Cortical Impoverishment in a Stable Subgroup of Schizophrenia: Validation Across Various Stages of Psychosis

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ABSTRACT

Background: 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 irrespective of illness stage, and if it relates to the glutamate hypothesis of schizophrenia.

Methods: We applied hierarchical cluster analysis to cortical thickness data from magnetic resonance imaging scans of three datasets in different stages of psychosis (n=288; 160 patients; 128 healthy controls) and studied the cognitive and symptom profiles of the observed subgroups. In one of the samples, we also studied the subgroup differences in 7-Tesla magnetic resonance spectroscopy glutamate concentration in the dorsal anterior cingulate cortex.

Results: Our consensus-based clustering procedure consistently produced 2 subgroups of participants. Patients accounted for 75%-100% of participants in one subgroup that was characterized by significantly lower cortical thickness. Both subgroups were equally symptomatic in clinically unstable stages, but cortical impoverishment indicated a higher symptom burden in a clinically stable sample and higher glutamate levels in the first-episode sample. There were no subgroup differences in cognitive and functional outcome profiles or antipsychotic exposure across all stages.

Conclusions: Cortical thinning does not vary with functioning or cognitive impairment, but it is more prevalent among patients, especially those with glutamate excess in early stages and higher residual symptom burden at later stages, providing an important mechanistic clue to one of the several possible pathways to the illness.

Trial Name: Tracking Outcomes in Psychosis (TOPSY)

URL: https://clinicaltrials.gov/ct2/show/NCT02882204 **Registration Number**: NCT02882204

1 INTRODUCTION

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 and 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 and 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 and Awad, 1993; Van Rheenen et al., 2017; Weinberg et al., 2016), clinical (Dickinson et al., 2018; Dollfus and Brazo, 1997; Talpalaru et al., 2019), physiological (Clementz et al., 2015), and neurobiological (Chand et al., 2020; Dwyer et al., 2018; Honnorat et al., 2019; Pan et al., 2020; Planchuelo-Gómez et al., 2020; Sugihara et al., 2017) 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.

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., 2020; Sugihara et al., 2017). 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., 2020; Sugihara et al., 2017), 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 (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 et al., 2013; Ho et al., 2011).

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 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, antipsychotic exposure rates, and functional stability. 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. To this end, we validated the stability of our clustering solution in the IQ-matched 'discovery' dataset in 2 other samples with patients (n=152) at different stages of schizophrenia. 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.

2 MATERIAL AND METHODS

2.1 PARTICIPANTS

Data used in the present study were obtained from three 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 second 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 other 2 samples, 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 and Liddle, 2014) and was approved by National Research Ethics Committee, Nottinghamshire (NHS REC Ref: 10/H0406/49).

The third dataset (TOPSY Dataset) was composed of 25 sex, age, parental socioeconomic status-matched healthy controls and 46 patients with first-episode psychosis (schizophrenia, schizoaffective or schizophreniform disorder) and minimal exposure to antipsychotics, recruited through Prevention and Early Intervention for Psychosis Program in London, Ontario, Canada (https://clinicaltrials.gov/ct2/show/NCT02882204). Recruitment of participants and data collection has been described previously (Limongi et al., 2021) and was approved by Western University Health Sciences Research Ethics Board (#108268).

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 samples were acquired in the CONN and TOPSY studies. In the CONN study, we used the Signs and Symptoms of Psychotic Illness (SSPI) (Liddle et al., 2002) to measure symptom severity and the Social and Occupational Functional Assessment Scale (SOFAS) to measure the overall functioning (Morosini et al., 2000) of patients. In the TOPSY project, the 8-item PANSS (PANSS-8) was used to measure symptom severity and SOFAS was also administered to index all participants' social functioning

(Morosini et al., 2000). These two samples did not have a detailed cognitive characterization that was available for the discovery dataset.

2.3 MRI AND MRS DATA ACQUISITION AND PROCESSING

The details of data acquisition in the NeuroCog and CONN projects (3.0-Tesla MRI), and the TOPSY (7.0-Tesla MRI) are provided in the Supplementary Information 7.1.

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).

The MRS voxel for the TOPSY study was placed in the dorsal anterior cingulate cortex (dACC; averaged MNI coordinates x = 1, y=16, z=38), one of the most affected brain regions that showed alterations in structure and levels of neurotransmitters in schizophrenia (Kiemes et al., 2021; Liloia et al., 2021). The processing of MRS spectra and quantification as well as quality assessment and voxel control procedures for glutamate and related metabolites glutamine and glutathione are described in our prior publication of the TOPSY sample (Limongi et al., 2021).

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 ("kl", "ch", "hartigan", "cindex", "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. [Results are presented in Supplementary Information 7.5].

3 RESULTS

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 (Supplementary Table 1).

3.2 CLUSTERING SOLUTION AND COMPOSITION

A visual inspection of the agglomerative hierarchical cluster analysis dendrograms (Supplementary Figures 1A-1C) 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; TOPSY: 10/16; Supplementary Figures 2A-2C). The same clustering procedure was re-applied to the patient samples only, and a two-cluster solution was again the most favoured solution (Supplementary Information 7.6). For each of the 3 datasets, a two-cluster solution was chosen based on the majority consensus.

With a two-cluster solution, the proportion of patients (Figures 1A-1C) varied significantly across clusters [NeuroCog: χ^2 (N = 136) = 15.186, $p < 0.0001$; CONN: χ^2 (N = 81) = 20.128, $p < 0.0001$; TOPSY: χ^2 (N = 71) = 5.206, $p = 0.02$], revealing a subgroup (Cluster 1) with mostly patients. The proportion of patients relative to healthy controls within Cluster 1 was 75.5%, 86.4%, and 100% in NeuroCog, TOPSY, and CONN samples, respectively. A larger second cluster comprised a relatively balanced ratio of patients and controls, with patients accounting for 40%, 41%, and 55% in the 3 datasets.

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 (Supplementary Material 7.4; Number of cortical regions that were significantly thinner in Cluster 1 after correction: 100/148 in NeuroCog, 11/148 in CONN, 29/148 in TOPSY). When examining patients only, 44/148 regions in NeuroCog, 7/148 regions in CONN and 17/148 regions in TOPSY showed significantly thinner cortex among Cluster 1 patients ($p < 0.01$ after Bonferroni correction; See Supplementary Table 2 for the top 5 cortical regions and Supplementary Figures 4 for thickness heatmaps), with few of the cortical regions showing a significantly higher thickness among cluster 1 patients (see vertexwise comparison in Supplementary Figure 5). 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.

3.4 Characteristics of Participants in Each Cluster

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 2A-2B). 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 2C).

Clinical Characteristics

Comparison of patients between clusters showed no significant difference in overall symptom severity measured by PANSS in the NeuroCog or TOPSY study (Figure 3A, 3C), 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 3B). There was no significant difference in antipsychotic medication (Figures 3D-3F) or duration of illness (Figures 3G-3I) 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 (Supplementary Figures 3).

Glutamatergic Metabolites Measures

In the TOPSY dataset, patients in the cortical impoverishment subgroup (Cluster 1) had significantly higher glutamate levels in dACC compared to patients from cluster 2 (bootstrapped p-value = 0.0168; Cluster 1 M[SD]= 7.16[1.48] vs. Cluster 2 M[SD]= 6.29[0.63]; Figure 4A). There was no significant difference in glutamine (bootstrapped p-value = 0.8157; Cluster 1 M[SD]= 1.06[0.38] vs. Cluster 2 M[SD]= 1.03[0.24]; Figure 4B) or glutathione (bootstrapped p-value = 0.2642; Cluster 1 M[SD]= 1.68[0.43] vs. Cluster 2 M[SD]= 1.54[0.29]; Figure 4C) levels between the two clusters.

4 DISCUSSION

4.1 DISCOVERY AND VALIDATION OF TWO THICKNESS-BASED SUBGROUPS

We identified two subgroups based on cortical thickness profiles across the whole brain. Similar subgroups were consistently seen across the 3 samples irrespective of illness duration, stage, or state, and the strength of the scanners used. 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 three 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 samples. 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 (Li et al., 2022; Palaniyappan, 2017). While scanning parameters varied across the three 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 three studies (Table 1: Global CT across three samples of healthy controls: $F(2,125)=0.72$, $p=0.49$).

