# IDENTIFYING NEURAL UNDERPINNINGS OF SCHIZOPHRENIA-SPECIFIC DISRUPTIONS IN COGNITION USING MAGNETIC RESONANCE IMAGING, INDIVIDUAL DIFFERENCES, AND GENETICS

by

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(Under the Direction of Jennifer McDowell)

## ABSTRACT

People with schizophrenia exhibit cognitive deficits that have wide-reaching effects on daily functioning and prognosis. Cognitive deficits are attributed to deviations in brain structure and function, including those related to brain morphometry, integrity of cognition-related networks, and activation of these networks during cognitive tasks. There are, however, questions of how specific cognitive deficits and associated brain deviations are to people with schizophrenia when compared to other psychiatric disorders with psychosis and to healthy people who show similar cognitive deficits. The series of studies proposed uses multiple psychosis groups and two healthy comparison groups, one group with high cognitive control and one group with low cognitive control, to differentiate which cognitive and brain deviations are specific to schizophrenia, rather than a general feature of psychosis or due to generalized deficits in cognition. Each study will address a different aspect of the brain that underlie cognitive deficits in schizophrenia. This will include multiple measures of brain structure, connectivity of three brain networks dominant in cognitive performance, and activation during antisaccades, a task related to performance on other cognitive tasks. As a follow-up analysis for the second and

third study, genetic effects on brain measures will also be performed. Genetics may provide a mechanistic explanation of why groups may be the same or different in spite of a psychiatric diagnosis. Using multi-modal data characterizing brain structure and function along with genetics and more appropriate comparison groups may help identify cognitive control deficits that are specific to schizophrenia which would aid in better targets for treatment and remediation.

INDEX WORDS: Cognition, Schizophrenia, Magnetic Resonance Imaging

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# CHAPTER 1

## INTRODUCTION

Schizophrenia is a psychotic disorder commonly characterized by delusions and hallucinations. A central feature of the disorder, however, are cognitive deficits, although they are not part of the diagnostic criteria. These deficits are present before disease onset [1], stable throughout the course of illness [2-4], and predict functional outcome [5, 6]. Cognitive deficits in schizophrenia are broad and include problems in inhibition, working memory, context processing, problem solving and reasoning, processing speed, and verbal memory, sometimes up to .5- 2 standard deviations below healthy comparison groups [7-12].

Given the wide-reaching effects of cognitive deficits in schizophrenia, identifying their neural underpinnings have been of particular interest. One means of identification is with magnetic resonance imaging (MRI), a technique using atomic nuclei to assess brain structure and function. MRI studies in people with schizophrenia report deviations in both, including those related to brain volume [13], connectivity [14], and activation during cognitive tasks [15]. While MRI studies are extensive, there are questions about the specificity of cognitive deficits and their neural underpinnings to schizophrenia[16, 17]. For example, there are other psychotic disorders falling on a symptom continuum with schizophrenia, like schizoaffective disorder and bipolar disorder, which also include cognitive deficits and associated brain deviations as core features [18-22]. These similarities beg the question of whether cognition-related deficits are a general feature of psychosis or specific to a particular psychotic disorder like schizophrenia. Another question is whether the brain deviations underlying cognitive deficits in schizophrenia are the same as

individuals in the healthy population who display similar deficits in cognition. Answers to these two questions are needed given discussions of using cognitive deficits as primary diagnostic criteria for schizophrenia rather than symptom criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)[17, 20, 23].

There are several approaches that may aid in identifying schizophrenia-specific deficits in cognition and the brain deviations that underlie them. In reference to comparing people with schizophrenia to other psychotic disorders, it is important to consider all disorders that include psychosis, especially in a way that addresses the symptom continuum they share[24]. The use of multivariate analyses also is advantageous to evaluate multiple cognitive measures and multiple brain measures; most studies addressing the neural underpinnings of cognitive deficits in schizophrenia are massively univariate and only focus on select cognitive measures and/or brain regions. In reference to comparing people with schizophrenia to healthy populations, an alternative and underutilized method is the use of 2 healthy comparison groups: a more traditional comparison group, people with high cognitive control (HCC), and a more appropriate comparison group to people with schizophrenia, people with low cognitive control (LCC). People with LCC are more similar to people with schizophrenia in their level of cognitive ability, but do not present with symptoms of psychosis [25]. Groups that are cognitively similar but have different diagnostic status may exhibit different deviations in brain circuitry, as poor cognitive control could arise from distinct underlying causes. Using both people with LCC and people with HCC as comparison groups to people with schizophrenia would help differentiate circuitry deviations that are specific to the disorder (only present in the schizophrenia group) from those that are due to generalized deficits in cognitive control (present in both the schizophrenia and LCC groups).

The primary goal of the proposed studies is to identify deviations in brain structure and function (as measured by MRI) related to cognitive deficits that are specific to schizophrenia. Study 1 will address if these deviations are specific to schizophrenia or common across all disorders involving psychosis. The aim is to use multiple psychosis groups and consider multiple measures of cognition and brain structure (gray matter volume, cortical thickness, cortical surface area, and gyrification). Psychosis groups will be determined based on a symptom continuum to better account for symptom overlap among the three psychotic disorders ranging from more schizophrenia-like to more bipolar-like[24]. To avoid massive univariate analyses and selection of specific regions of interest, multivariate methods will evaluate cognition and brain relationships across the cortex. How brain measures jointly influence cognitive deficits across the psychosis spectrum also will be considered. The use of a symptom-based classification system in addition to multivariate statistical methods may provide insight into deviations in cognition and brain that are present across the psychosis continuum generally, and in schizophrenia-like disorders specifically.

Studies 2 and 3 will address whether neural underpinnings of cognitive deficits in schizophrenia are different from that of healthy controls with similar cognitive deficits. These studies will use 2 healthy comparison groups (HCC and LCC) to identify schizophrenia-specific disruptions in resting-state connectivity and task-based activation as measured by the blood oxygen level dependent (BOLD) signal. Resting state analyses will focus on the integrity of lateralized frontal-parietal and default mode networks, which are implicated in diverse cognitive abilities[14, 26-29]. Task-based analyses will focus on activation during the performance of antisaccades[30]; antisaccades are frequently used to asses cognitive control in schizophrenia[31-35] and are related to other aspects of cognition[33, 36].

In studies 2 and 3, genetics will be used to further differentiate LCC and schizophrenia groups from each other. Genetics contribute to cognitive abilities via effects on neurotransmitter systems [37] and brain structure [38] and function [39, 40]. Including genes along with MRI measures may offer further insight into neural deviations that differentiate people with schizophrenia from people with LCC or those that are common to both groups, especially since gene effects are more closely related to brain measures than they are to observable behavior. Focus will be placed on genes that directly or indirectly target the dopamine system. Dopamine availability affects cognitive ability [41-44] and dopamine circuitry is disrupted in schizophrenia [45].

# CHAPTER 2

# LITERATURE REVIEW

## Brain Structure and Cognition

Cortical structure is comprised of several components: brain volume (a 3D measure of gray matter), cortical thickness (a measure of distance between gray/white matter boundaries and the pial surface), surface area (a measure of cortical expansion), and gyrification (a ratio measure of the amount of cortex in sulci to the amount of cortex on gyral surfaces). Evaluation of brain structure may give insight into cognitive underpinnings given that the developmental trajectory of certain cortical measures mirror the emergence and decline of specific cognitive abilities [46, 47]. Among healthy adults, better cognition is generally associated with larger brain volumes [48, 49], thicker cortex [50], larger surface area [51], and greater gyrification [52, 53]. These relationships, however, can be regionally specific and extremes in either direction can reflect pathology [54, 55]. There are caveats to research evaluating relationships between brain structure and cognition. One is the large variety of cognitive assessments available for study. The level of cognitive assessment (i.e. tests of generalized intelligence vs. tests of specific cognitive functions) may affect the types and number of structural relationships observed [56]. Additionally, multiple structural measures are not typically evaluated in the same analysis. Given the interdependence between measures of volume, cortical thickness, and surface area, structural correlates of cognition might be clearer when multiple structural measures are considered jointly [52, 57, 58].

## Brain Structure and Cognition in Psychosis

There are significant overlaps on multiple biological and clinical features across schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis [59]. Among these features are cognitive deficits[18-22] and deviations in brain structure[60, 61]. People with schizophrenia are the subject of most studies, with volume being the most consistently evaluated structural brain measure related to cognitive deficits. In schizophrenia, cognitive deficits are associated with smaller cortical volumes[62, 63], thinner cortices [50, 55], smaller surface area [55, 64], and less gyrification[65]. Other psychiatric groups involving psychosis show similar disruptions in cognition and brain structure[19, 60, 61, 66], although studies of these additional disorders are sparse and sometimes report results that are inconsistent with a psychosis-general impairment[18, 55, 67]. Additional problems stem from collapsing psychosis groups into a single sample, as is often done with schizophrenia and schizoaffective groups, and failing to differentiate bipolar disorder with and without psychosis. There also is an issue of symptom overlap among, and substantial heterogeneity within psychotic disorders, suggesting categorizations outlined by the DSM are fuzzy and do not represent discrete disorders. The nature of psychosis samples along with small sample sizes has made it difficult to determine which concomitant deficits in cognition and brain structure are specific to schizophrenia and which are features across all psychotic disorders. Study 1 will attempt to address the specificity of cognitive and structural deviations to schizophrenia by using multiple psychosis groups and multivariate analyses, which will consider multiple measures of cognition and brain structure across the cortex. A symptom continuum also will be used for psychosis group construction to address the symptom overlap across psychotic disorders.

## Resting State Connectivity and Cognition

Cognition arises from the cooperation of multiple brain regions [68]. Cooperation, or shared information processing, is referred to as connectivity and is measured by correlating BOLD signal fluctuations across regions over time. BOLD signals that fluctuate in the same direction result in positive correlations and index stronger connectivity among regions, whereas BOLD signals that fluctuate opposite each other result in negative or anti-correlations, and index differentiation between regions. Brain regions with temporally coherent BOLD signals form functional networks that not only are apparent during performance of cognitive tasks, but are visible at rest when the brain is not engaged in a specific task. These large-scale resting state networks (RSNs) are intrinsic to the brain's architecture [68], consistent across time [69], and influence brain function during task states [70].

One such RSN is the Frontal Parietal Network or FPN which is composed of lateral prefrontal cortex (lPFC), anterior cingulate, and posterior parietal cortex [71]. The FPN includes regions that support sustained attention, working memory, and response selection, making it a superordinate control system that integrates information between external and internal processes [72]. Connectivity of regions within the FPN at rest are related to activation of the same regions during a variety cognitive tasks [70]. The FPN also interacts with another well-studied RSN, the default mode network (DMN). The DMN (composed of medial PFC, posterior cingulate, and bilateral angular gyrus) supports self-referential processing and is suppressed during cognitive task performance [73]. Successful cognition favors strong within-network FPN connections and strong anti-correlations between the FPN and DMN [74] (see Figure 2). Such a configuration supports efficient local processing while minimizing system-wide noise. See Figure 2.1 for a

summary of functional connectivity principles and relationships between FPN and DMN in reference to cognition.

FPN and DMN in healthy populations-individual differences

Measures of FPN and DMN connectivity are used to characterize cognitive abilities in healthy populations. The strength of connections within and across these networks predict brain activation during cognitive tasks and account for individual differences in the BOLD signal [28, 75] and behavior. Better cognitive performance is associated with stronger connections between the FPN and other task-positive regions like the cerebellum [29], dorsal ACC (dACC), and fronto-insular cortex [26]. The cerebellum is implicated in the timing of cognitive operations [76] whereas the dACC and the insula work together with the FPN (dlPFC specifically) to set base levels of activity, aiding in response maintenance and selection [26]. Stronger anti-correlations at rest between the FPN (dlPFC) and the DMN (medial PFC) are also correlated with better cognitive performance [27]. Although this general pattern supports effective cognition, studies in healthy populations are limited. Methods are typically restricted to simply correlating connectivity metrics with some measure of cognitive performance within the same sample of healthy individuals[27]; there is often no selective recruitment for individuals with poor cognition.

FPN and DMN in schizophrenia

Schizophrenia is frequently characterized as a disconnection syndrome [77, 78] with abnormalities in the way large scale networks communicate with each other. Disrupted connectivity is correlated with many aspects of the disorder including cognitive impairment [79, 80]. These connectivity disruptions are frequently found within the FPN and manifest primarily as hypo-connectivity of the dlPFC with a variety of regions (e.g. temporal cortex , parietal cortex, thalamus, and striatum [81, 82]) and other cognition-related networks (e.g. cerebellar and cingulo-

opercular networks [83]). Hyper-connectivity of the dlPFC and regions outside the FPN, however, are found primarily in sensory and motor regions [84]. Hyper-connectivity also is apparent in the relationship between the FPN and DMN nodes, indicating a lack of differentiation between the two networks [85, 86]. Overall, it seems that people with schizophrenia show two patterns of connectivity deviation: (1) hypo-connectivity within the FPN and regions/networks that actively support cognitive performance and (2) hyper-connectivity between the FPN and regions that either support lower-order processes or are anti-correlated with task-positive networks. Study 2 will attempt to identify if the two aforementioned connectivity deviations are specific to schizophrenia by looking at connectivity of the FPN and DMN in schizophrenia compared to healthy people with similar deficits in cognition.

## Antisaccades as Measures of Cognitive Control

Saccades are fast eye movements used to foveate a target[87]. Antisaccades require subjects to inhibit the prepotent response to look toward a suddenly appearing visual stimulus, and instead, look to the mirror image location[30]. Antisaccade tasks are frequently used to assess cognitive control and are suitable proxies of other cognitive abilities because they involve several higher-order operations (e.g. response inhibition, manipulation of visuospatial information in working memory, and goal-directed responding [88]). Healthy participants make errors (looking toward the peripheral target instead of away) about 20% of the time [89]. Errors reflect the inability to suppress a task-irrelevant response in favor of a task-relevant one and are considered failures in cognitive control.

Antisaccade performance is supported by neural circuitry that is well-characterized and includes the dorsal lateral PFC (dlPFC), supplementary and frontal eye fields (SEF and FEF respectively), posterior parietal cortex (PPC), visual regions, basal ganglia, and thalamus [34, 90-94].

Two nodes that are particularly important to the cognitive control aspect of the task are the dlPFC and FEFs. Those with dlPFC lesions have heightened antisaccade error rates [95], whereas those with FEF lesions have slower correct reaction times [96]. The dissociation between lesion effects on the dlPFC and FEFs suggests that the dlPFC is responsible for inhibition of the proponent response and task rule implementation [97-100], whereas the FEFs are responsible for triggering the correct antisaccade response [95, 101]. Other regions associated with cognitive control during the antisaccade task are the inferior parietal lobe and thalamus[102], although their contribution is more related to stimulus detection, attentional shifts, and spatial working memory[93, 103, 104].

