 0.2,
                      jit_seed = 321)
  variable_raincloud <- raincloud_1x1(data=variable_rain,
                                #colors = (c('dodgerblue','darkorange')),
                                #fills = (c('dodgerblue','darkorange')),
                                size = 1.5,
                                alpha = .6,
                                ort = 'h') +
    scale_x_continuous(breaks=c(1,2), labels=c("Subgroup 1",
"Subgroup 2"), limits=c(0, 3)) +
    xlab("Patients") +
    theme_classic()
  return(variable_raincloud)
}

#Glutamate raincloud
Glu_raincloud <- Plot_raincloud(variable = "Rest_Glu")
Glu_raincloud + ylab("Glutamate Concentrations in dACC")
#Thickness raincloud
Thickness_raincloud <- Plot_raincloud(variable =
"MeanThickness")
Thickness_raincloud + ylab("Mean Cortical Thickness")
#Age raincloud
Age_raincloud <- Plot_raincloud(variable = "Age")
Age_raincloud + ylab("Age")
#MLT raincloud
MLT_raincloud <- Plot_raincloud(variable = "Mean-MLT")
MLT_raincloud + ylab("Mean length of T-units")
#repeated contents lemmas raincloud
RCL_raincloud <- Plot_raincloud(variable =
"repeated_content_lemmas")
RCL_raincloud + ylab("Repeated contents lemmas")
#total words raincloud
words_raincloud <- Plot_raincloud(variable = "Mean-nwords")
words_raincloud + ylab("Total number of words per 1-minute
task")
#DUP&DDD distribution
```

	ggplot(TOPSY_Language2_patient, aes(x=DUP_Weeks, fill = cluster)) + geom_density(alpha=.3) + xlim(0,120) + xlab("Duration of untreated psychosis in weeks") ggplot(TOPSY_Language2_patient, aes(x=DDD_LifeTime, colour = cluster)) + geom_density() + xlim(0,25) + xlab("DDD lifetime exposure")

Appendix G. Journal Copyright Policies



Note: This screenshot is obtained from the Frontiers webpage on their journal policies on reusing text from published manuscript (https://www.frontiersin.org/guidelines/policies-and-publication-ethics).



Note: This screenshot is obtained from the Elsevier (publisher for Schizophrenia Research) webpage on their journal policies on reusing text from published manuscript (https://www.elsevier.com/about/policies/copyright).

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Curriculum Vitae

Education

MSc Western University, Schulich School of Medicine and Dentistry 2020-2022
Neuroscience

BSc York University, Faculty of Health 2015-2019
Specialized Honours in Psychology

Publication and Presentations

Paper Published

Liang, L., Silva, A. M., Jeon, P., Ford, S. D., MacKinley, M., Théberge, J., & Palaniyappan, L. (2022). Widespread cortical thinning, excessive glutamate and impaired linguistic functioning in schizophrenia: A cluster analytic approach. *Frontiers in Human Neuroscience*, 16. https://www.frontiersin.org/articles/10.3389/fnhum.2022.954898

Liang, L., Heinrichs, R. W., Liddle, P. F., Jeon, P., Théberge, J., & Palaniyappan, L. (2022 May). Cortical impoverishment in a stable subgroup of schizophrenia: Validation across various stages of psychosis. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2022.05.013

Oral Presentations

Liang, L., Heinrichs, RW., Liddle, PF., Jeon, P., Theberge, J., & Palaniyappan, L. (2022 Jan). Cortical Impoverishment Subgroup in Schizophrenia: Cross Validation Across Various Stages of Psychosis. Douglas Research Centre Seminar Series. Youtube Link: https://www.youtube.com/watch?v=yeG3GaMt1CY

Poster/Oral Presentations

Liang, L., Silva, AM., McKinley, M., Jeon, P., Ford, SD., Theberge, J., & Palaniyappan, L. (2022 April). Widespread Cortical Thinning Associates with Excessive Glutamate and Impaired Linguistic Functioning in a Subgroup of Schizophrenia: A Cluster Analytic Approach. Poster presented at 2022 Annual Congress of the Schizophrenia International Research Society (SIRS), Florence, Italy. Paper presented at Western Neuroscience Research Day, London, ON Canada.

Liang, L., Heinrichs, W., & Palaniyappan, L. (2021). Do Cognition and Psychopathology Vary With Cortical Structure? Neuroanatomical Subgroups Based on Cortical Thickness in Schizophrenia. Biological Psychiatry, 89(9, Supplement), S123–S124. https://doi.org/10.1016/j.biopsych.2021.02.319. Poster presented at the 2021 Annual Congress of the Schizophrenia International Research Society. Poster presented at the 2021 Society of Biological Psychiatry Virtual Meeting.

Liang, L., & Heinrichs, W. (2019, April). Cluster Analysis on Cortical Thickness of Default Mode Network-Associated Regions in Patients with Schizophrenia and Healthy Controls. *Schizophrenia Bulletin, 45*(Supplement_2), 289. https://doi.org/10.1093/schbul/sbz018.505. Poster presented at the 2019 Annual Congress of the Schizophrenia International Research Society, Orlando, FL, USA. Paper presented at the 49th Annual Ontario Psychology Undergraduate Thesis Conference, Toronto, ON.

Funding History

BrainSCAN Graduate Studentship Program **2020-2022**
Annual funding of $25,000 for 2 years supporting individuals who pursue a collaborative research project in cognitive neuroscience.

Neuroscience Graduate Student Travel Award **2021-2022**
Competitive awards of $500 per conference to graduate students who present their work as a first-author poster or oral presentation.

York University Continuing Student Scholarship **2016-2019**
Awarded to students who have achieved outstanding academic results in the previous year.

Professional Affiliations

Schizophrenia International Research Society, 2019 – Present
Member

Hong Fook Mental Health Association, 2017 – Present
Mental Health Ambassador, Volunteer Development Committee Member