Previous cluster analytic studies based on cortical thickness generally selected one clustering validation method to determine the optimal number of clusters (Pan et al., 2020; Sugihara et al., 2017). 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 Supplementary 7.3, 7.6 and 7.7). 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 (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., 2020).

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 45-68% 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.

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., 2020; Dwyer et al., 2018; Pan et al., 2020; Planchuelo-Gómez et al., 2020). Although some studies have related a longer illness duration (Dwyer et al., 2018; Pan et al., 2020; Planchuelo-Gómez et al., 2020) and higher medication exposure (Pan et al., 2020; Sugihara et al., 2017) 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., 2018; Pan et al., 2020; 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., 2020, 2017), 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 severity of symptoms 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. [See Discussion 4.4 below for a discussion on an exception to this generalisation].

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 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, 2006). 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.

Finally, 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). Structural impoverishment and glutamate dysregulations appear to share similar risk gene variants (Schultz et al., 2011), and are both associated with treatment resistance (Egerton et al., 2018; 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). 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 focussed 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). [See Supplementary Information 7.5 for results and discussion on subgroup differences in correlations between symptom, cognition and treatment resistance].

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 2 other samples with different demographic, clinical, treatment exposure profiles and glutamatergic measures. While the healthy subjects in our discovery sample (group matched for IQ with patients) likely differed from their peers in the two validations samples, majority of healthy controls in each of the 3 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, hierarchical cluster analysis forced participants to belong to one group or another and generated mutually exclusive subgroups. However, as can be seen in the heat maps

(Supplementary Figures 4), the cortical thickness patterns between the two clusters had a modest overlap. Another disadvantage of using hierarchical clustering is that the multivariate patterns that separated the two subgroups in one dataset cannot be re-applied to other samples. Third, we lacked prospective data to confirm the stability of the reported clusters. Fourth, 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.

4.6 FUTURE DIRECTIONS

The diagnostic construct of schizophrenia is a relatively stable nosological entity that lacks the corresponding neurobiological features observable in all patients in the category. 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. In our investigation of the heterogeneity of schizophrenia, the cluster solutions we derived were highly dependent on the choice of the variables we employ. 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.

4.7 CONCLUSIONS

In summary, the anatomical data-driven two-cluster solution presented here emerges as an invariant feature across illness stages, acute symptom severity, functional status, and treatment exposure. A cortically impoverished subgroup with possible glutamatergic excess and a higher likelihood of persistent symptoms despite clinical stability likely exists in schizophrenia. While cortical thinning is neither necessary nor sufficient for clinical expression, a specific mechanistic pathway operating via glutamate

excess and resulting in higher residual symptom burden may present with cortical impoverishment in schizophrenia.

5 TABLE

Table 1. Demographic, cognitive and clinical information.

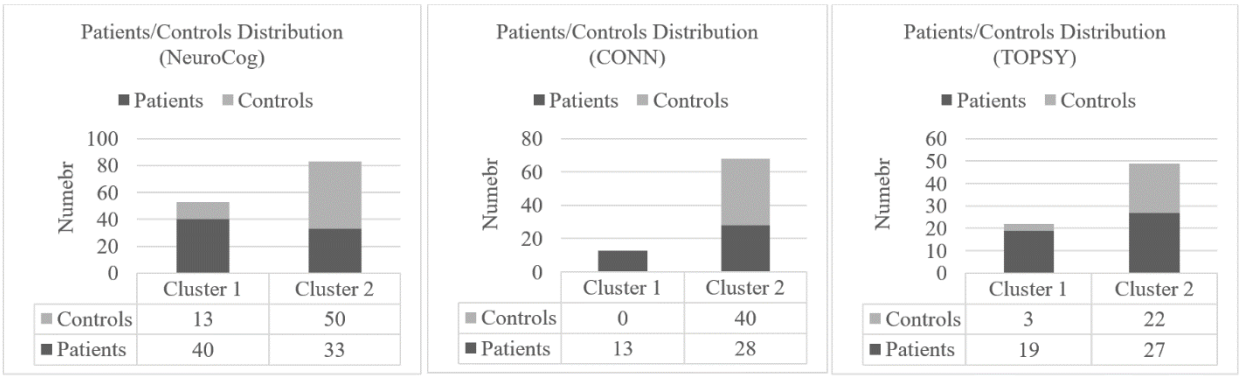
		NeuroCog Study 'Discovery' Dataset			CONN Study 'Validation' Dataset			TOPSY Study 'Validation' Dataset		
		Patients		**Controls**	**Patients**		**Controls**	**Patients**		**Controls**
Demographics	N	73		63	41		40	46		25
	Age	41.42 ± 10.48		38.87 ± 11.46	33.63 ± 9.24		33.40 ± 9.10	22.78 ± 4.18		21.68 ± 3.51
	Female/male	29/44		24/39	10/31		11/29	8/38		10/15
	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		-	41.48 ± 12.23		83.00 ± 4.86
MRI data	Global CT, mm	2.45 ± 0.37		2.53 ± 0.37	2.43 ± 0.38		2.44 ± 0.38	2.45 ± 0.36		2.50 ± 0.36
		Patients Only			**Patients Only**			**Patients Only**		
Symptom Severity	PANSS or SSPI *(Median [IQR])*	PANSS-30: 61[51, 70]			SSPI: 11[5, 18]			PANSS-8: 23[20, 28.5]		
	Min-max normalized score	0.20 ± 0.087			0.15 ± 0.093			0.34 ± 0.12		
Clinical Information	Duration of Illness *(Median [IQR])*	17 [9.75, 25], in years			6 [4, 14], in years			10 [4, 23], in weeks		
Antipsychotic Medication	DDD	Median	Mean	IQR	Median	Mean	IQR	Median	Mean	IQR
		1.00	1.30	[0.73, 1.66]	1.25	2.03	[0.42, 2.84]	0.19	0.29	[0.00, 0.40]

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):

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

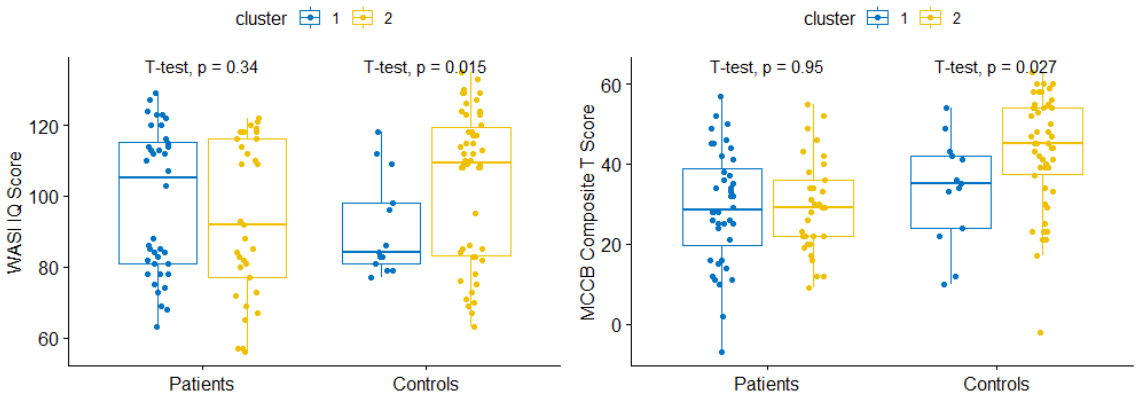
where x is a patient's total score while $\min(x)\ and\ \max(x)$ are the minimum and maximum scores of the scales.

6 FIGURES



(A) NeuroCog Study (B) CONN Study (C) TOPSY Study

Figures 1. Distribution of patients and healthy controls in the two thickness-based clusters across the three studies.