Antisaccades in healthy populations-individual differences

Antisaccade error rates typically reported in the healthy literature are around 20%[105], although there can be substantial variability in this measure within healthy populations[106, 107]. Variability in antisaccade performance is evaluated in terms of variability in the central executive component of working memory [107], which is responsible for maintaining task goals in the face of interference from internal and external stimuli via implementation of controlled attention [88, 108]. Such abilities are important for the antisaccade task in that people need to maintain task rules (look away from the peripheral cue) while inhibiting a response that introduces high levels of interference due to its prepotency. People who score low on central executive measures, or those with low cognitive control (LCC), perform worse on antisaccade tasks than people with high cognitive control (HCC). They often make more errors and are slower to generate correct responses [88, 107].

Individual differences in healthy antisaccade performance is reflected in neural circuitry. Schaeffer et al. [109] found that poor performers (participants with LCC) under activated frontal

and parietal regions compared to good performers (participants with HCC), although this effect was driven by error trials only; no differences existed between groups on correct trials. Evidence from other cognitive control paradigms that asses individual differences and effects on brain activation are mixed, with some showing hyper-activation [110, 111] and others showing hypo-activation [112, 113] of brain circuitry in those with LCC compared to those with HCC. Still others have shown that those with LCC demonstrate both hyper- and hypo-activation localized to sensory (lower order) and frontal (higher order) regions respectively (unpublished data [114]). These differences, however, may be attributable to the focus on individual component processes (encoding, maintenance, retrieval etc.) [115], making it difficult to generalize findings to the antisaccade task.

Antisaccades in schizophrenia

People with schizophrenia show cognitive control deficits that are reflected in antisaccade behavioral performance. They consistently commit more antisaccade errors and take longer to initiate correct antisaccades [33, 116], similar to those with frontal lesions [98, 117-119]. Although still apparent, less severe deficits are reported in unaffected first degree relatives of people with schizophrenia, indicating shared genetic variation between disease risk and antisaccade deficits [90, 116, 120, 121]. Deviations in unaffected relatives also suggests that antisaccade disruptions are not a consequence of disease chronicity or antipsychotic medication.

The cause of antisaccade deficits in schizophrenia has been somewhat debated. It is unclear whether people with schizophrenia have problems with response inhibition (suppressing the response to look toward the visual cue) [122], working memory (maintaining task rules) [123], voluntary response implementation (generation of the correct antisaccade to the mirror image location) [124], or performing these operations simultaneously. Regardless of the cause, neural

deviations underlying poor performance in schizophrenia are apparent and include under activation of several regions of saccade circuitry (FEF, cingulate, visual regions, basal ganglia) [90, 125], although the most consistently reported neural deviation is under-activation of the dlPFC [34, 90, 126]. Both behavioral and neural deviations related to the antisaccade task also exist despite relatively intact behavioral performance and neural circuitry underlying visually guided prosaccades [127, 128]. This indicates that the eye movement system itself is intact in schizophrenia and further supports that the problem lies in the cognitive control aspects of the task. Study 3 will attempt to identify if antisaccade-related deviations are specific to schizophrenia by looking at brain activation during antisaccade performance in schizophrenia compared to healthy people with similar deficits in cognition. Activation during correct and error trials also will be considered since differences between groups that are cognitively similar could be due to deficits in neural processing during correct trials, error trials, or both.

## Genetics and Cognition: The Role of Dopamine

Genes have downstream effects on neural signaling that contribute to differences in cognition. Dopamine is a modulatory neurotransmitter present in circumscribed regions responsible for cognitive performance [129-131]. Specifically, levels of synaptic dopamine in PFC are directly related to neural network properties and contribute to cognitive abilities via the ratio of D1 to D2 stimulation [132]. More synaptic dopamine biases extra-synaptic D1 stimulation and potentiates NMDA and GABA (indirectly) currents [133-135], stabilizing neuronal assemblies and increasing the signal to noise ratio [136, 137]. This stabilization supports sustained neural activity, which is related to the maintenance of information during cognitive task performance. While network stability is generally positive, excessive D1 stimulation also can be harmful, causing unperturbable levels of stability contributing to cognitive inflexibility. On the other hand, less

synaptic dopamine biases intra-synaptic D2 stimulation and reduces NMDA and GABA currents [138], destabilizing neuronal assemblies and reducing the signal to noise ratio. Destabilization causes disorganized spread of activation and is a source of distractibility during cognitive performance [139, 140].

While other neurotransmitter systems are related to cognitive abilities, genetic effects on dopamine function are the best characterized and most directly related to distinct regions known to be involved in cognition[41, 136, 139]. Dopamine receptors also are present on both glutamatergic pyramidal cells (D1 receptors) [141] and GABAergic interneurons (D2 receptors) [142], which allows for the modulation of both excitatory and inhibitory currents. Furthermore, dopamine is one of the primary neurotransmitter systems disrupted in schizophrenia[45, 143]. Studies 2 and 3 will examine genetic effects on brain function and how they may be different between people with schizophrenia and healthy people with poor cognition. See Table 2.1 for a brief description of targeted dopamine-related genes and the single nucleotide polymorphisms (SNPs) of interest; table also includes relevant biological information regarding its relationship to dopamine signaling and known effects on cognition.

**Table 2.1 Description of Genes**

| Gene | Cytogenic Location | Gene Product | Function | SNP | Variants (alleles) | Variant Effects | Effect on Cognition (+/-) |
|---|---|---|---|---|---|---|---|
| [1,2] COMT | 22q11.21 | Enzyme | Primary means of synaptic dopamine removal in PFC. | rs4680 | A/Met | Lower activity enzyme- increases synaptic dopamine and biases extrasynaptic D1 receptor stimulation= network stability | + |
| | | | | | G/Val | Higher activity enzyme- decreases synaptic dopamine and biases intrasynaptic D2 receptor stimulation=network instability | _ |
| [3-6] RGS4 | 1q23.3 | Protein | Influences downstream effects of dopamine by regulating timing and duration of GPCR receptor signaling (g-protein mediated) | rs2661319 SNP18 | G | Unknown. SNP is intronic and may be dependent on COMT genotype. | + |
| | | | | | A | | _ |
| [7,8] AKT1 | 14q32.32 | Enzyme | Influences downstream effects of D2 stimulation via inhibition of the GSK-3β signaling pathway (non-g-protein mediated). | rs1130233 SNP4 | G | Higher AKT levels-decreased response to D2 receptors and more GSK-3β inhibition | + |
| | | | | | A | Lower AKT levels-increased response to D2 receptors and less GSK-3β inhibition (exacerbation of D2 stimulation) | _ |

* Listed are gene names, location (chromosome and position), gene products, and their relation to dopamine function. SNPs are listed by their current dbSNP ID #. Genetic variation within each SNP is listed under the variant column, followed by their effects on cognition (+ indicates beneficial effects, - indicates detrimental effects).
D1 = dopamine receptor type 1, D2 = dopamine receptor type 2; GSK-3β= glycogen synthase kinase 3 beta
[1]Bilder, Volavka, Lachman, & Grace [144]
[2]Winterer & Weinberger [145]
[3]De Vries et al. [146]
[4]Lipska et al. [147]
[5]Nicodemus et al. [148]
[6]Ettinger et al. [149]
[7]Gogos et al. [130]
[8]Tan et al. [150]

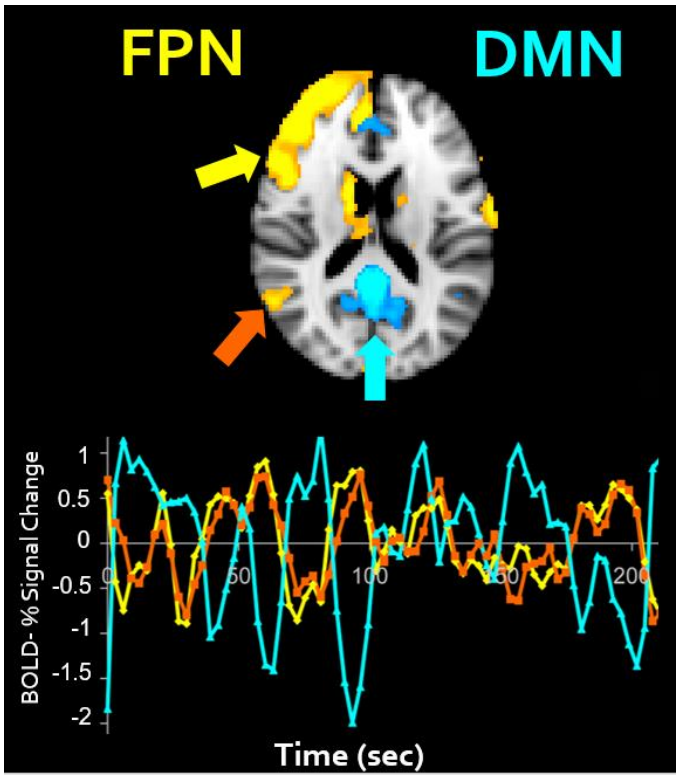



**Figure 2.1** *RSNs Related to Cognitive Control.* Top image shows the spatial pattern of the two cognitive control related RSNs of interest. Yellow regions are those included in the FPN (only right FPN shown) and blue regions are those included in the DMN. Bottom figure shows example BOLD signal time courses from each of the regions indicated by an arrow. The FPN and DMN are anti-correlated, meaning their BOLD signal time courses fluctuate opposite each other (opposing patterns of blue and yellow time courses and blue and orange time courses). The amount of anti-correlation between these two networks is associated with better cognitive control abilities. Strong positive correlations within the FPN (shown by regions indicated by the yellow and orange arrows and respective time courses) also are associated with better cognitive control abilities.

# CHAPTER 3

# EVALUATING RELATIONSHIPS BETWEEN NEOCORTICAL BRAIN ANATOMY AND COGNITION IN PSYCHOSIS USING A MULTIVARIATE ANALYSIS OF BRAIN VOLUME, CORTICAL THICKNESS, SURFACE AREA, AND GYRIFICATION

[1] Rodrigue, A. L., McDowell, J. E., Tandon, N., Keshavan, M.S., Tamminga, C. A., Pearlson, G. D., Sweeney, J. A., & Clementz, B. A. submitted to *JAMA Psychiatry*, 1/11/17

## Abstract

Cognitive deficits are pronounced in psychotic disorders. Their relation to structural brain imaging measures have not been systematically investigated in a way that integrates multiple MRI and cognitive measures in a large sample and in a way that addresses the symptom heterogeneity across and within psychosis diagnoses. Objectives included 1) Characterize the bi-directional relationship between cognition and brain structure in psychotic disorders using a multivariate approach and 2) Identify differences in brain structure/cognition and their bi-directional relationship along a psychosis symptom continuum. Four canonical correlation analyses were performed between 14 cognitive measures and structural brain measures (volume, cortical thickness, surface area, and local gyrification indices) extracted from 68 neocortical regions of interest. Participants were 423 people with a DSM diagnosis of schizophrenia-SZ, schizoaffective-SAD, or bipolar disorder-BP and 240 healthy controls-HC that had scores on all cognitive and structural measures of interest. The Schizo-Bipolar Scale was used to create continuum-based psychosis groups (BP-like, SAD-like, SZ-like).

Across the sample (N = 663, % male = 47, mean age = 36.2, SD =12.4), general cognitive ability was associated with larger volumes and thicker cortices, but smaller surface area in frontal/parietal regions. Spatial working memory capacity and inhibitory control were associated with larger volume and surface area across the brain, particularly in frontal/temporal regions. Faster response speed was associated with larger volume across the cortex and thicker cortices in frontal regions. In summary, the relationship between general cognitive ability and brain structure best-distinguished psychosis groups from each other, whereas response speed, spatial working memory, and inhibitory control best distinguished the SZ-like group.

## Introduction

There are significant overlaps on multiple biological and clinical features across schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis [1]. Among these features are cognitive impairments[2-6], which are present before disease onset [7], reasonably stable throughout the course of illness [8-10], and predict functional outcome [11, 12]. The range of serious cognitive impairments observed in patients with psychotic disorders include behavioral inhibition, working memory, context processing, problem solving and reasoning, processing speed, and verbal memory [13-18].

Alterations in brain structure are well established in psychotic disorders, and therefore represent a potential cause of cognitive impairments. Among healthy individuals, better cognition is generally associated with larger brain volumes [19, 20], thicker cortex [21], larger surface area [22], and greater gyrification [23, 24]. These relationships, however, can be regionally specific [25, 26], vary across neuroanatomic measures, and extremes in either direction can reflect pathology. Importantly, structural measures are not independent, and their relation to cognition might be clearer when considered jointly [23, 27, 28].

The most common structural neuroimaging finding related to cognition in psychotic disorders has been reduced volumes of frontal and temporal cortex, especially in schizophrenia [29]. Studies in bipolar disorder are relatively sparse, and often focus on deep structures including hippocampus, amygdala, thalamus, and basal ganglia [26, 30-32] (although some studies have reported relationships between alterations in frontal cortex and cognition [33, 34]). Findings are less consistent than in schizophrenia [35-37] and the presence of psychosis not fully addressed. Studies of these relationships in schizoaffective disorder are uncommon. Additionally, sometimes schizoaffective individuals are included in schizophrenia samples [38]. This classification is

consistent with a recent meta-analysis concluding that the volumetric and cognitive deficits in schizoaffective disorder may be closer to those seen in schizophrenia [39, 40] than those seen in bipolar disorder [41].

Poor cognition in psychosis also has been associated with thinner cortex [21, 42-44] and lower gyrification indices [24, 45]. With regard to these measures, there is some evidence for diagnostic specificity between bipolar disorder and schizophrenia [26, 46], but samples comparing disorders in brain-cognition relationships have been relatively small. Cortical surface area is the least investigated measure despite its stronger association with genetic variance in cognition relative to cortical thickness, at least in healthy controls [28].

In general, studies of neuroanatomy-neurocognition relationships has been constrained by limited sample sizes, limited cognitive assessment, and selective focus on a particular structural measure or brain region of interest. Uncertain overlap across and heterogeneity within diagnoses further limits comparison of psychotic disorders/syndromes. The purpose of this study was to characterize relationships between cognition and brain structure in a large group of psychosis patients (schizophrenia, schizoaffective disorder, and bipolar disorder) using a data-driven, multivariate approach. This method allows for the simultaneous analysis of multiple cognitive domains and structural brain measures (volume, cortical thickness, surface area, and gyrification) in order to define bi-directional relationships between them. A secondary aim was to evaluate how these bi-directional relationships differ along the psychosis continuum using a dimensional classification method to address symptom heterogeneity within and across psychosis groups. We hypothesized that brain-behavior relationships, as identified via our multivariate approach, would be more disrupted in individuals with schizophrenia-like features and least disrupted in those

with bipolar-like features, with those with schizoaffective-like features falling intermediate between the two.

## Methods

### Participants

Patients with schizophrenia (SZ), schizoaffective disorder (SAD), or bipolar disorder (BP) with psychosis (as defined by the DSM IV-TR) and healthy controls (HC) were recruited as part of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)[47]. Six hundred and seventy eight participants (423 people with psychosis and 240 healthy controls) had complete datasets (scores on all cognitive and brain structure measures) (see Table 3.1). This study was approved by the Institutional Review Boards at all sites and all participants provided written informed consent (See eMthods for further details).