(A)

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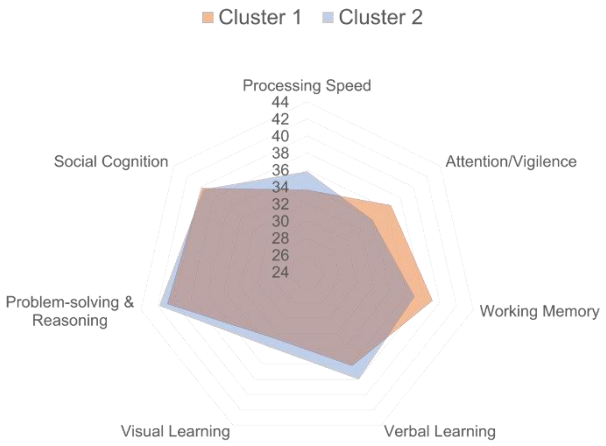
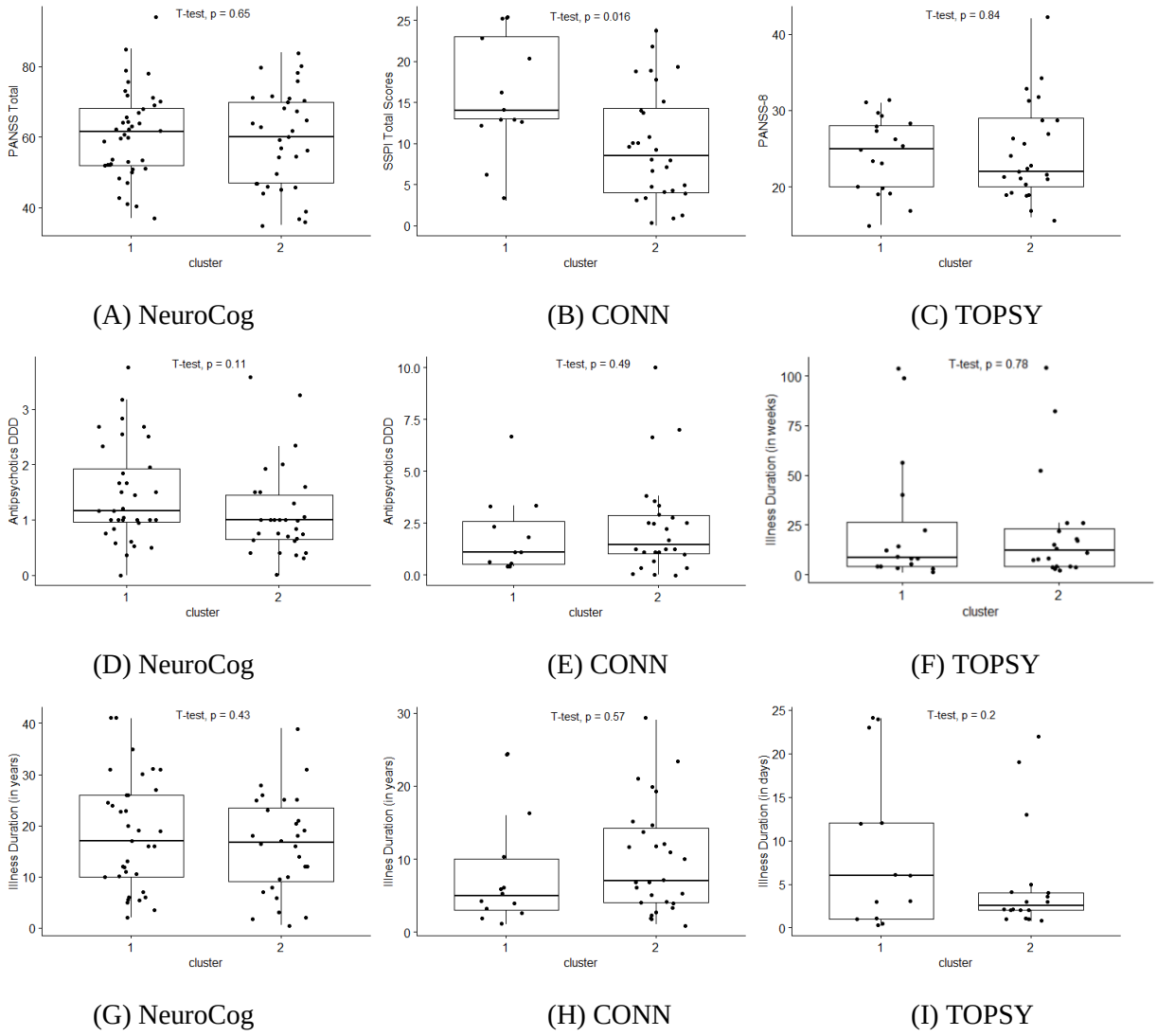
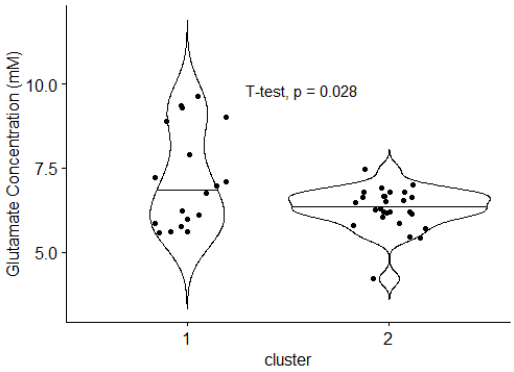


(C)

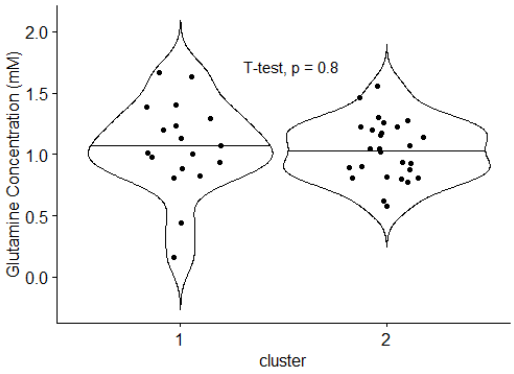
Figures 2. Comparisons of cognitive characteristics of members in each cluster in the NeuroCog 'Discovery' Sample. (A) WASI: Wechsler Abbreviated Scale of Intelligence; (B) MCCB: MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; (C) Seven 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.



Figures 3. Comparisons of clinical characteristics of patients in each cluster. (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) Symptom severity of patients in TOPSY sample measured by 8-item PANSS. (D-F) Antipsychotic medication defined daily dose (DDD) calculated according to World Health Organization of patients in three samples. (G-I) Duration of illness measured in years or days for the three samples, respectively.



(A)



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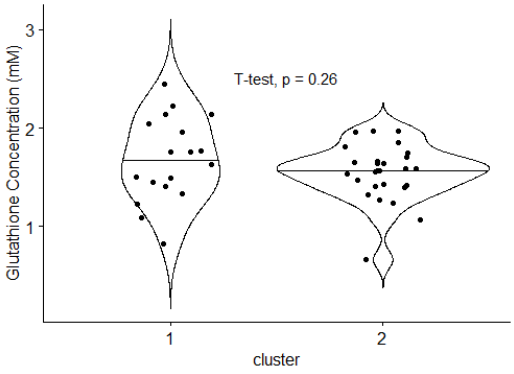


(C)

Figures 4. Comparisons of glutamatergic neurometabolite concentrations (mM) in dorsal anterior cingulate cortex of patients in each cluster in the TOPSY sample.

7 SUPPLEMENTARY INFORMATION

7.1 MRI IMAGE ACQUISITION

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.

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.

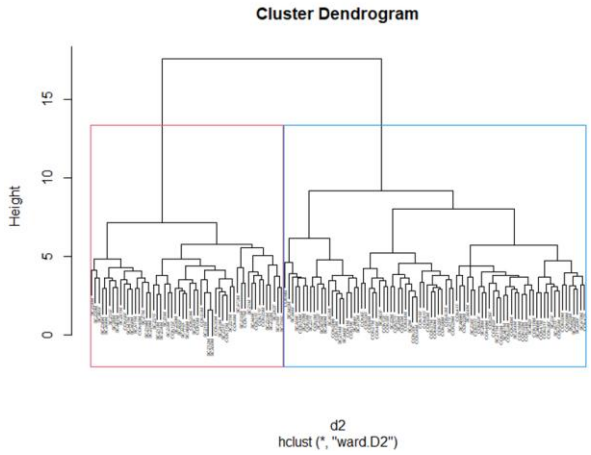
TOPSY 'Validation' Dataset: All MR images were acquired on a 7.0-Tesla Siemens (Erlangen, Germany) Magnetom MRI scanner using a 32-channel head coil at the Centre for Functional and Metabolic Mapping (CFMM), Robarts Research Institute, Western University. High-resolution T1-weighted sequences were collected for co-registration with the echo planar (EPI) and had the following parameters: acquisition time = 9 min 38 s; TR/TE = 6000/2.83 ms; flip angles = 4°, 5°; FOV (read, phase) = 240 mm, 100%; number of slices = 63; slice thickness = 0.75 mm.

7.2 SUPPLEMENTARY TABLE

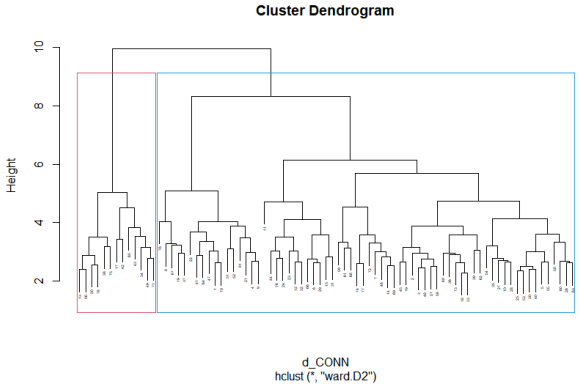
Supplementary Table 1. Medication information of patients i*n the NeuroCog study*

	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
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%)

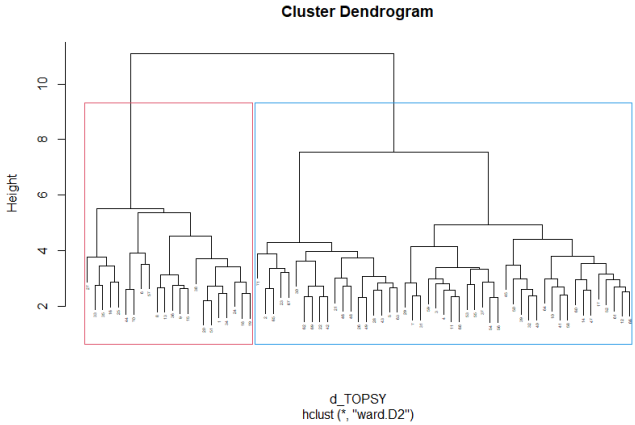
7.3 SUPPLEMENTARY FIGURES



(A) NeuroCog Study

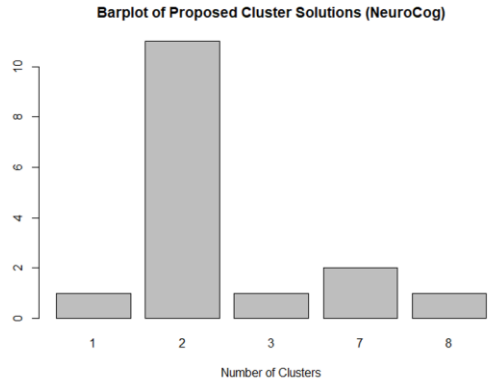


(B) CONN Study

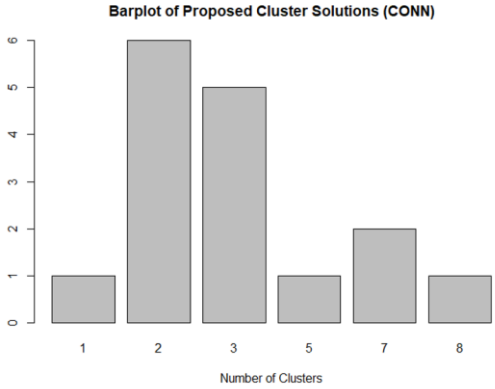


(C) TOPSY Study

Supplementary Figures 1. Hierarchical cluster dendrogram of three different samples.



(A) NeuroCog Study



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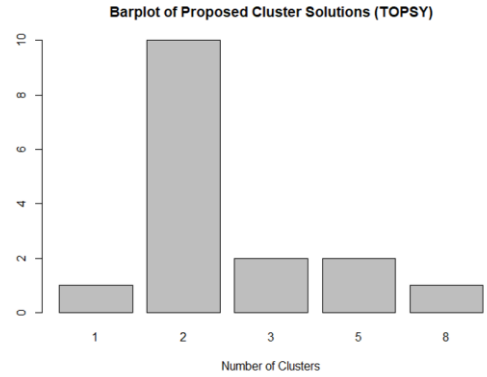
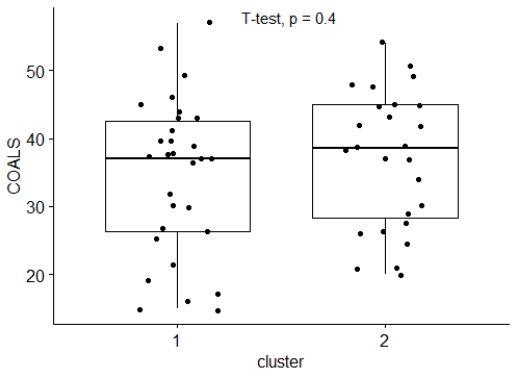
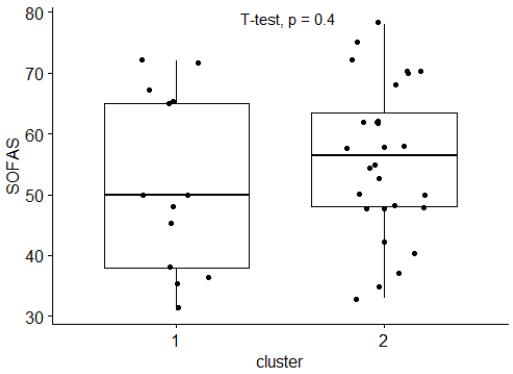


(C) TOPSY Study

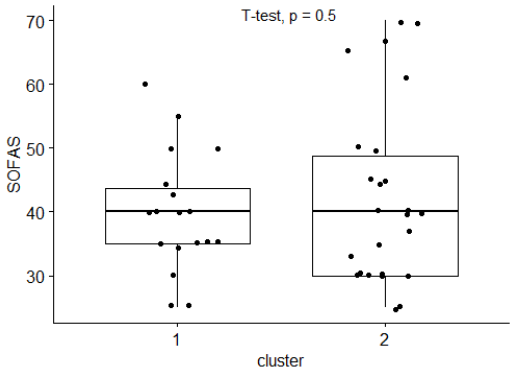
Supplementary Figures 2. Barplots of the frequency of prososed cluster solutions .