### Cognitive Assessment

Cognitive assessments included the reading sub-test of the Wide Range Achievement Test 4th edition (WRAT IV) [48], Brief Assessment of Cognition in Schizophrenia (BACS) battery [49], the spatial span of the Weschler Memory Scale (WMS-III) [50], the Dot Probe Expectancy task (DPX) [51, 52], and antisaccades (AS) [53]. Procedures and findings for each cognitive measure from the B-SNIP study are available in previous reports [16, 17, 54, 55]. See Methods Supplement and Supplement Table 3.1. for descriptive data for cognitive measures.

### MRI Structural Imaging

Brain gray matter volume (GMV), cortical thickness (CT), cortical surface area (CSA), and local gyrification indices (LGI) were obtained from 68 regions of interest from high-resolution T1-weighted scans (see Supplement Table 3.2). Methods Supplement contain further

details on structural MRI processing. MRI acquisition parameters and findings with morphometric parameters used in this study are available in prior reports [56-58].

Statistical Analysis

To evaluate the bi-directional relationship between cognition and neocortical brain structure, we performed four canonical correlation analyses (CCAs) (one for each structural measure) across all groups using Statistic Analysis System (SAS) software (SAS Institute Inc., Cary, NC). Variables were14 cognitive measures and the structural measures extracted from each ROI. Results are correlated pairs of latent variates (one cognitive and one structural), whose relationships and components can be interpreted by examining the loadings of individual measures on the latent structure, much like principal components analysis (see Methods Supplement for details).

The second set of analyses evaluated the bi-directional relationship between CCA pairs (brain-behavior relations) across a psychosis symptom continuum. A symptom-based dimensional approach was preferred given that symptoms overlap significantly across DSM psychosis diagnoses. The psychosis continuum was defined using the Schizo-Bipolar Scale (SBS) as in prior studies [59, 60] : SBS scores closer to 0 indicate more BP-like features, whereas scores closer to 9 indicate more SZ-like features [61]. To remain consistent with the number of DSM diagnoses in our sample, but still gain the advantage of an ordered psychosis continuum, we used three groups defined by Schizo-Bipolar Scale scores: a group with BP-like features (scores 0-2), SAD-like features (scores 3-6), or SZ-like features (scores 7-9) (see Methods Supplement for details). For significant pairs in each CCA ($p < .0125$), average scores on the latent cognitive and structural variates, as well as the relationship between them, were calculated for each group. Latent score means and correlation coefficients (Fisher Z transformed) were

compared using one-way ANOVAs and differences among groups were evaluated with subsequent pair-wise tests corrected.

## Results

### Canonical Correlation Pairs

There were two significant canonical pairs for the GMV, CT, and CSA analyses, and one significant pair for the LGI analysis. All significant correlations were positive (ranging from r = .42 to r = .55), meaning higher scores on latent cognitive variates were associated with higher scores on latent structural variates. See Results Supplement, Supplement Table 3.4-3.5, and Supplement Figure 3.1 for more detials.

### Variate Loadings

For each CCA pair, loading values (correlations, -1 to 1) of individual measures were used to interpret the nature of the latent variates (see Figure 3.1). Signs of loadings (positive or negative) were used to interpret how scores on individual measures related to the latent variates: positive values indicate higher scores on individual measures, negative values indicate lower scores on individual measures. Loadings, therefore, indicate which aspect of cognition is captured in each analysis, which structural characteristics they are associated with, and the nature of the relationship between them. The latent cognitive variate from the first CCA pair of each analysis was related to general cognitive ability [62] (Figure 3.1a). Better generalized cognition was associated with larger volumes, thicker cortex, and smaller surface area in mostly frontal/parietal regions (Figure 3.1c). Regional loadings for the gyrification analysis were weak, with no regions loading above .3 or -.3 (values often interpreted as moderate effects).

The latent cognitive variate for the second CCA pair was related to more specific cognitive abilities. The latent cognitive variate in the second CCA pair for the GMV and CSA

analyses was related to spatial working memory and inhibitory behavioral control (Figure 3.1b). Better spatial working memory ability and inhibitory control was associated with larger volume and surface area in frontal and temporal regions (Figure 3.1d). In the CSA analysis, regions loading higher than .3 in pair 2 were different than those that loaded higher than .3 in pair 1, indicating that bigger CSA is not always better and may be regionally and cognitively specific. The second cognitive variate in the CT analysis was related to response speed (Figure 3.1b). Slower reaction times were associated with smaller volumes and thinner cortex in frontal/temporal and select parietal regions (Figure 3.1d).

Psychosis Continuum Analyses

For each significant CCA pair, mean cognitive and structural latent scores and the correlation between them were calculated for psychosis groups (generated from the Schizo-Bipolar Scale) and healthy controls. Results of the ANOVAs and pair-wise tests of group means are presented with multiple testing correction but see Supplement Table 3.6 for corrected and uncorrected p-values. Furthermore, associations between latent scores, symptom measures, and medication were negligible and were not considered for further analysis (see Results Supplement and Supplement Table 3.7).

The first CCA pair showed a similar pattern across psychosis groups, analyses, and variates (Figure 3.2a). HC and BP-like groups had the best overall cognition (HCvsSAD: GMV, $p < .001$; CT, $p = .38$; CSA, $p = .02$; LGI, $p = .01$, HCvsSZ: GMV, $p < .001$; CT, $p < .001$; CSA, $p < .001$; LGI, $p < .001$, BPvsSAD: GMV, $p = .02$; CT, $p = .02$; CSA, $p = .03$; LGI, $p = .27$, BPvsSZ: GMV, $p < .001$; CT, $p < .001$; CSA, $p < .001$; LGI, $p < .001$), largest regional volume (HCvsSAD: $p < .001$, HCvsSZ: $p < .001$, BPvsSAD: $p < .001$, BPvsSZ: $p < .001$), thickest cortices (HCvsSAD: $p = .01$, HCvsSZ: $p < .001$, BPvsSAD: $p = .004$, BPvsSZ: $p < .001$), and

smallest surface area (HCvsSAD: $p < .17$, HCvsSZ: $p < .02$, BPvsSAD: $p = .93$, BPvsSZ: $p = .40$) although differences in surface area did not survive multiple testing correction (see Supplement Table 3.6). The SZ-like and SAD-like groups showed the opposite pattern, with the worst overall cognition, smallest volume and thickness, and largest surface area. The correlation between the cognitive and structural variates was stronger in the SZ-like and SAD-like groups compared to healthy controls for GMV and LGI (HCvsSZ: GMV, $p = .002$, LGI, $p = .01$, HCvsSAD: GMV $p = .01$, LGI, $p = .04$) and compared to the BP-like group for CT (BPvsSZ: $p = .05$, BPvsSAD: $p = .02$) (Figure 3.2c).

Patterns of latent scores for the second CCA pair were more complex (Figure 3.2b) and more specific to the SZ-like group. For the GMV and CSA analyses, all psychosis groups displayed lower cognitive latent scores than healthy controls (HCvsBP: GMV, $p < .001$, CSA, $p < .001$, HCvsSAD: GMV, $p = .03$, CSA, $p = .003$, HCvsSZ: GMV, $p < .001$, CSA, $p < .001$), but only the SZ-like group showed deviations in structural latent scores related to GMV. Differences among psychosis groups, however, for the GMV analysis did not survive multiple testing correction (see Supplement Table 3.6, SZvsHC: $p < .001$, SZvsBP: $p = .85$, SZvsSAD: $p= .93$). Although alterations were primarily specific to those with SZ-like features, the strength of the correlation between spatial working memory and GMV and CSA was somewhat stronger for the BP-like group (Figure 3.2d, GMV: BPvsHC, $p = .01$, BPvsSAD: $p = .13$, BPvsSZ: $p = .47$, CSA: BPvsHC, $p = .006$, BPvsSAD: $p = .05$, BPvsSZ: $p = .05$).

The second CCA pair in the CT analysis identified additional disruptions specific to those with SZ-like features (Figure 3.2b). The SZ-like group had the highest cognitive and structural latent scores, indicating that they had the slowest response speed and thinnest cortex compared to other groups although again, some comparisons did not survive multiple comparison correction

(Cognitive variate: SZvsHC: $p < .001$, SZvsBP: $p = .07$, SZvsSAD: $p = .43$, Structural Variate: SZvsHC: $p = .04$, SZvsBP: $p = .93$, SZvsSAD: $p = .93$, see Supplement Table 3.6).

## Discussion

Although brain-behavior relations in psychotic disorders are of considerable interest, the relationship between cognitive deficits and MRI indices of brain structure has yet to be examined using multivariate methods in a large sample across psychotic disorders. The CCAs captured novel aspects of brain structure and cognition involving both general and more specific cognitive abilities. Furthermore, our secondary analyses identified deficits in brain-behavior relationships related to groups based on a psychosis symptom continuum.

General cognitive ability (represented by the first cognitive variate in each CCA) was associated with brain structure in frontal/parietal regions (see Supplement Figure 3.2), which are extensively linked to diverse cognitive functions dependent on attentional load and cognitive demand [63-65]. Correlations between general cognition and GMV and CT were positive and consistent with studies of healthy individuals [22, 24, 26], whereas correlations between general cognitive ability and CSA were negative. Studies correlating CSA and cognition have shown inconsistent results, with some showing positive correlations [22, 26, 28] and others showing negative [66] or no correlations between the two measures (in healthy controls) [67]. The use of ICV as an adjustment variable may contribute to the negative relationship between general cognitive ability and CSA found in our analysis. When the effect of ICV is accounted for, the relationship between CSA and other structural measures like CT can be negative [68], so it is not unreasonable for larger volumes and thicker cortex to be paired with smaller surface areas. Since this pattern of structural measures was related to better general cognitive ability and more apparent in the healthy group, it could be that more neuronal bodies (as measured by larger volume and thicker

cortices) in a smaller space make for a more efficient brain. Such a configuration may enhance local neural processing and shorten the distance neural signals need to travel. Future research should replicate relationships among these structural measures and test these hypotheses.

Associations between general cognition and cortical structure across psychosis groups were consistent with a psychosis severity continuum, with more BP-like manifestations on one end and more schizophrenia-like manifestations at the other, as reported in previous B-SNIP publications [16-18, 56, 69]. Considering SZ-like and BP-like groups as endpoints on a continuum of psychotic disorders, however, does not explain patterns observed in the SAD-like group, which shares symptom features with both diagnoses, but in the present analyses, was more similar to the SZ-like group. Both the SZ-like and SAD-like groups also had the strongest correlations between cognitive and structural variates, suggesting that factors impacting brain-behavior systems may be shared across these disorders causing anatomical deficits that translate to wide-reaching generalized deficits in cognition.

The second CCA pairs identified cognitive components related to specific cognitive abilities and characterized alterations that were associated with the SZ-like group. For GMV and CSA analyses, all psychosis groups showed impairments in spatial working memory ability and inhibitory behavioral control compared to healthy controls; cognitive deficits, however, were only associated with structural deviations in the SZ-like group. This was in the form of smaller GMVs, particularly in the temporal lobe (red and orange regions in Supplement Figure 3.2), which is often reported as smaller in schizophrenia compared to healthy people [70] and people with bipolar disorder [71]. In terms of latent correlations, the BP-like group showed the strongest correlation between spatial working memory and frontal/temporal surface area (yellow and orange regions in Supplement Figure 3.2), even though they did not display greater structural

deficits compared to healthy controls or other psychosis groups. This pattern could indicate that although surface area is not likely altered in bipolar disorder, small alterations could have larger effects on cognition than in healthy people or other psychosis groups.

The second pair in the CT analysis also pointed to disruptions specific to the SZ-like group. The SZ-like groups displayed the slowest response speeds, a neural behavioral deficit long known to be altered in psychotic disorders [72-74]. Regions associated with slow response speed in the SZ-like group included lateral and medial regions of frontal cortex and posterior parietal cortex, which pass sensory information to motor systems to guide the initiation of behavior [75-77]. Furthermore, slow processing of sensory input and behavioral responses in schizophrenia exists even after accounting for the effects of poor generalized cognition[78-80] as was seen in this study.

For the SAD-like group, the tendency to be more similar to the SZ-like group, as evidenced in the first CCA pair, was not apparent in the second CCA pair. The SAD-like group was either more like the BP-like group (e.g. the structural variate of the GMV analysis in Figure 3.1b) or displayed a completely different pattern (e.g. the cognitive variate of the GMV and CSA analyses in Figure 3.1b), indicating that those with SAD-like features exhibit a more complex relationship between cognition and brain anatomy. Lack of consistency in the SAD-like group to follow a particular pattern suggests that this group was neither synonymous with the SZ-like group (as suggested by CCA pair one) nor were they intermediates on a continuum between the BP-like and SZ-like groups (as suggested by CT CCA pair two).

Gyrification analyses were limited in defining cognition/structure relationships. There were no significant associations between LGI measures and specific cognitive abilities (no significant CCA pairs beyond the first pair) and no regions loaded higher than .3 in the first CCA

pair related to general cognitive ability. Lack of sufficiently high loadings on the structural variate suggests a weak and non-specific effect of gyrification and could be due to limited shared genetic influence between LGI measures and other measures of brain structure like GMV, CSA, and CT.

Limitations of the study include the potential effects of medication on both cognition and brain structure. Effect sizes between daily CPZ dose and all latent variables were small and consistent with existing literature [5, 10, 58, 81-83], suggesting that acute drug effects were not likely a major confound to our study. Association between latent variables and symptoms were similarly small. Previous studies of relationships between symptoms and brain structure have produced sparse results, with most linking specific symptoms with specific brain regions (e.g. hallucinations and superior temporal gyrus) [82, 84, 85]. We may not have captured such associations because patients were relatively stable clinically during study participation. Another limitation is that CCA is dependent on the variables included. This study, however, focused on a large number of cognitive tasks covering multiple cognitive domains affected in psychosis with tests that are well-studied and known to be sensitive to deficits in psychotic disorders. We used multiple morphometric analyses of 68 regions across the neocortex, thus we did not consider some brain regions (e.g. amygdala and basal ganglia) known to be involved in cognition in psychotic disorders. This limitation stems from our focus on multiple parallel morphometric measures of neocortex.

## Conclusion

This study used multivariate methods to consider relationships between brain structure and cognitive measures in a large sample across psychosis disorders to address a major question about disturbances in brain-behavior systems in psychosis. Brain-behavior patterns were clearer

and stronger for analyses reflecting generalized cognitive ability, and best distinguished psychosis groups. This pattern is consistent with the overriding importance of generalized cognitive impairment in psychotic disorders across patient groups [5, 86]. Brain-behavior relationships associated with specific cognitive domains showed more moderate differentiations between groups and reflected primarily alterations specific to those with SZ-like features. The SAD-like group did not demonstrate any consistent pattern in brain-behavior relationships relative to other psychosis groups. Understanding the contributions of brain anatomy to cognition in psychosis may identify possible mechanisms underlying cognitive impairments, leading to better remediation approaches and more targeted individualized pharmacological treatments.