(A) NeuroCog Study



(B) CONN Study



(C) TOPSY Study

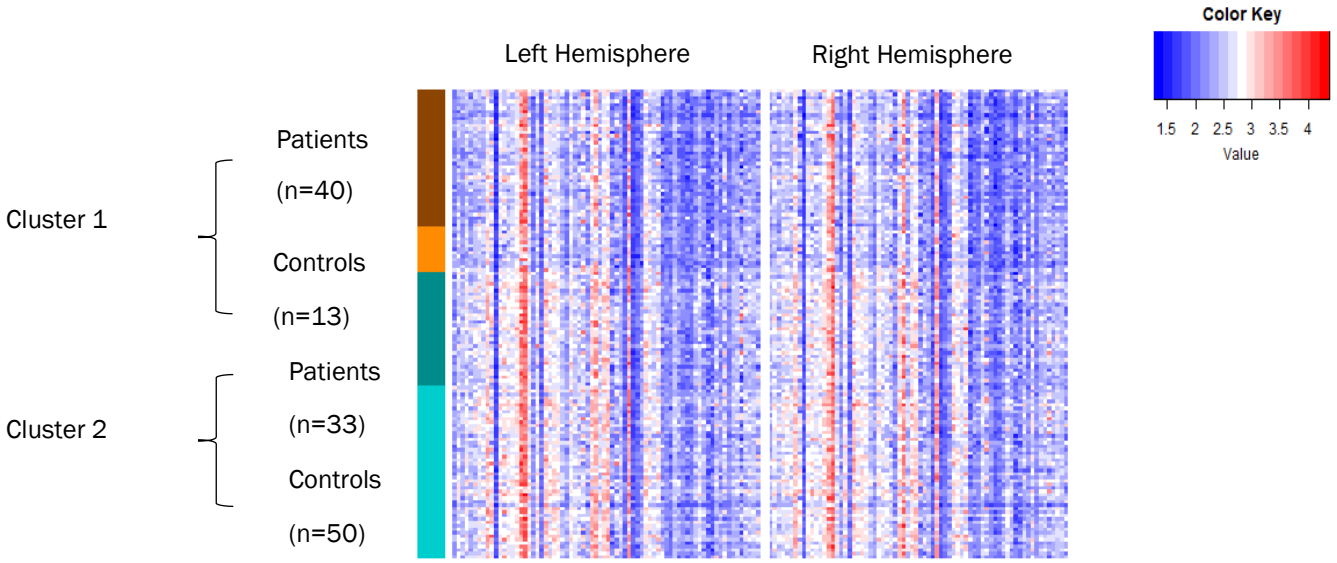
Supplementary Figures 3. Comparisons of functional competence of patients in each cluster.

(A) Independent living skills measured by Canadian Objective Assessment of Life Skills (COALS) in the NeuroCog sample; (B-C) General functioning measured by SOFAS in the CONN and TOPSY samples.

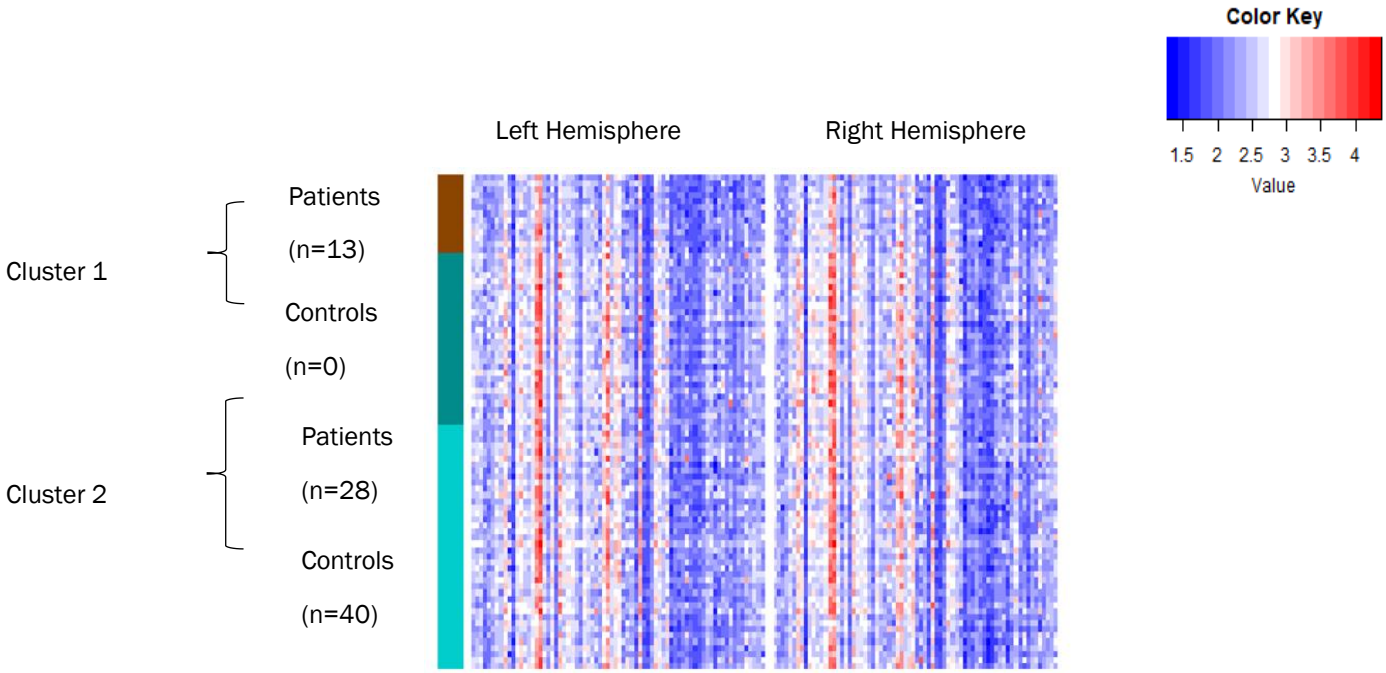
7.4 NEUROANATOMICAL COMPARISONS BETWEEN THE TWO CLUSTERS

Supplementary Table 2. Top 5 cortical parcellations that showed largest effect sizes in thickness between patients of the two clusters

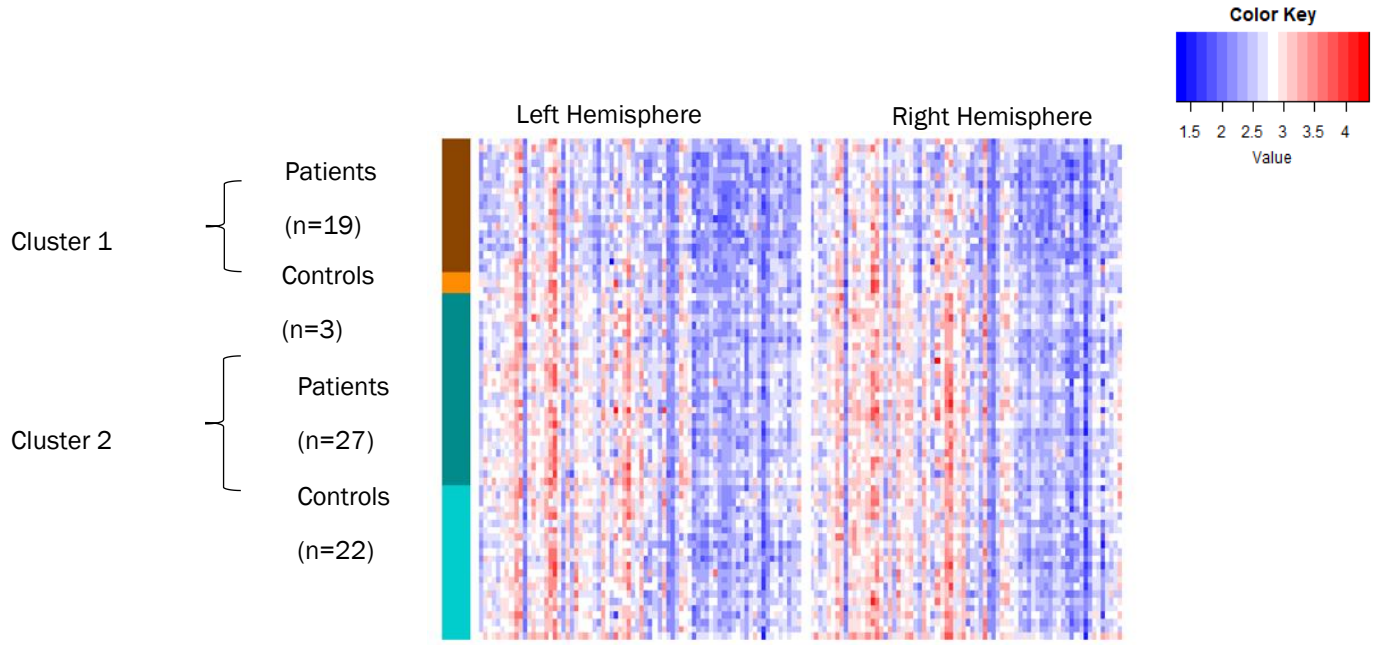
NeuroCog sample	CONN sample	TOPSY sample
R superior frontal gyrus	R planum temporale or temporal plane of the superior temporal gyrus	L middle frontal gyrus
R middle posterior cingulate gyrus and sulcus	L planum temporale or temporal plane of the superior temporal gyrus	R planum temporale or temporal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