**Table 3.1** Sample Characteristics

| | SZ-like (N=159) | | SAD-like (N=135) | | BP-like (N=129) | | HC (N=240) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Demographics** | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Findings |
| Age (yrs) | 35.1 | 12.0 | 36.1 | 12.2 | 35.8 | 13.3 | 37.5 | 12.5 | $F(3, 659) = 1.3$ |
| Education (yrs) | 13.0 | 2.2 | 13.1 | 2.2 | 14.4 | 2.3 | 15.1 | 2.5 | $F(3, 656) = 33.8$[a] |
| | N | % | N | % | N | % | N | % | |
| Male | 109 | 69 | 51 | 38 | 40 | 31 | 115 | 48 | $\chi^2(3)= 47.5$[b] |
| Race | | | | | | | | | |
| Caucasian | 75 | 47.2 | 64 | 47.4 | 99 | 76.7 | 160 | 66.7 | $\chi^2(3)= 39.3$[c] |
| African American | 77 | 48.4 | 65 | 48.1 | 24 | 18.6 | 62 | 25.8 | $\chi^2(3)= 47.2$[c] |
| Other | 7 | 4.4 | 6 | 4.4 | 6 | 4.6 | 18 | 8.5 | $\chi^2(3)= 2.6$ |
| **Clinical Variables** | Mean | SD | Mean | SD | Mean | SD | | | |
| Illness duration (yrs) | 13.7 | 11.1 | 17.1 | 12.5 | 17.0 | 12.3 | -- | -- | $F (2, 402) = 3.8$[d] |
| PANSS | | | | | | | | | |
| Total | 66.9 | 16.5 | 63.4 | 15.4 | 54.6 | 14.5 | -- | -- | $F (2, 412) = 22.8$[e] |
| Positive | 17.3 | 5.5 | 16.5 | 5.2 | 13.1 | 4.7 | -- | -- | $F (2, 414) = 24.8$[e] |
| Negative | 16.9 | 6.0 | 14.4 | 4.4 | 12.4 | 4.5 | -- | -- | $F (2, 414) = 28.6$[f] |
| YMRS | 5.7 | 5.2 | 6.9 | 6.2 | 6.2 | 7.0 | -- | -- | $F (2, 409) = 1.5$ |
| MADRS | 9.4 | 8.1 | 13.1 | 10.0 | 10.8 | 9.5 | -- | -- | $F (2, 412) = 5.9$[d] |
| **Medications** | N | % | N | % | N | % | | | |
| Antipsychotic | 150 | 94 | 114 | 84 | 89 | 69 | -- | -- | $\chi^2(2)= 33.2$[g] |
| Lithium | 9 | 6 | 17 | 13 | 40 | 31 | -- | -- | $\chi^2(2)= 36.1$[g] |

Groups were those determined using the Shizo-Bipolar Scale. SZ-like=those with more schizophrenia like features, SAD-like= those with more schizoaffective like features, and BP-like= those with more bipolar like features. PANSS= Positive and Negative Symptom Scale, YMRS=Young Mania Rating Scale, MADRS=Montgomery Asberg Depression Rating Scale

[a] SZ, SAD < BP < HC

[b] Males: HC, SAD, BP < SZ

Females: HC < BP

[c] African Americans: HC, BP < SZ

[d] SZ < SAD

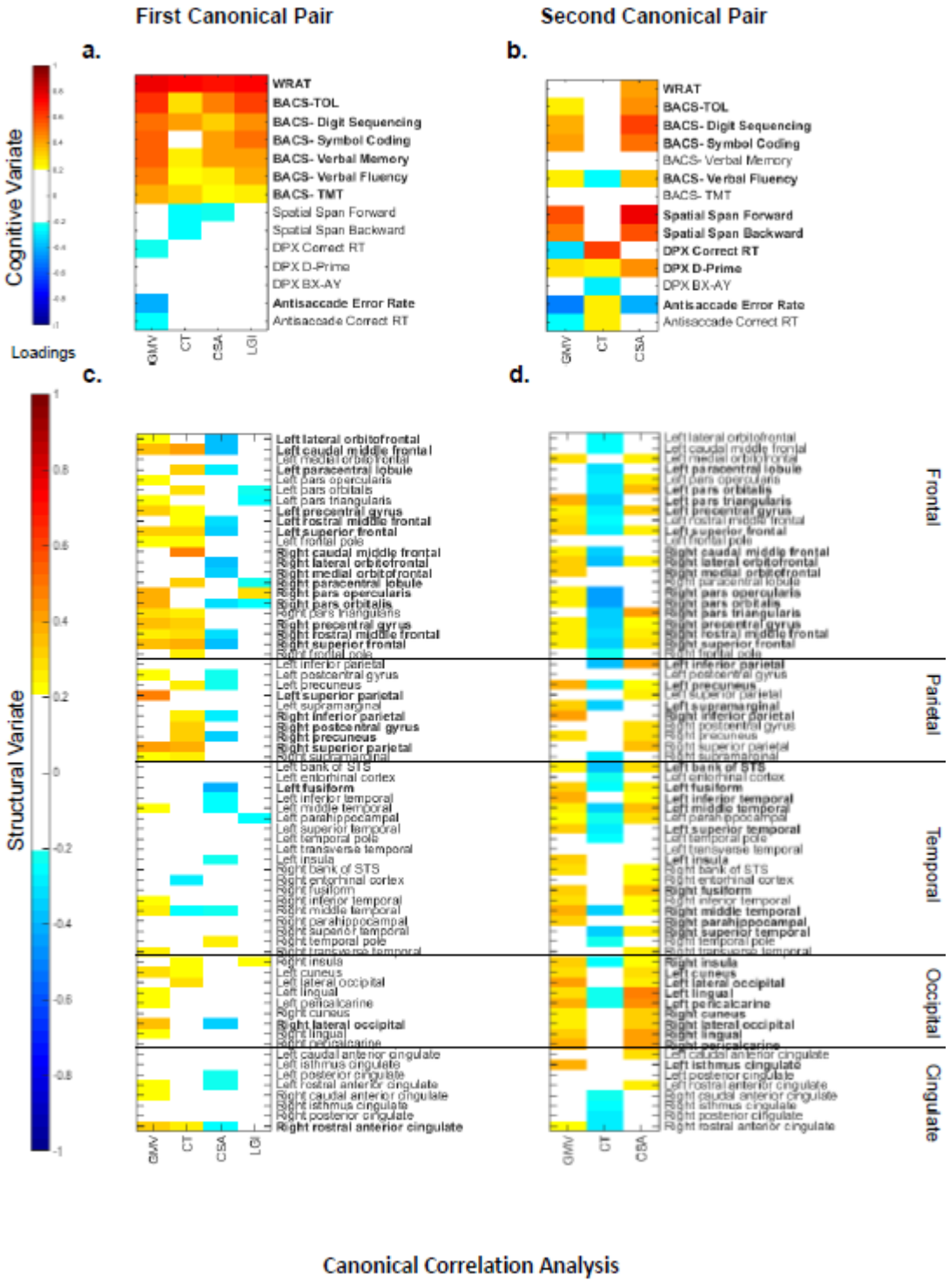
[e] SZ, SAD < BP

[f] SZ < SAD <BP

[g] Antipsychotics: BP < SAD < SZ

Lithium: SZ, SAD < BP

**Figure 3.1** *Loadings.* Heat maps show the loadings (correlations) of individual cognitive (a and b) and structural measures (c and d) with their respective latent variates. Cognitive measures are ordered by assessment protcol; structural measures are ordered by lobe. Bolded measures displayed "moderate-strong" loadings (above .3 or -.3) on the latent variate in one or more CCAs. For clarity, loadings between -.2 and .2 are shown in white.
WRAT= Wide Range Achievement Test; BACS= Brief Assessment of Cognition in Schizophrenia; TOL= Tower of London; TMT= Token Motor Task; DPX= Dot Probe Expectancy task; RT= Reaction Time; GMV= Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis.




Canonical Correlation Analysis

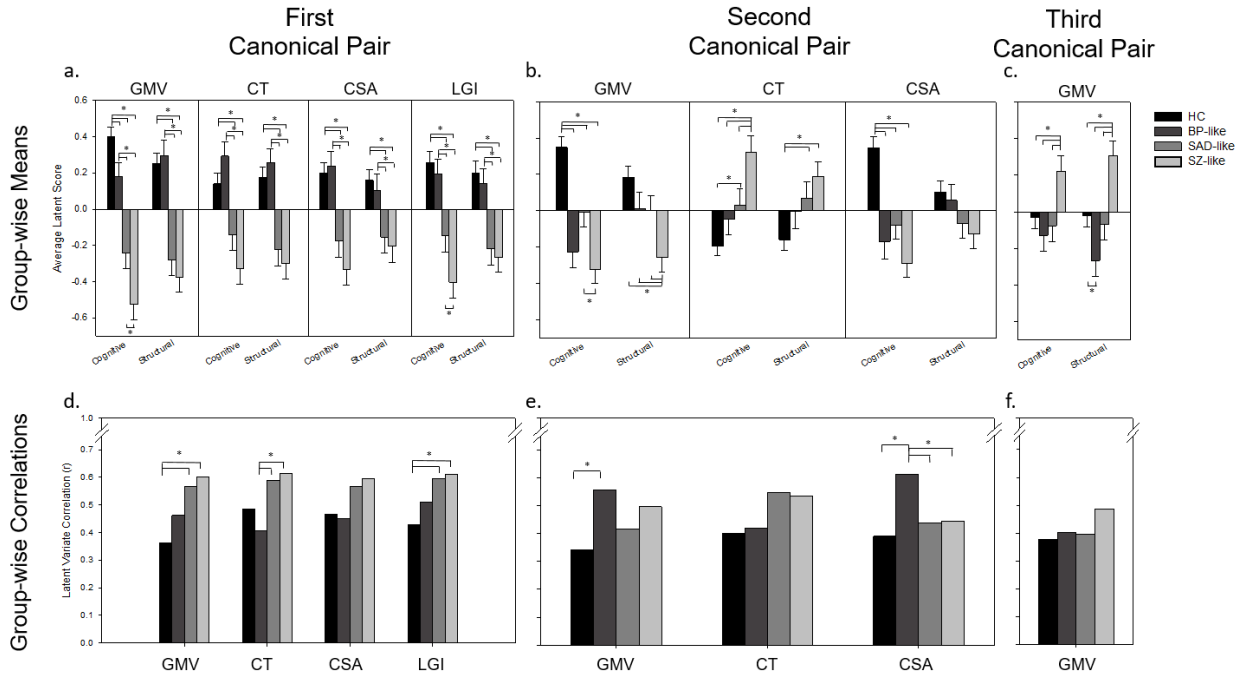



**Figure 3.2** *Group Differences.* Bars in the top figure (a and b) show average latent scores (standard error) calculated from the cognitive and structural variates in each CCA (GMV, CT, CSA, and LGI analyses). Bars in the bottom figure (c and d) show correlation coefficients between cognitive and structural variates for each group and each CCA. Significant differences between groups ($p < .05$) are shown with bars and asterisks.
GMV= Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis; HC= Healthy Controls; BP= Bipolar; SAD= Schizoaffective; SZ= Schizophrenia

# CHAPTER 4

# INTEGRITY OF COGNITIVE CONTROL-RELATED RESTING STATE NETWORKS IN SCHIZOPHRENIA COMPARED TO HEALTHY PEOPLE WITH POOR COGNITIVE CONTROL

[1]Rodrigue, A.L, Pierce, J. E., Schaeffer, D. J., Clementz, B. A., & Mcdowell, J. E. Submitted to Schizophrenia Research, 5/10/17

## Abstract

Cognitive control deficits in schizophrenia have been attributed to alterations in functional connectivity of resting state networks (RSNs), especially in the right and left frontal/parietal and default mode networks (RFPN, LFPN, and DMN respectively). Healthy comparison groups, however, often exhibit superior cognitive control performance, meaning differences between groups could be due to poor cognition rather than the presence of a schizophrenia diagnosis. This study used two healthy comparison groups, one with high cognitive control (HCC) and one with low cognitive control (LCC), in addition to a schizophrenia group, to distinguish connectivity alterations that are specific to schizophrenia and those that are due to general deficits in cognitive control.

Using resting state functional magnetic resonance imaging, we found that most connectivity alterations were present in both LCC and schizophrenia groups: connectivity patterns either did not differ between the two groups or differed in a graded fashion. Two connectivity alterations were specific to those with LCC and involved more extreme instances of expected connections between networks. The lack of schizophrenia-specific alterations in resting state connectivity related to cognitive control may change the way we think about cognitive deficits in schizophrenia and how they are treated and remediated.


## Introduction

Deficits in cognitive control are common in schizophrenia [23, 202, 203] and contribute to poor functional [204, 205] and clinical outcomes [203]. These deficits could be due to functional connectivity disruptions in brain networks as identified by resting state functional magnetic resonance imaging (rsfMRI) [77, 78, 206]. These “resting state networks” (RSNs) are intrinsic to the brain’s

architecture [68], consistent across time [69], and influence behavior [26, 29] and brain function during task states [28, 70, 75, 207].

Three commonly evaluated cognitive control RSNs in schizophrenia are the right and left frontal-parietal networks and the default mode network (RFPN, LFPN, and DMN respectively). Both FPNs are task-positive networks and include regions that support sustained attention, working memory, and response selection, making them superordinate control systems that integrate information between external and internal processes [72]. The DMN, a task negative network, composed of medial prefrontal cortex, posterior cingulate, and bilateral angular gyrus, supports self-referential processing and is typically suppressed during cognitive control task performance [73]. Successful cognition favors strong connections within task-positive networks, like the FPNs, and strong anti-correlations between task-positive and task-negative networks, like between the FPNs and DMN [27, 74]. Connectivity alterations in schizophrenia are typically manifest in three ways: 1) weaker connections within the FPNs and their connections to other higher-order task-relevant regions [81, 82] 2) stronger connections between the FPNs and sensory/motor regions [84], regions not typically involved in the network, and 3) weaker anti-correlations between the FPNs and DMN [85, 86].

Studies of cognitive control-related RSNs are common in schizophrenia, but an important methodological consideration is that psychiatric groups are often compared to healthy individuals that have superior performance on cognitive control tasks. Differences between groups therefore, could be due to poor cognition rather than the presence of a schizophrenia diagnosis. Patterns associated with poor cognitive control in healthy comparisons are, in fact, often similar to those observed in people with schizophrenia [26, 27, 29, 208]. It is important to note, however, that results in healthy comparisons are frequently based on correlations within a single

sample of individuals, most of which do not show cognitive deficits as severe as people with schizophrenia.

Methods correcting for group-wise differences in cognitive control performance include the use of covariates or matching groups using IQ or similar variables. The use of covariates can be problematic [209, 210] and matching may not capture the full picture of cognitive control ability in healthy comparison populations. One remedy is the inclusion of two healthy comparison groups: a more traditional comparison group, people with high cognitive control (HCC), and a more appropriate comparison group to people with schizophrenia, people with low cognitive control (LCC). People with LCC are more similar to people with schizophrenia in their level of cognitive control, but do not present with symptoms of psychosis. Groups that are more cognitively comparable may exhibit similar or distinct disruptions, given poor cognitive control could arise from several underlying causes. Using *both* healthy people with LCC and healthy people with HCC as comparison groups would not only identify connectivity disruptions specific to schizophrenia, but also provide a clearer picture of the cognitive control/connectivity variability in healthy comparisons.

We evaluated three of the most commonly studied brain networks related to cognitive control in the schizophrenia literature (RFPN, LFPN, and DMN) using resting state fMRI and three groups: healthy comparisons with LCC, healthy comparisons with HCC, and people with schizophrenia. Goals included determining if the three aforementioned patterns of connectivity alterations commonly found in people with schizophrenia were specific to the disorder (only present in the SZ group) or due to general deficits in cognitive control (present in the SZ and LCC group compared to the HCC group). Based on the present literature in healthy comparisons,

we hypothesized that the aforementioned patterns would be shared between people with schizophrenia and healthy people with LCC.

## Methods

### Participants

Description of participant characteristics are in Table 4.1. Schizophrenia participants (N=31) were recruited from the community and outpatient facilities in Athens, GA and Augusta, GA USA. High and low comparisons participants were selected from a subset of participants (N=233) recruited from the community in Athens, GA and defined based on scores from a series of complex working memory SPAN tasks. SPAN tasks have good test-retest reliability [211] and predict performance on higher order and lower order cognitive control tasks [88, 212] (See APPENDIX B for further details).

Participants were administered the Non-Patient or Patient Edition of the Structured Clinical Interview for DSM-IV TR and excluded for substance abuse within the last month and/or substance dependence within the last 6 months. Healthy comparison participants were further excluded for past history of psychosis or mood disorders. All participants were free from contraindications for MRI (metal in the body and pregnancy) and reported no history of head trauma. Participants signed informed consent and were paid for their time. There were no significant differences in age across groups ($F(2, 88) = 1.9$, $p = .15$) and SPAN composite scores did not differ between LCC and SZ groups ($t(56)= 1.39$, $p = .16$).

### Procedure and Imaging Parameters

MRI data were collected at the Bio Imaging Research Center at the University of Georgia, using a 3T GE Signa MRI (General Electric Medical Systems, Milwaukee, Wisconsin, USA) and an 8-channel head-coil. A high resolution structural scan was conducted to identify the

plane of the anterior and posterior commissure (AC-PC) and for later use in the preprocessing of functional images (T1–weighted 3D FSPGR, repetition time (TR) = 8.1 ms, echo time (TE) = 3.1 ms, flip angle = 20°, field of view (FOV) = 240 mm × 240 mm, matrix size = 256 × 256, 150 axial slices, in-slice resolution = 0.94 × 0.94 mm, slice thickness = 1.2 mm). A rsfMRI scan also was collected, with the first four volumes discarded to account for scanner stabilization (T2*-weighted gradient echo whole brain EPI sequence oblique to the angle of the AC-PC plane, repetition time (TR) = 5000 ms, TE = 25 ms, flip angle = 90°, FOV = 256 mm × 256 mm, matrix size = 128 × 128, 55 oblique slices, in-slice resolution = 2 × 2 mm, slice thickness = 2.4 mm, 108 volumes, total scan time = 9 min). We used a TR of 5000 ms to achieve 55 slices of full brain coverage while maintaining the ability to capture low frequency signals of interest. During the resting state scan, participants were instructed to fixate on a centrally located cross that was viewed through a mirror box on top the head coil.

## Data Analysis

### *Individual Level Preprocessing*

Individual preprocessing used FMRIB Software Libraries (FSL, version 5.0.1; Oxford, United Kingdom) (see APPENDIX B for further details). Probabilistic Independent Component Analysis (PICA, [213]) was performed on each participant's preprocessed resting state scan to identify artifacts related to physiological noise, scanner artifacts, or additional effects of motion. ICA components representing artifacts were identified using both spatial and temporal characteristics outlined by Kelly et al. [214] and removed. Groups did not differ in the number of components retained after artifact and noise removal ($F(2, 86)= 1.27$, $p = 0.29$) nor did they differ in the amount of absolute motion ($F(2, 86)= .55$, $p = 0.58$) during scanning.

*Group Level Analysis*

Following a procedure previously used in our laboratory [215, 216], individual preprocessed data were temporally concatenated across all participants, creating a single 4D dataset (three spatial dimensions and time). The 4D dataset was entered in a group-level PICA, which identified common resting state networks across participants. Automatic dimensionality estimation was used to avoid under- or over-fitting. Resulting components were visually inspected and correlated (using fslcc) with known maps in the literature [71] to confirm the presence of the resting state networks of interest (RFPN, LFPN, and DMN) in our sample.

Networks from the group-level PICA were then fed into the dual regression procedure in FSL to obtain a correlation value for each voxel with the large-scale resting state networks identified by the group PICA [217-219] (see APPENDIX B for further details). Analyses of dual regression results were conducted in AFNI [220] using a one-way ANOVA for each RSN of interest. Statistical maps were threshold at $p < .05$ and corrected for multiple comparisons using a Monte Carlo simulation derived in AFNI [221]. The minimum number of voxels constituting a cluster was 184.

## Results

The group-level PICA returned 35 components. Components representing the RSNs of interest were correlated with those identified in Beckmann et al. [71] (LFPN: $r = 0.45$, RFPN: $r = 0.57$, DMN: $r = 0.68$) (see Figure 4.1). Group-level analyses of RSNs identified alterations in regional brain connectivity in all three networks. In the analysis of the DMN, connectivity alterations were apparent in the right superior frontal gyrus (SFG) and right cuneus. In the analysis of the FPNs, connectivity alterations were apparent between the RFPN and the right fusiform gyrus (FG) and between the LFPN and the right inferior frontal gyrus (right IFG), left inferior temporal

gyrus (ITG), right insula, and the right posterior cingulate cortex (PCC) (See Figure 4.2 and Table 4.2).

No connectivity alterations were exclusively present in the schizophrenia group. For a majority of significant regions, the two groups with poor cognitive control (LCC and schizophrenia) either did not differ from each other, or differed from each other in a graded fashion when compared to the HCC group. Poor cognitive control in the LCC and schizophrenia groups was related to three distinct patterns of connectivity alterations: 1) weaker within-network connections in a task-positive network (LFPN and left ITG), 2) weaker connections between one of the task-positive networks and a region related to another cognitive control RSN, the salience network (LFPN and right insula), and 3) less differentiation between RSNs and regions not typically involved in the RSN (DMN and right cuneus and right SFG; RFPN and left FG).

One pattern of connectivity alterations was specific to the LCC group. These alterations were manifest as greater differentiation between the LFPN and regions typically anti-correlated with the network (right PCC, right IFG). In both instances, there were no differences in connectivity between the SZ and HCC group.

## Discussion

Deficits in the integrity of large scale RSNs like the FPNs and DMN contribute to cognitive control deficits in schizophrenia. It has been difficult to determine whether these deficits are part of a syndrome's unique defining features or secondary to its primary manifestations. Using two healthy comparison groups, the present results indicate the latter, with no substantial differences in connectivity alterations between schizophrenia and healthy people with low cognitive control. Schizophrenia and LCC groups either did not differ from each other, or differed from each other in a graded fashion compared to the HCC group, indicating a

difference in severity rather than a difference in kind between the two groups. These results are consistent with a previous study done by our group using diffusion tensor imaging (DTI) on some of the same individuals to evaluate the structural integrity of tracts related to cognitive control [208]. The schizophrenia group and LCC group either a) did not differ from each other in terms of fractional anisotropy and radial diffusivity or b) displayed a similar ordered continuum as that seen in the present functional analyses, with the LCC group falling intermediate between the schizophrenia and HCC groups.

Patterns of functional connectivity associated with poor cognitive control were consistent with previous reports. Groups with poor cognitive control showed weaker connections within task-positive networks [81, 82, 222] and weaker connections between task-positive networks and regions involved in other cognitive control-related networks. This was evidenced by weaker connections between the LFPN and the left ITG, a region included in the LFPN and positively correlated with it (See Figure 4.1) and weaker connections between the LFPN and right insula, a hub region of the salience network. The insula is involved in the early stages of cognitive control by guiding attention and signaling events for further processing [223]. It also serves as a modulator between the FPNs and DMN [223, 224] and its connection to both networks is reduced in schizophrenia [225, 226]. These connections however, were also reduced in our healthy LCC group.

Poor cognitive control was associated with less differentiation between unrelated regions and the respective RSN [84], particularly related to visual processing regions (right cuneus and left FG), and less differentiation between task-positive and task-negative networks. This pattern was apparent in the weaker anti-correlations between the DMN and the right SFG, a region located in the RFPN. Again, both patterns have been reported in people with schizophrenia [227, 228], but were also present in our healthy LCC group.

There were two connectivity alterations that were specific to the LCC group. Both were related to the LFPN and its connection to regions typically anti-correlated with the network: the right PCC, part of the DMN, and the right IFG, part of the RFPN. The LCC group exhibited an exaggeration of normal anti-correlations compared to the other two groups. Anti-correlations between these networks tend to increase during the transition from childhood to adulthood as cognitive control develops [229] and are typically representative of good cognitive control in healthy adults [27]. This pattern, therefore, may be a compensatory mechanism that is not present in people with low cognitive control and concomitant psychosis. Anti-psychotic medication also may remedy this altered connection in people with schizophrenia, making them similar to the HCC group. These hypotheses require future studies to better understand connectivity alterations unique to healthy people with low cognitive control.

Anti-psychotic medication could be a limitation in the present analysis, especially for regions showing a graded response across the three groups. Altered connectivity patterns like those found in this study have been identified in both unaffected relatives and those at ultra-high risk for developing psychosis [228, 230, 231], groups whose data are not confounded by anti-psychotic medication. Furthermore, approximately one-third of our sample was unmedicated (see Table 4.1). The graded nature of some connectivity patterns could also be due to the presence of psychosis symptoms in the schizophrenia group. Although there are reports of associations between connectivity alterations and psychosis symptoms [232, 233], there were no correlations between PANSS scores and connectivity within clusters that showed a graded pattern between the LCC and schizophrenia groups (see APPENDIX B Supplement Table 4.1).

This study evaluated and quantified differences in connectivity across three groups: people with schizophrenia, healthy people with LCC, and healthy people with HCC. The use of

all three groups identified connectivity alterations that have not been previously reported in healthy individuals with LCC, highlighting the importance of including healthy individuals at both extremes of the cognitive control spectrum. There were no connectivity alterations specific to the schizophrenia group, with a majority being shared with the LCC group. Connectivity alterations distinguishing all groups from each other were graded, only differing in terms of severity (HCC > LCC > SZ, HCC < LCC < SZ). For these alterations, more severe alterations in the schizophrenia group did not seem to be the result of anti-psychotic medication or the presence of psychosis symptoms. The nature of differences between healthy people with low cognitive control and people with schizophrenia and how they compare to those with HCC may contribute to the way we think about cognitive control and its neural substrates, including how we identify mechanisms behind poor cognition in psychosis and how cognitive deficits in the disorder may be better treated and/or remediated.

**Table 4.1** Subject Characteristics

| | HCC (N=28) | LCC (N=29) | SZ (N=31) |
|---|---|---|---|
| SPAN composite | 0.68 (0.32) | -1.49 (0.88) | -1.94 (1.27) |
| Age (years) | 33 (11) | 37 (11) | 38 (11) |
| Gender (male) | 17 | 12 | 14 |
| Handedness (right, left, ambidextrous) | 25, 2, 1 | 27, 3, 0 | 26, 3, 2 |
| Psychotropic Medication | | | |
| Anti-psychotic (typical, atypical, both) | 0, 0, 0 | 0, 0, 0 | 3, 15, 1 |
| Anti-cholinergic | 0 | 0 | 1 |
| Anti-depressant | 0 | 0 | 8 |
| Anti-anxiety | 0 | 0 | 1 |
| Polypharmacy | 0 | 0 | 11 |

[a]Cells show N's for each item except Age and SPAN composite, which are shown as means (std. dev.). Two LCC participants were missing SPAN data due to technical difficulties. Polypharmacy was defined as taking more than one psychotropic medication. One SZ subject taking an atypical anti-psychotic was also taking Lithium. Ten SZ participants were unmedicated. HCC = high cognitive control group; LCC = low cognitive control group; SZ = schizophrenia group.

**Table 4.2** Regional Differences in Connectivity

| Resting State Network (RSN) | Cluster IN/OUT of RSN | Anatomical Location | Peak t-statistic MNI coordinates x | y | z | Size (voxels) | Cluster in other network | Effect |
|---|---|---|---|---|---|---|---|---|
| DMN | OUT | R. Superior Frontal Gyrus | 16 | 52 | 24 | 206 | RFPN | [b]HCC < LCC, SZ |
| | OUT | R. Cuneus | 8 | -82 | 47 | 204 | -- | [b]HCC < LCC < SZ |
| RFPN | OUT | L. Fusiform Gyrus | -44 | -32 | -16 | 184 | -- | [b]HCC < LCC, SZ |
| LFPN | IN/pos | L. Inferior Temporal Gyrus | -54 | -54 | -18 | 212 | -- | [b]SZ < LCC < HCC |
| | IN/neg | R. Inferior Frontal Gyrus | 42 | 10 | 26 | 236 | RFPN | [c]LCC < HCC, SZ |
| | OUT | R. Posterior Cingulate | 6 | -54 | 20 | 350 | DMN | [c]LCC < HCC, SZ |
| | OUT | R. Insula | 46 | -10 | 10 | 200 | -- | [b]SZ < LCC < HCC |

[a]Clusters from the results of the one-way ANOVAs for each RSN. The first column denotes the RSN analysis. The second column denotes if the cluster was inside (IN) or outside (OUT) the RSN analyzed (determined using maps obtained with the group-level ICA-refer to Figure 1). The third, fourth, and fifth columns denote the anatomical location, the XYZ coordinates of the peak voxel, and the cluster size. The sixth column denotes whether the cluster was a part of another RSN in our analysis regardless of whether it was inside or outside the original RSN. The final column denotes the nature of the pair-wise differences in connectivity among the three groups ($p < 0.05$). pos = positive; neg = negative; DMN = default mode network; RFPN = right frontal parietal network; LFPN = left frontal parietal network; HCC = high cognitive control group; LCC = low cognitive control group; SZ = schizophrenia group.