(A) NeuroCog Study

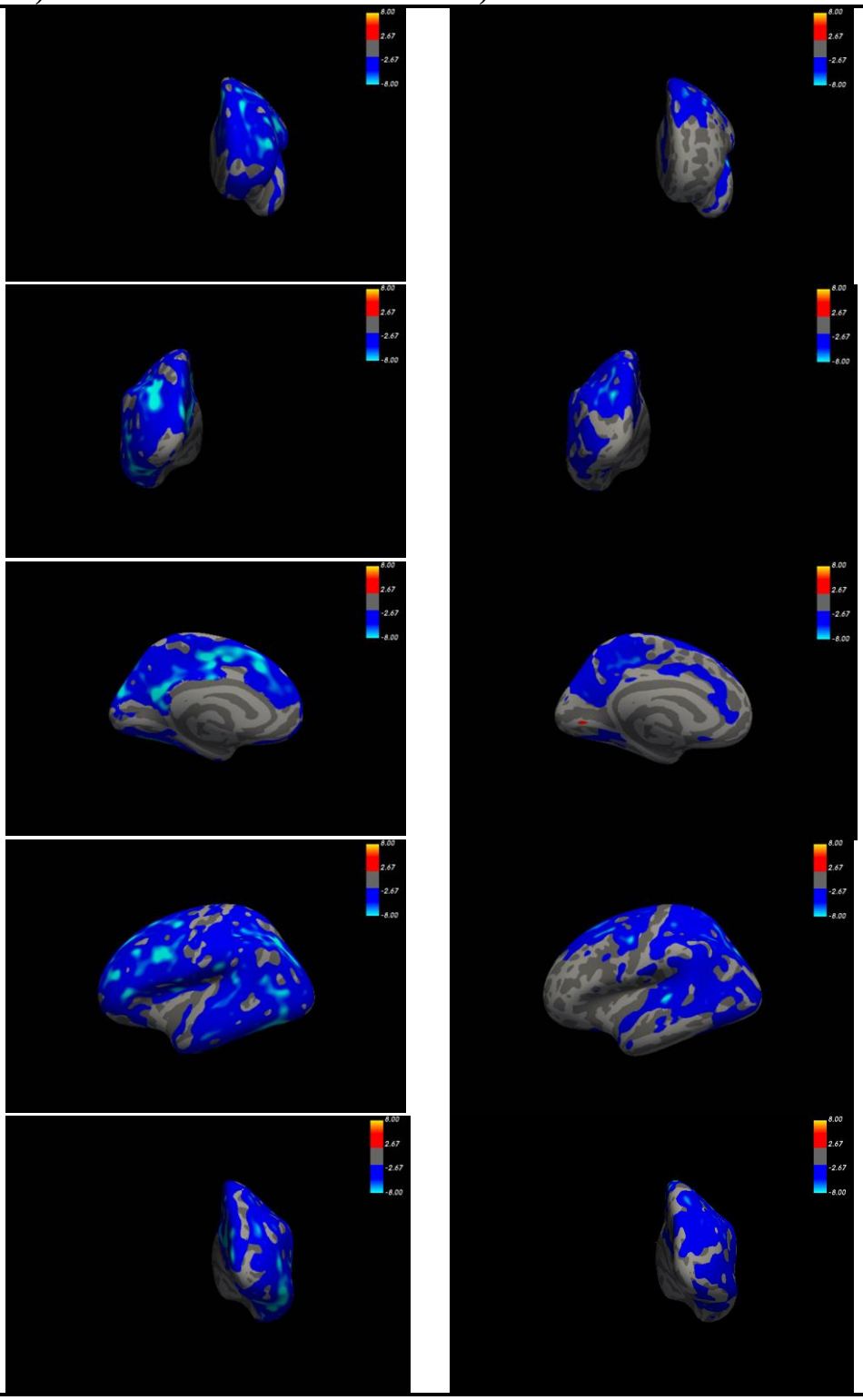


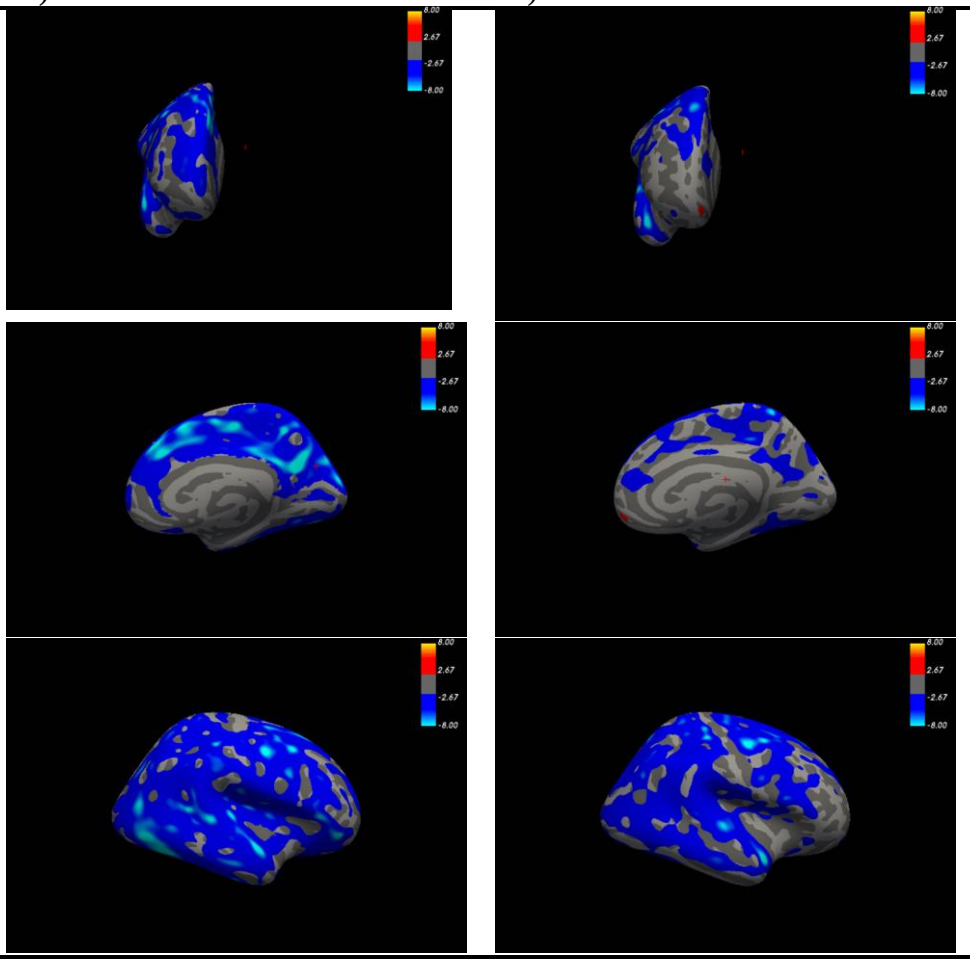
(B) CONN Study



(C) TOPSY Study

Supplementary Figures 4. Heatmaps of cortical thickness values of 74 cortical regions in the left and right hemispheres for patients and controls in Cluster 1 and Cluster 2, respectively. Cortical thickness was measured in millimetres and displayed as colours ranging from blue (thinner cortex) to red (thicker cortex) as shown in the key. The colours of the side bar on the left correspond to the following participant category: Brown, cluster 1 patients; Orange, cluster 1 controls; Blue, cluster 2 patients; Teal, cluster 2 controls.

	‘NeuroCog’ Discovery Dataset (Cluster 1 N = 49; Cluster 2 N = 67)	‘TOPSY’ Validation Dataset (Cluster 1 N = 22; Cluster 2 N = 49)
Left Hemisphere		
Right Hemisphere		

	‘NeuroCog’ Discovery Dataset (Cluster 1 N = 49; Cluster 2 N = 67)	‘TOPSY’ Validation Dataset (Cluster 1 N = 22; Cluster 2 N = 49)
		

Supplementary Figure 5. Cortical thickness maps of differences between members of the two clusters in the discovery and a validation dataset of early stage sample, respectively. Note that 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.

7.5 EXPLORATORY ANALYSIS OF SYMPTOMS, COGNITION, AND MEDICATION

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). We assessed whether the expected relationship between negative symptoms and cognitive deficits differed between the 2 subgroups identified based on thickness profiles. In the discovery dataset, 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 (Supplementary Figure 6B). Negative symptom-cognition correlation coefficients were significantly different between subgroups ($z = -2.234$, $p = 0.013$). Cognitive deficits did not show a significant relationship with positive symptom severity in either subgroup (Supplementary Figure 6A).

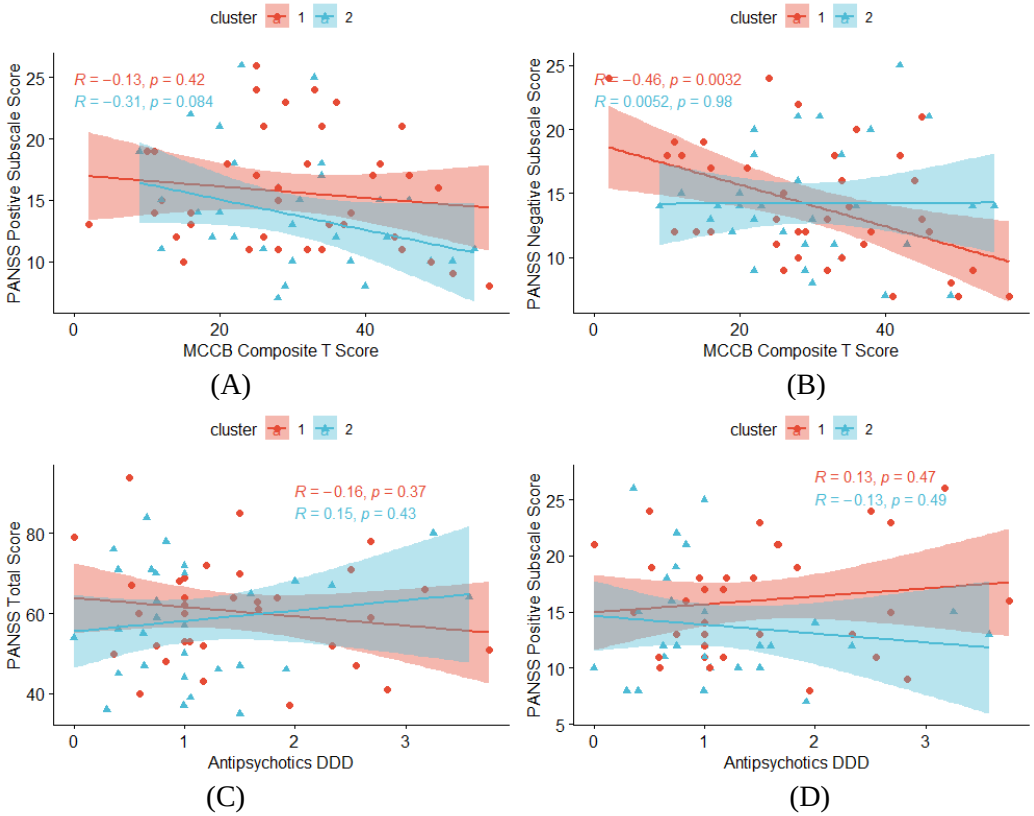
Both illness severity and antipsychotic medication dose have been implicated in cortical thickness changes in schizophrenia (Andreasen et al., 2013; Lepage et al., 2020). We examined whether both thickness-based subgroups of patients had the same relationship between higher doses of antipsychotics and higher symptom severity. There was no correlation between antipsychotic exposure and overall or positive symptom burden in Cluster 1 or Cluster 2 (Supplementary Figures 6C-6F), but an increase in antipsychotic exposure was associated with different directions of change in negative symptom severity in Cluster 1 and Cluster 2 ($z = -1.987$, $p = 0.023$; Supplementary Figure 6E).

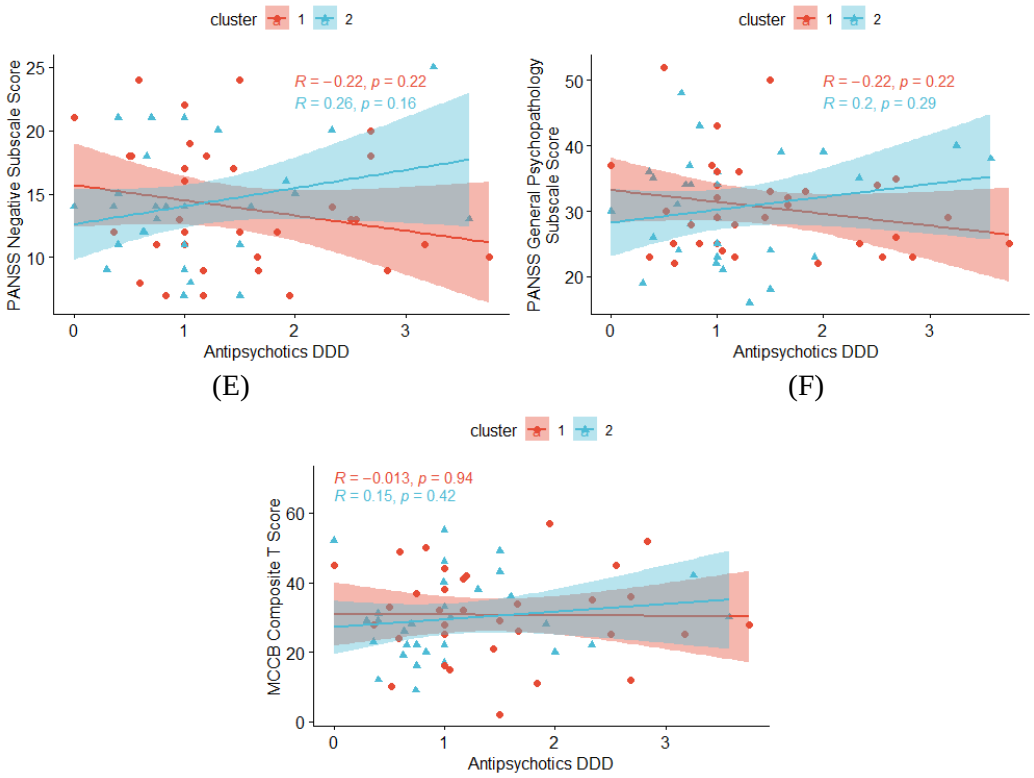
Additionally, antipsychotic exposure and cognitive abilities were not significantly associated (Supplementary Figure 6G), and the two subgroups did not show a difference in this relationship ($z = -0.687$, $p = 0.246$).

The relationships among positive symptoms, negative symptoms, cognitive performance, and antipsychotic dosage in the two clusters are summarized in Supplementary Figure 7A-7B.

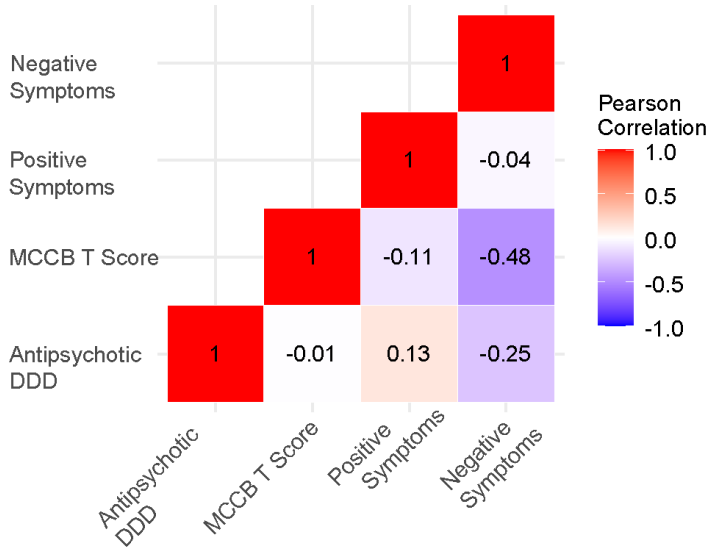
The above exploratory analyses were limited to the discovery dataset as we did not have cognitive data from the validation datasets. The results indicated a relationship between negative symptom severity and

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.