[b]Alterations related to poor cognitive control

[c]Alterations specific to the LCC group

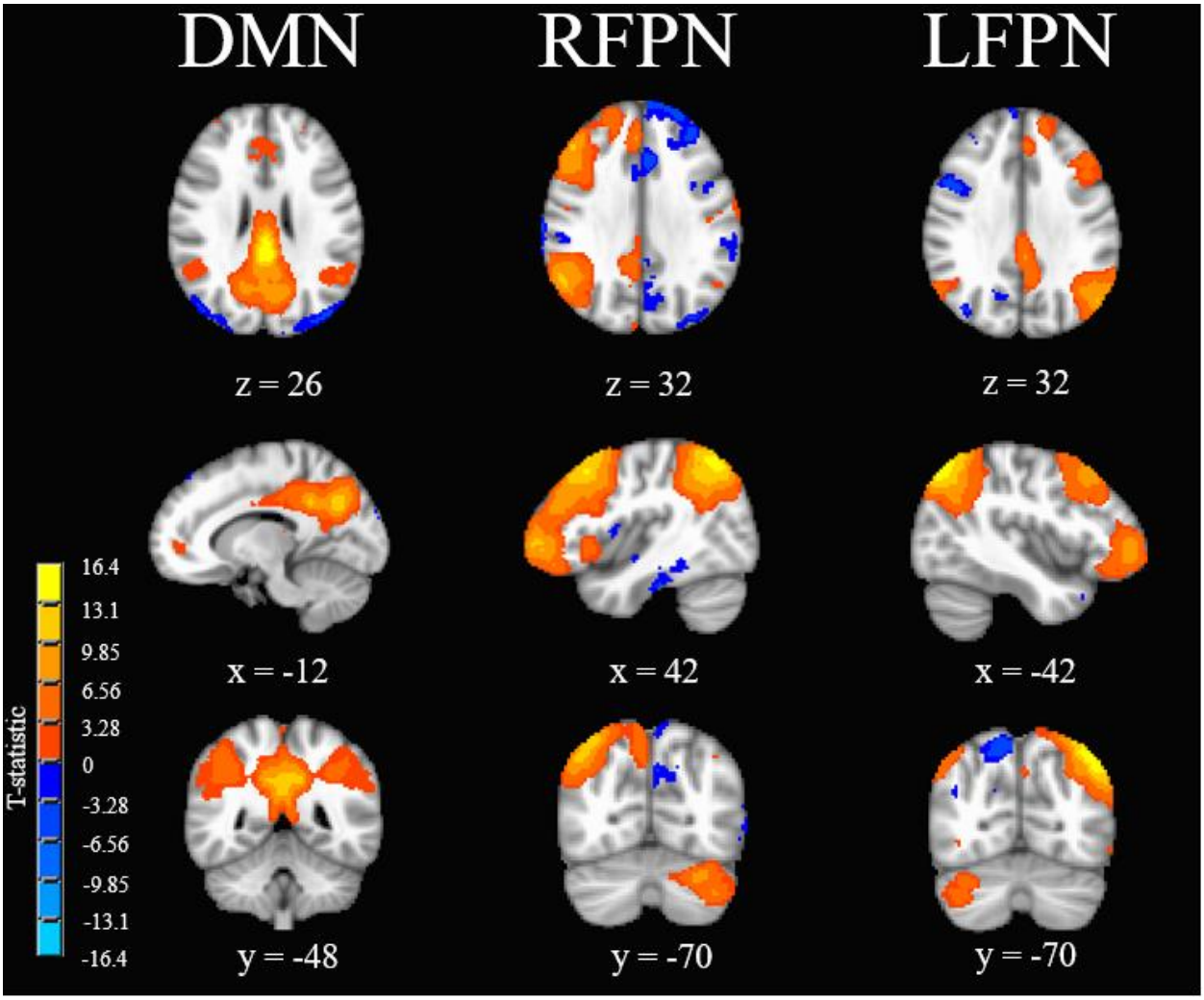



**Figure 4.1** *RSN Maps*. Maps of the three RSNs of interest obtained from the group-level PICA overlaid on an MNI template of the brain's anatomy (XYZ coordinates in MNI space). Values are t-statistics (threshold $p < .05$); warm colors indicate regions in the network that are positively correlated with each other, cool colors indicate regions in the network that are anti-correlated with warm color regions. Images are shown in radiological orientation. DMN = default mode network; FPN = frontal parietal network.

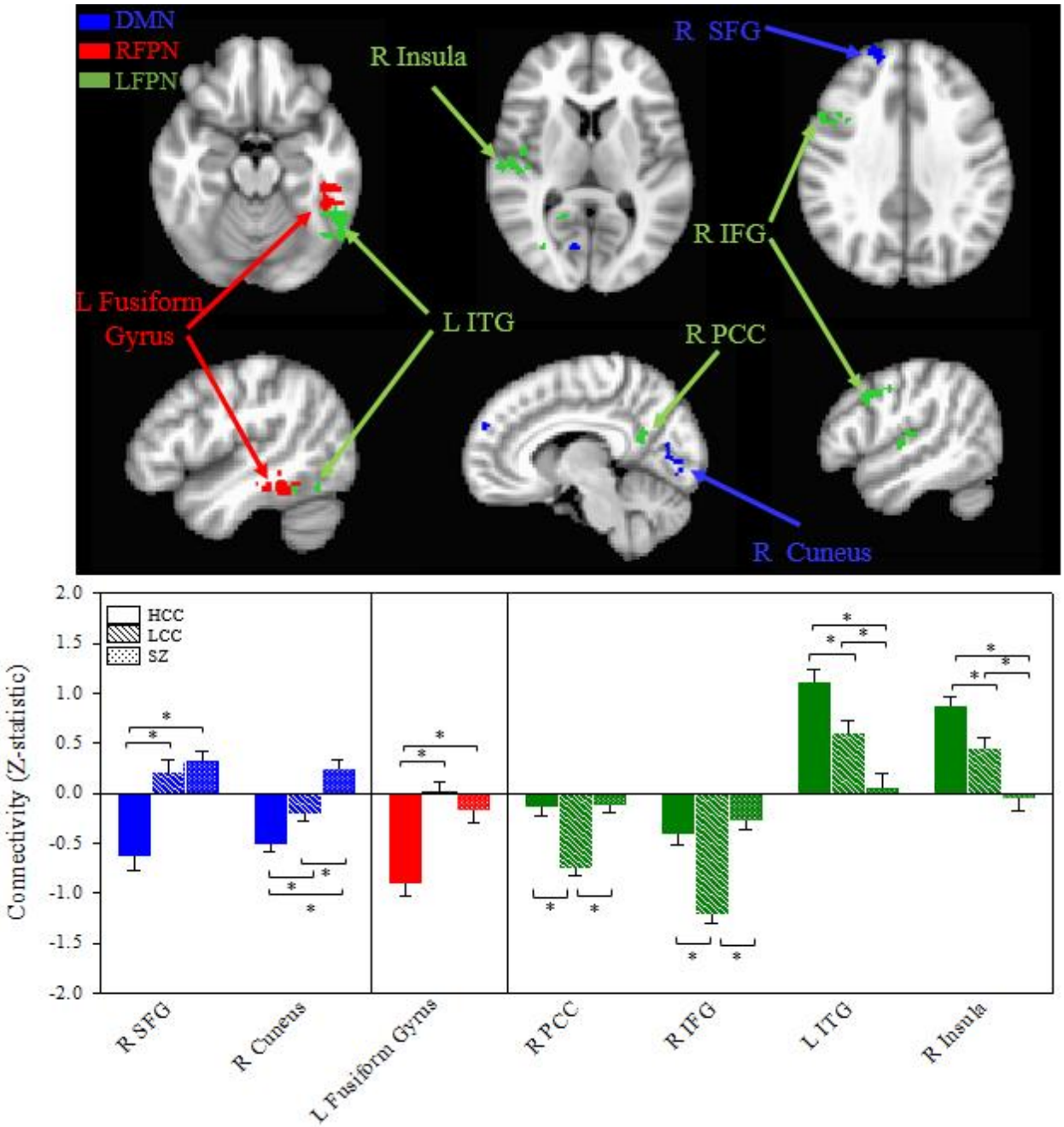



**Figure 4.2** *Group-wise Connectivity Differences.* Top image shows clusters that significantly differed across groups (as identified by one-way ANOVAs on each network) overlaid on an MNI template of the brain's anatomy (top row: z = -18, z = 8, z = 34; bottom row: x = 46, x = -8, x = -52). Images are shown in radiological orientation. Bottom graph shows mean connectivity (SE) of clusters in the top image in each group (HCC, LCC, and SZ). Colors indicate which RSN analysis the cluster was identified in: blue= DMN, red= RFPN, green= LFPN.
DMN = default mode network; RFPN = right frontal parietal network; LFPN = left frontal parietal network; HCC = high cognitive control group; LCC = low cognitive control group; SZ = schizophrenia group.

# CHAPTER 5

# EVALUATING THE SPECIFICITY OF COGNITIVE CONTROL DEFICITS IN SCHIZOPHRENIA USING ANTISACCADES, FUNCTIONAL MAGNETIC RESONANCE IMAGING, AND HEALTHY INDIVIDUALS WITH POOR COGNITIVE CONTROL

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## Abstract

Cognitive control involves attention, inhibition, and working memory, and is impaired in people with schizophrenia. Neural correlates of these disruptions are frequently evaluated using antisaccade tasks and functional magnetic resonance imaging (fMRI). Behavioral and imaging studies of antisaccade tasks, however, often compare people with schizophrenia to high performing healthy people, making it unclear if antisaccade-related disruptions are specific to schizophrenia or due to generalized deficits in cognitive control. This study used two healthy comparison groups in addition to people with schizophrenia (SZ): healthy people with high cognitive control (HCC), who represent a more typical comparison group to people with schizophrenia, and healthy people with low cognitive control (LCC), who perform similarly on antisaccade measures as people with schizophrenia. Using two healthy comparison groups may help determine which antisaccade-related deficits are specific to schizophrenia (distinguish SZ from LCC and HCC groups) and which are due to poor cognitive control in general (distinguish the LCC and SZ groups from the HCC group). The effect of COMT genotype (rs4680) on fMRI measures also was tested to further parse differences between the LCC and SZ group.

People with SZ and healthy individuals with HCC or LCC performed an antisaccade task during fMRI acquisition. Differences in activation during correct and error trials were evaluated. For both trial types, LCC and SZ groups showed under-activation of saccade circuitry. There was a SZ-specific disruption in the left superior temporal gyrus and insula during error trials (less activation in the SZ group compared to the LCC and HCC group). Additionally, there was a group by COMT genotype interaction in the right inferior frontal gyrus and insula during antisaccade errors. Results indicate that differences related to antisaccade errors may distinguish people with SZ from healthy individuals with low cognitive control.

## Introduction

Cognitive control involves attention, inhibition, and working memory and can be assessed using antisaccade tasks. During antisaccade tasks, participants fixate on a central target. When a cue appears in a peripheral location in the horizontal plane, they are instructed to direct their glance to the mirror image location (opposite direction, same distance from center) [30]; glances toward the cue are errors and considered failures of cognitive control. Antisaccades measure cognitive control because successful performance requires several cognitive operations: attention to a visual cue, inhibition of the pre-potent response to look toward the cue when it appears, and the generation of a voluntary response (the glance in the opposite direction), while engaging working memory for task rules [107, 234]. Antisaccades are supported by regions distributed throughout the brain (supplementary and frontal eye fields, posterior parietal cortex, and subcortical regions) [34, 90-94], although frontal regions like the dlPFC are particularly important given that lesions result in elevated antisaccade error rates [98, 117-119].

Antisaccade tasks are frequently used as a research tool to evaluate cognitive control disruptions in schizophrenia (see [235-237] for reviews). People with schizophrenia make more antisaccade errors than healthy comparisons and sometimes exhibit slower reaction times when they perform a correct antisaccade response [34, 35, 90, 116, 121, 122, 238, 239]. Neural disruptions underlying poor antisaccade performance in schizophrenia have been identified using functional magnetic resonance imaging (fMRI) and include under-activation of the frontal eye fields (FEFs), visual regions, basal ganglia, and most consistently the dlPFC when compared to healthy controls [34, 90, 103, 122, 125, 126, 240]. Under-activation of other frontal regions also is apparent during antisaccade errors, including the anterior cingulate and insula, indicating that additional deficits in error processing may contribute to poor antisaccade performance [241]. Deviations in both

behavior and brain circuitry are seen in first degree relatives [90, 120, 242], supporting that antisaccade-related disruptions are not a consequence of disease chronicity or antipsychotic medication [32, 243, 244].

While antisaccade-related disruptions in schizophrenia are well-established, many studies compare people with schizophrenia to healthy groups who have intact cognitive control [31, 33, 245]. Antisaccade-related deficits in schizophrenia, therefore, could be due to differences in cognitive ability rather than specific to the disorder. Some evidence that this may be the case comes from studies of healthy people that perform just as poorly as people with schizophrenia on antisaccade tasks [88, 106]. Healthy individuals who have poor antisaccade performance exhibit similar underlying brain disruptions as people with schizophrenia, including under-activation of frontal regions during both correct and error antisaccade trials [106]. These same healthy individuals, however, also exhibit hyper-activation in visual regions, which is not reported in people with schizophrenia. The lack of inclusion of low performing healthy individuals and people with schizophrenia in the same study design makes direct comparisons between the two groups difficult, leaving the question open as to whether antisaccade-related disruptions are specific to schizophrenia.

This study uses two healthy comparison groups: people with intact cognitive control, who are representative of healthy comparison groups commonly used in the literature (referred to here as the high cognitive control group-HCC), and people who have low cognitive control as a more representative comparison sample for the schizophrenia group (referred to here as the low cognitive control group-LCC). By including two healthy comparison groups, we may isolate antisaccade disruptions that are specific to schizophrenia (differentiate the schizophrenia group from the LCC and HCC groups) from those that are due to general deficits in cognitive control

(differentiate the LCC and schizophrenia group from the HCC group). Additionally, we will evaluate activation associated with correct and error trials, given that poor cognitive control could arise from separable disruptions related to correct responses, error responses, or both.

Another way to further disentangle groups that are cognitively similar is to evaluate genotype effects on brain function. Similar levels of cognitive control-related activation between groups could have different underlying genetic influences. We performed an exploratory analysis of COMT genotype on correct and error antisaccade activation in the LCC and schizophrenia groups. We chose the COMT gene (rs4680 Val/Met), given its connection with prefrontally mediated behavior and brain function [246-248], which is essential to successful antisaccade performance. Typically, more Val alleles are associated with poor behavioral performance [39] and disruptions in underlying brain circuitry [149, 248]. A study using antisaccades, however, found a trend level effect of more Val alleles being associated with fewer antisaccade errors [249] in both schizophrenia and healthy individuals; another study found no association between antisaccade performance measures and COMT genotype [250]. Considering COMT genotype effects on neuroimaging measures may be more beneficial, given that brain measures are closer to gene products than behavior.

We hypothesized that the schizophrenia and LCC groups would show similar deficits in antisaccade performance compared to the HCC group. We also hypothesized that disruptions underlying poor performance would manifest as under-activation of brain circuitry, particularly in frontal regions, in both the LCC and the SZ group, although hyper-activation in visual regions may be uniquely present in the LCC group. We expected that more Val alleles would be associated with better behavioral performance, but their effects on brain activation may be different for schizophrenia and LCC groups.