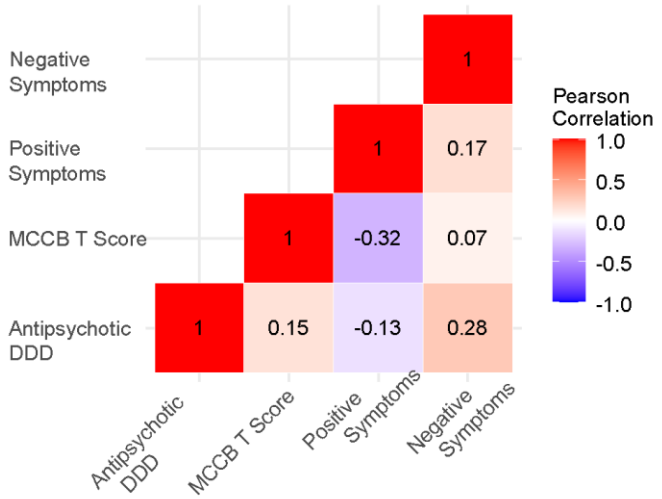




Supplementary Figures 6. Relationships between cognitive test scores, symptoms severity measurements and antipsychotics defined daily dose in Cluster 1 and Cluster 2 patients, respectively in the NeuroCog Sample. MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; PANSS: Positive and Negative Syndrome Scale; DDD, defined daily dose calculated according to World Health Organization.



(A) Cluster 1 Patients

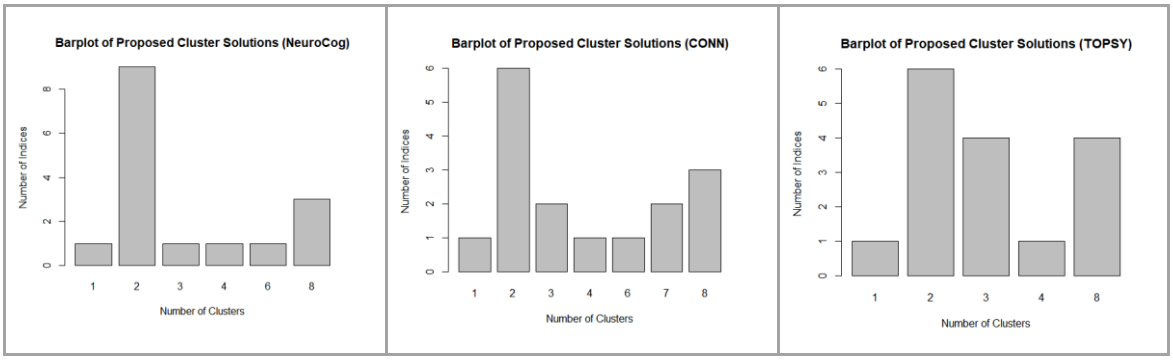


(B) Cluster 2 Patients

Supplementary Figures 7. The correlation matrix heatmap of PANSS positive, negative subscale scores, antipsychotic defined daily dose (DDD) and MCCB composite T scores for patients in Cluster 1 and Cluster 2.

7.6 CLUSTERING PATIENTS ONLY

We applied the same clustering procedure to patients only in the three datasets. The statistical steps included obtaining Destrieux (Destrieux et al., 2010) atlas-based cortical thickness values, adjusting for age with linear regression, running agglomerative hierarchical cluster analysis (Euclidean distance and Ward's method), and finally evaluating cluster solutions with multiple cluster validity indices. Out of 16 cluster validity indices, 9, 6 and 6 indices suggested a two-cluster solution in the NeuroCog, CONN and TOPSY samples, respectively (Supplementary Figures 8). This indicates that morphology-based subgrouping is agnostic of disease status and provides a stable 2-cluster solution with or without the data from healthy subjects.



(A) NeuroCog (B) CONN (C) TOPSY

Supplementary Figures 8. Barplots of the frequency of prososed cluster solutions.

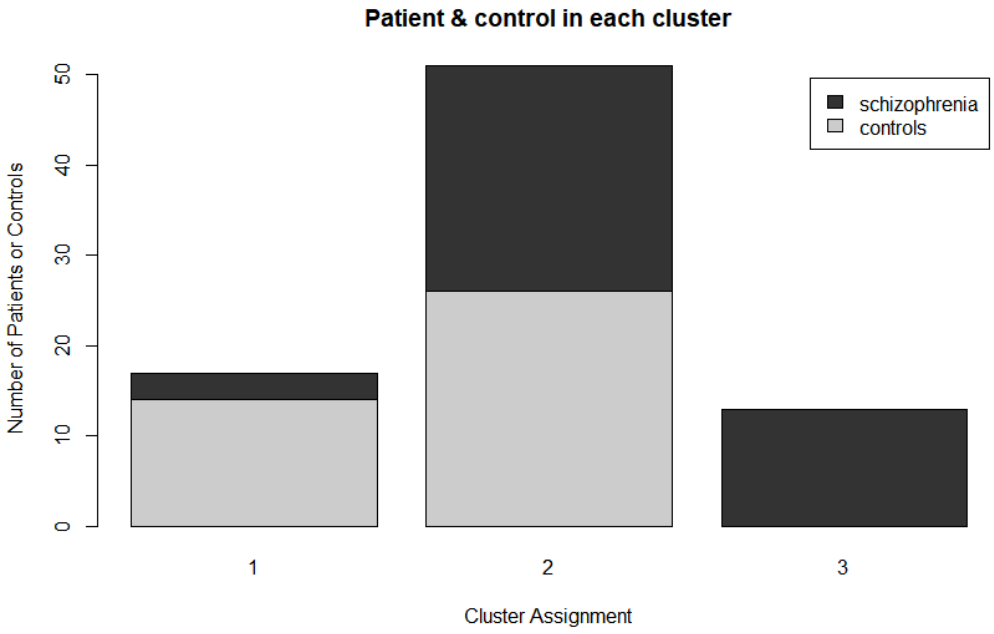
Supplementary Table 3. 'Cortical impoverishement' subgroup membership when clustering is carried out with or without the data from healthy controls.

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
TOPSY 'Validation' Dataset Patients only		FEP-only clustering	
		Cortical Impoverishment	Non-impoverished
Whole sample clustering	Cortical Impoverishment	19	0
	Non-impoverished	4	23

Note that 67 out of the 72 patients identified as cortically impoverished with whole-sample approach, are correctly identified with patient-only approach, providing a subgroup-level accuracy of 93%.

7.7 RESULTS OF A THREE-CLUSTER SOLUTION IN CONN

Out of the 16 cluster validity indices, 5 indices suggested that a three-cluster solution was also potentially meaningful to explore heterogeneity in the CONN sample. If we are to separate the CONN sample into three subgroups, a healthy subjects-dominated subgroup with only 3 patients emerges (Supplementary Figure 9). This third cluster further explained the heterogeneity in healthy controls. Members of the patient-dominant cluster remained the same as the previously identified 'cortical impoverishment' subgroup from the two-cluster solution. This further supported that patients and controls overlapped in cortical thickness patterns and that the patients are more likely to be the members of the 'cortical impoverishment subgroup.



Supplementary Figure 9. Barplots of the frequency of prososed cluster solutions .

DECLARATION OF INTEREST

LP reports personal fees from Janssen Canada, Otsuka Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Sunovion and Otsuka Canada outside the submitted work. LP is the convenor of DISCOURSE in Psychosis, an international consortium of researchers interested in the study of language in psychosis.

RWH receives book royalties from Oxford University Press.

LL, JT, PJ and PFL report no conflict of interest.

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