# Methods

## Participants

Sample characteristics are described in Table 5.1. Schizophrenia subjects (N=23) were recruited from the community and outpatient facilities in Athens, GA and Augusta, GA USA; healthy subjects were recruited from the community in Athens, GA. High and low healthy comparison groups were drawn from a large initial sample (N = 235 mean age = 31 years, SD = 11.5; 53% female) and defined based on a composite score calculated from averaging the z-transformed scores of three complex working memory "SPAN" tasks: reading span (R-SPAN), operation span (O-SPAN), and symmetry span (Sym-SPAN) [251]. Details of participant classification are in the supplement.

Participants were administered the Non-Patient or Patient Edition of the Structured Clinical Interview for DSM-IV TR. Exclusion criteria for both groups included substance abuse within the last month and/or substance dependence within the last 6 months. Additional exclusions for comparison subjects included having a first-degree relative with psychosis or past history of a psychotic or mood disorder. All subjects were free from contraindications for MRI (metal in the body and pregnancy) and reported no history of head trauma. All subjects signed consent forms and were paid for their time. Study procedures were reviewed and approved by the University of Georgia Institutional Review Board.

## Antisaccade Task Design

Participants performed two antisaccade runs of 60 trials in the scanner using an event-related design. Stimuli were 1.5º gray filled circles presented on a black background. Stimuli and task timing are shown in Figure 5.1. Each trial began with the stimuli located in the center of the screen, followed by its disappearance and reappearance at ± 5º or 10º from center in the

horizontal plane. Participants were told to look at the stimuli when it was in the center and execute a glance in the opposite direction, same distance from center, when it appeared in one of the four peripheral locations.

Procedure and Imaging Parameters

MRI data were collected at the Bio Imaging Research Center at the University of Georgia, using a 3T GE Signa MRI (General Electric Medical Systems, Milwaukee, Wisconsin, USA) and an 8 channel head-coil. Participants were given task instructions before being positioned in the scanner. A high resolution structural scan was conducted to identify the plane of the anterior and posterior commissure (AC-PC) and for later use in preprocessing. Following the structural scan, participants completed two functional scans while performing the antisaccade task. Scan parameters are listed in the supplement. Participants viewed the stimuli on a screen positioned at their feet (174 cm from the nasion) via a mirror box placed on top of the head coil (16 cm above and in front of the eyes). Stimuli were displayed using Presentation Software (Neurobehavioral Systems, Albany, CA) and eye movements during the scan were recorded using the IView X MRI-LR system with a sampling rate of 60 Hz (SensoMotoric Instruments, Berlin, Germany).

DNA extraction and Genotyping

All processing of genetic material was performed by the Georgia Genomics Facility in Athens, GA USA. DNA extraction from saliva samples followed procedures provided by Oragene. See supplement for further details.

## Analysis

### *Antisaccade Behavior*

Eye movement data from the scanner environment were scored using an in-house program generated in MATLAB (The Mathworks Inc., Natick, MA, USA). Antisaccade trials were scored for initial direction (correct or incorrect response) and correct reaction time (time taken to initiate a correct response). Trials with no response, blinks at stimulus onset, anticipatory saccades (faster than 90 ms RT from peripheral stimulus onset or during the gap window), or with insufficient data quality due to loss of pupil tracking were considered unscorable and eliminated from behavioral analysis. Error rate (number of error trials/total number of scorable trials × 100) and average correct reaction time were calculated for each participant. Means were compared with one-way ANOVAs followed by Tukey-Kramer post hoc comparisons.

### *Imaging*

Imaging analysis was performed with Analysis of Functional NeuroImages (AFNI)[220] following an established procedure in our laboratory (see supplement for details) [252, 253]. Time series were analyzed with a generalized least squares time series fit after temporal auto-correlation estimation using the Restricted Maximum Likelihood Model procedure in AFNI (REML; ARMA (1,1)). The time series fit used a model with separate regressors for correct and error trials that were specific to each subject's behavioral performance; non-scorable trials were incorporated as a separate regressor to avoid inclusion in the baseline. The model also included regressors for linear, quadratic, and cubic drift as well motion regressors (3 translational and 3 rotational) from the alignment step as regressors of no interest.

Group analyses were performed with mixed-effects multilevel analysis (MEMA), which accounts for heterogeneity within groups by taking into account the accuracy and precision of estimates from individual parameter estimates. This makes group-level analysis less susceptible to spurious results when the variance in the effect of interest within a group is comparable to the variance across groups or when outliers are present (for details see Chen et al. 2012). Two MEMA analyses were performed to determine if there were activation differences between each of the three groups: one for correct trials and one for error trials.

*Genetics*

To determine if there were differential genetic effects on activation between the two groups with poor cognitive control (LCC and SZ), group by genotype ANOVAs were performed on activation measures in clusters that were significant in each MEMA analysis (correct trials and error trials). Because COMT variation has its strongest effects in frontal cortex [39, 246, 247],we restricted testing genotype effects to significant frontal regions.

## Results

### Antisaccade Behavior

Error rates and correct reaction times for each group are shown in Figure 5.2. There were significant differences in error rate among the three groups ($F(2, 68) = 5.7$, $p = .005$). Groups with poor cognitive control (LCC and SZ) had higher error rates than the HCC group (HCC: $M = .23$, SD = .19, LCC: $M = .42$, SD = .23, SZ: $M = .39$, SD = .19). Individuals with schizophrenia were slightly slower at executing correct antisaccade responses than both healthy groups, but this was not statistically significant ($F(2, 68) = 1.9$, $p = .14$). The proportion of scorable trials did not differ across groups (HCC: $M = .85$, SD = .13; LCC: $M = .82$, SD = .12; SZ: $M = .85$, SD = .10; $F(2,68) = .41$, $p = .66$). The proportion of corrected errors also did not differ across groups

indicating that all participants understood the task and performed the task with sufficient motivation (HCC: $M$ = .88, SD = .12; LCC: $M$ = .86, SD = .15; SZ: $M$ = .85, SD = .12; $F(2,68) = .34$, $p = .71$).

Imaging

All groups showed robust activation during correct and error trials (see supplement Figure 5.1). Circuitry activation during correct and error antisaccades was reduced in both the LCC and SZ groups (see Figure 5.3 and Table 5.2). Both LCC and SZ groups showed significantly lower activation than the HCC group in inferior frontal gyrus (IFG) and anterior insular regions. In the remaining clusters (for both correct and error trials), the LCC group displayed intermediate levels of activation between the SZ and HCC group, although there were no significant differences between the HCC and LCC groups in these clusters as determined by the MEMA analysis. The exception was bilateral precuneus and left superior temporal gyrus (STG), where error related activation was reduced in the SZ group only. Differences between the SZ and HCC group, however, were only significant for the left STG/insula cluster ($t(42) = 2.19$, $p = .03$)

Genetics

COMT genotype was available for 39 subjects: 18 in the LCC group and 21 in the SZ group (see table in Figure 5.4). There were no significant differences in the distribution of genotypes across groups. Clusters tested for genotype effects in the correct analysis included the right IFG/insula from the HCC > LCC comparison (cluster a.) and bilateral cingulate from the HCC > SZ comparison (cluster b.). Clusters tested for genotype effects in the error analysis included the right IFG and left IFG/insula from the HCC > LCC comparison (clusters d. and e.),

and the right IFG/insula and bilateral cingulate from the HCC > SZ comparison (cluster g. and h.).

There were no significant genotype effects on antisaccade behavioral measures or activation during correct antisaccade trials. There was, however, a group by genotype interaction in the error analysis in the right IFG and insula (cluster d. and g.) ($F(2, 33) = 5.92$, $p = .006$) . Subjects with the most Val alleles in the SZ group displayed less activation in fronto-insular regions, whereas subjects with the most Val alleles in the LCC group displayed greater activation in fronto-insular regions. Differential genotype effects were observed despite no differences in the overall level of antisaccade error activation in the IFG/insula between the LCC and SZ groups.

## Discussion

People with schizophrenia exhibit cognitive control deficits as evidenced by poor antisaccade performance and circuitry deviations. To investigate the specificity of these patterns to schizophrenia versus those associated with overall effects of poor cognitive control, we used two healthy comparison groups (HCC and LCC). Performance on the antisaccade task did not differ between the LCC and SZ groups, although both groups performed worse than the HCC group. Circuitry deviations underlying poor antisaccade performance showed a similar pattern. Both LCC and SZ groups showed circuitry-wide under-activation compared to the HCC group. In instances where the LCC group differed from the SZ group, the LCC group fell intermediate between the SZ group and the HCC group, indicating a difference in severity rather than kind of deviation when compared to people with schizophrenia. Under-activation of saccade circuitry in both the SZ and LCC groups was mostly consistent with previous reports [90, 106, 126, 255], although we did not see hyper-activation of visual regions in the LCC group [106]. There were, however, two

deviations related to activation during antisaccade errors that were present in the SZ group and not the LCC group.

Deviations in behavioral performance and underlying brain activation in the SZ group did not seem to be the consequence of anti-psychotic medication use or the presence of psychosis symptoms, both of which have been associated with cognition [256, 257]. SZ-specific disruptions in activation were not correlated with psychosis symptom measures or chlorpromazine daily dose equivalent (see supplement Table 1). Furthermore, the LCC group did not have a psychiatric disorder and were not taking anti-psychotic medication, yet showed similar levels of activation as the SZ group in other regions.

For correct and error trials, under-activation in the LCC and SZ groups was predominant in the IFG, insula, cingulate cortex, and temporal cortex. Overlap of under-activated regions between correct and error trials is not surprising given that fronto-insular and cingulate cortices comprise a distributed network that is active during multiple stages of cognitive processing: cue presentation (related to initial processing of behaviorally relevant cues), task performance (related to task set maintenance), and error related processing [258]. Fronto-insular and cingulate regions also are active across tasks requiring responses that involve more than one competing response set [259, 260], like antisaccade tasks, and provide vital information to dorsal attention systems via inputs to the dorsal lateral prefrontal cortex (DLPFC) [258, 261].

Fronto-insular and cingulate regions are responsible for a number of cognitive operations relevant to antisaccade performance. The IFG, particularly the right hemisphere, is involved in inhibitory control as well as action updating and selection when non-dominant responses are required [262-264]. Inhibition, while one component of antisaccade tasks, is important for successful performance in that people must suppress the competing and more dominant response of looking

toward the peripheral cue, and instead, program a "non-dominant" response in the other direction. Additionally, the right IFG and insula are part of the ventral attention network, which allows for orientation to behaviorally relevant stimuli and redirection of attention during cognitive control [265, 266]. Fronto-insular activation is particularly salient for unexpected cues that require reorientation of attention [261]. Attentional processes are central to antisaccade performance given the spatial uncertainty of the peripheral cue, the initial requirement to covertly attend to it, followed by switching attention to the opposing location. Under-activation of fronto-insular regions during correct responses may indicate deficits in both inhibition and attentional allocation that may make people with poor cognitive control (LCC and SZ groups) susceptible to higher antisaccade error rates regardless of psychiatric diagnosis.

Fronto-insular regions and cingulate cortex show significant activation during error commission and are essential for successful error processing. These same regions reach peak activation early, before other control regions like the dlPFC [94, 258], indicating that they may feed forward information to top-down portions of saccade circuitry to adapt future behavior. Ham and colleagues [267] suggest a hierarchy of regions that communicate information immediately after an error has occurred, starting with the right insula. The insula serves as an output hub to the cingulate, which then provides error-related signals to dlPFC, resulting in post-error adjustments in behavior [267]. Blunted error responses, in the form of fronto-insular and cingulate under-activation, are common in people with schizophrenia and contribute to poor behavioral performance [241, 268-270], although we observed similar patterns in the LCC group. LCC and SZ groups correct errors to the same degree as the HCC group. LCC and SZ groups, therefore, do not have problems detecting errors, but instead, may have problems using immediate feedback from error commission to establish and implement appropriate task sets, making errors more

common. This interpretation seems likely given involvement of fronto-insular and cingulate regions in task set implementation [258].

Although both LCC and SZ groups had poor antisaccade performance and displayed under-activation of relevant circuitry regions, there were two aspects of error processing that distinguished the SZ group from the LCC group. One was the suppression of the left STG and more posterior parts of the insula during antisaccade errors. A similar pattern also was seen in the same regions in the right hemisphere, but this did not significantly differ from the LCC group. As part of the error-related network previously described, the STG co-activates with, and structurally connects to fronto-insular regions [271-274]. STG activation is modulated based on prior responses and outcomes and is thought to be involved in subsequent action assessment and selection based on this prior information [275]. From this description, the STG seems to be related to more sustained processing of error-related information, whereas the cingulate and more anterior regions of the insula provide immediate communication of error-related activity. Both LCC and SZ groups displayed under-activation of the fronto-insular and cingulate regions, but only the SZ showed a suppression of the STG. The aforementioned pattern could mean that while the disruption of immediate error-related processing is common to groups that have poor cognition, more sustained forms of error processing are more specific to people with schizophrenia.

The second, and related, SZ-specific disruption was differential genetic effects on activation of the left IFG and insula during errors. The group with the most Val alleles in the SZ group had the lowest activation, whereas the group with the most Val alleles in the LCC group had the highest activation. There is a lack of information on COMT effects on error activation as measured by fMRI, but healthy people with more Val alleles show heightened post-error

negativity as measured by electroencephalography (EEG) [276-278]. Heightened post-error response magnitude, like STG activation, is used to further influence future behavior. Post-error negativity also is associated with activation of cingulate cortex [279], which interacts with fronto-insular regions during error processing and were active during errors in this study. Opposing patterns of genetic effects on fronto-insular activation may indicate that the Val allele does not influence error-related activation the same way in the SZ-group. Differential gene effects on circuitry activation may be due to differences in underlying brain chemistry between people with SZ and those with LCC, particularly related to dopamine function [143]. Due to the small sample size, interpretations of differential genetic effects in this study should be taken with caution and warrant further replication.

This study used two healthy comparison groups, people with HCC and people with LCC, to better understand SZ-specific deficits in cognitive control. SZ-specific disruptions were only seen during error trials and results pointed to disruptions in the ability to sustain error-related information to inform future behavior. Both groups with poor cognitive control, however, showed dysfunction of a distributed network of fronto-insular and cingulate regions during processing of correct and error responses. Dysfunction of this circuitry likely contributes to deficits in attention, task set implementation, and additional deficits in error-related processing. Understanding the neural differences and similarities between groups that display similar behavioral performance may inform models of cognitive control, especially in disorders like schizophrenia where deficits in cognitive control are common, but treatment is limited.

**Table 5.1** Subject Characteristics

| | HCC (N=21) | LCC (N=27) | SZ (N=23) |
|---|---|---|---|
| SPAN composite | .64 (.31) | -1.35 (.88) | -1.55 (1.1) |
| Age (years) | 33.6 (12.6) | 38.9 (10.5) | 39.9 (10.7) |
| Gender (male) | 14 | 13 | 9 |
| Handedness (right, left, ambidextrous) | 19, 1, 1 | 25, 3, 0 | 19, 2, 2 |
| Psychotropic Medication | | | |
| Unmedicated | | | 6 |
| Anti-psychotic (typical, atypical, both) | - | - | 2, 10, 1 |
| Anti-depressant | - | - | 5 |
| Benzodiazepines | - | - | 2 |
| Polypharmacy | - | - | 8 |

Cells show N's for each item except SPAN composite and Age, which show mean (SD.). Four participants were missing SPAN data (one HCC and three LCC and one HCC) due to technical difficulties. Polypharmacy was defined as taking more than one psychotropic medication. One SZ subject was taking Lithium in addition to antipsychotics and one SZ subject was taking Adderal. HCC = high cognitive control group; LCC = low cognitive control group; SZ = schizophrenia group.

**Table 5.2** MEMA Analysis Results

| Analysis | Hemi-sphere | Region | x | y | z | Cluster Size (voxels) | Letter in Figure 3 |
|---|---|---|---|---|---|---|---|
| Correct Trials | | | | | | | |
| HCC > LCC | | | | | | | |
| | R | IFG/Insula | 35 | 20 | 7 | 45 | a |
| HCC > SZ | | | | | | | |
| | R/L | Cingulate | 0 | 12 | 34 | 88 | b |
| | R | MTG/STG | 55 | -32 | -1 | 57 | c |
| Error Trials | | | | | | | |
| HCC > LCC | | | | | | | |
| | R | IFG | 46 | 17 | 9 | 66 | d[1] |
| | L | IFG/Insula | -44 | 14 | 12 | 82 | e[2] |
| HCC > SZ | | | | | | | |
| | R | STG/Insula | 48 | -31 | 9 | 149 | f |
| | R | IFG/Insula | 42 | 16 | 9 | 140 | g[1] |
| | R/L | Cingulate | 0 | 9 | 38 | 74 | h |
| | R/L | Thalamus | -2 | -13 | 14 | 47 | i |
| | L | STG/Insula | -43 | -13 | 12 | 221 | j[2,3] |
| LCC > SZ | | | | | | | |
| | R/L | Precuneus | -48 | -22 | 11 | 52 | k |
| | L | STG/Insula | 1 | 51 | 35 | 176 | l[3] |

Significant clusters from the MEMA analysis for correct and error trials. XYZ coordinates are in talairach space and indicate center of mass for each cluster. Some clusters extended beyond a single region, primarily between the insula and temporal regions. Superscript numbers indicate clusters that spatially overlapped with each other among comparisons. HCC = high cognitive control; LCC = low cognitive control; SZ = schizophrenia; IFG = inferior frontal gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus.

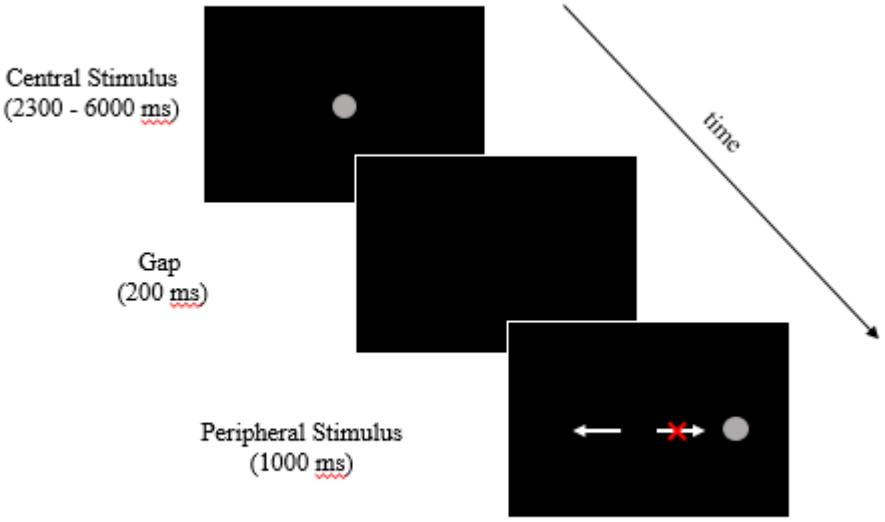



**Figure 5.1** *Stimuli and Timing*. Participants performed 120 trials across two runs of an antisaccade task (60 trials in each run). The above image outlines a single trial, which began with a central stimulus. Central stimulus timing was pseudorandomly jittered between 2300 and 6000 ms in order to deconvolve the stimulus-related hemodynamic response in the rapid event-related design. A 200 ms gap was then introduced followed by the peripheral stimulus. Participants were given 1000 ms while the peripheral stimulus was present to execute a glance in the opposite direction. The white arrow pointing to the left indicates a correct response (a glance away from the peripheral stimulus) and the white arrow pointing to the right with the red "X" indicates an incorrect response (a glance toward the peripheral stimulus). Arrows and the red X were not present during the task.

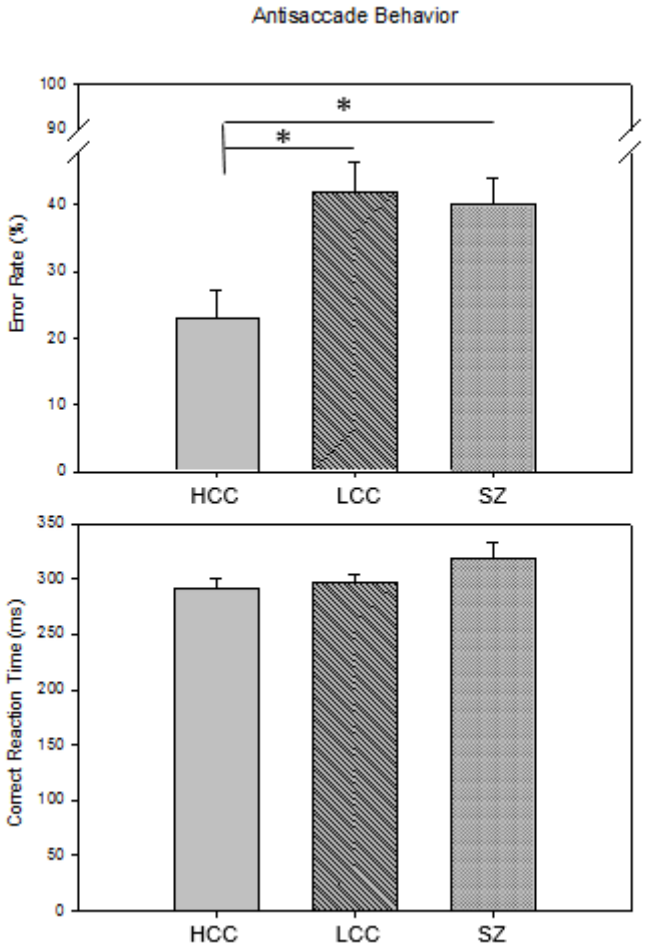



**Figure 5.2** *Group Differences in Antisaccade Behavior*. Bars show mean (SE) antisaccade error rate (top) and mean (SE) correct reaction time (bottom) for each group. Asterisks indicate significant differences between groups $p < .05$ (HCC vs. LCC: $t$ (46) = -3.2, $p$ = .005; HCC vs. SZ: $t$ (48) = -2.62, $p$ = .02).

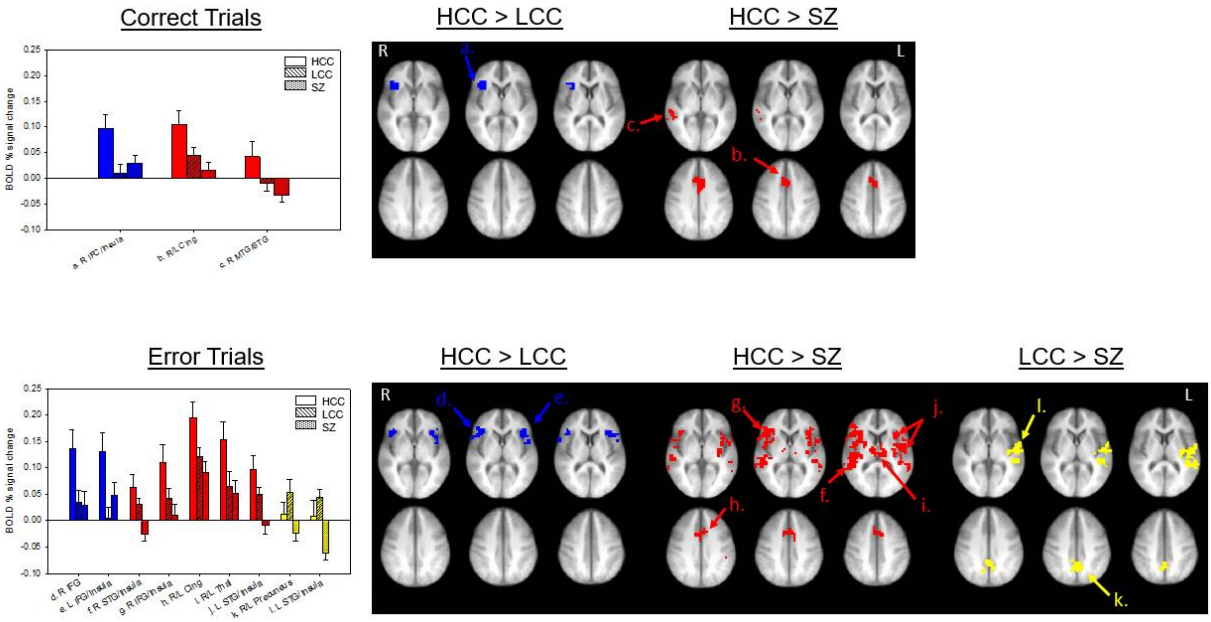
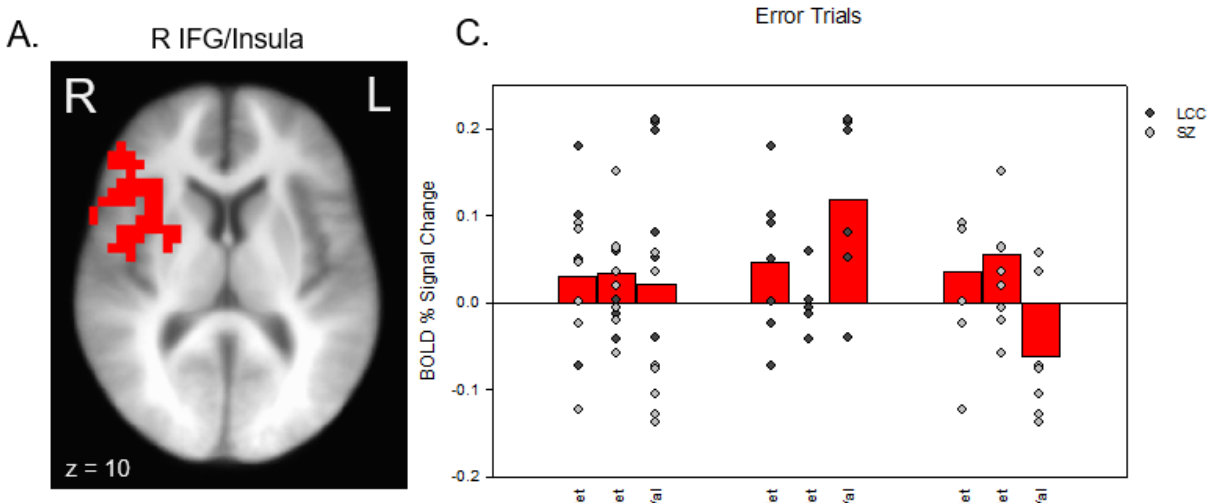



**Figure 5.3** *Group-wise Differences in Antisaccade Activation*. Top panel shows group-wise differences in correct antisaccade activation. Bottom panel shows group-wise differences in error antisaccade activation. Colors indicate in which comparison the cluster was significant. Bars (SE) show levels of activation for each group in each labeled cluster from Table 2. Clusters are shown on an anatomical image averaged across all subjects in talairach space (top z = 2, 6, 10; bottom z = 31, 35, 39). HCC = high cognitive control; LCC = low cognitive control; SZ = schizophrenia; IFG = inferior frontal gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus.




B.

| | All Subjects | LCC | SZ |
|---|---|---|---|
| Met/Met | 13 | 7 | 6 |
| Met/Val | 13 | 5 | 8 |
| Val/Val | 13 | 6 | 7 |

**Figure 5.4** *Group × Genotype Interaction*. There was a significant group by genotype interaction in the right inferior frontal gyrus and insula (clusters d. and g. in Figure 2). Given that cluster d. almost completely overlaps with cluster g. spatially, data for the interaction effect is shown for cluster g. only. A. Cluster g. shown on an anatomical image averaged across all subjects in talairach space. B. Table listing N for each genotype group. C. Bars showing mean level of antisaccade error activation in cluster g. by genotype (Met/Met, Val/Met, Val/Val) across the whole sample, the LCC group, and the SZ group. Dots show individual level activation within each group (dark gray = LCC, SZ = light gray). HCC = high cognitive control; LCC = low cognitive control; SZ = schizophrenia; IFG = inferior frontal gyrus.

# CHAPTER 6

# CONCLUSION

Cognitive deficits and associated structural and functional brain deviations have long been considered hallmarks of schizophrenia. There are mixed results, however, as to whether these deficits are specific to schizophrenia or present in other disorders that involve psychosis. Furthermore, it is unclear if cognitive deficits in schizophrenia are due to similar or disparate neural disruptions as those seen in healthy people with similar cognitive abilities. The three studies described here attempted to answer these questions by using appropriate comparison groups (multiple psychosis groups and two healthy groups divided by cognitive ability) in addition to considering multiple measures of cognition and brain.

Study 1 addressed the specificity of cognitive deficits and associated brain deviations in schizophrenia by evaluating the relationship between cognition and brain structure in schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, and healthy controls. Multivariate analyses were used to consider 14 measures of cognition and 4 measures of brain structure in 68 regions across the cortex while grouping psychotic disorders on a symptom continuum. There was evidence for specific schizophrenia-like disruptions in both cognition and brain structure related to more targeted cognitive abilities: the relationship between response speed and cortical thickness and the relationship between working memory and brain volume. General cognitive ability, while often the worst in the schizophrenia-like group and associated with the largest deficits in brain structure, was similar to those with schizoaffective-like illness.

Studies 2 and 3 addressed the specificity of neural disruptions underlying cognitive deficits in schizophrenia compared to healthy controls who experience similar cognitive difficulties. These studies focused on brain function in the form of resting state and task-based fMRI, which evaluated the connectivity of cognitive networks and activation during a cognitive task (antisaccades) respectively. Resting-state analyses did not reveal schizophrenia-specific disruptions in the FPNs or DMN, networks essential for successful cognitive performance. All network disruptions present in the schizophrenia group were seen in the healthy LCC group, although sometimes to a lesser extent. Similar results were reported in the task-based analysis. The schizophrenia and LCC group had higher antisaccade error rates than the HCC group and displayed similar deviations in brain activation during both correct and error antisaccade trials. There were, however, two exceptions to this pattern related to antisaccade errors. Schizophrenia-specific alterations were seen in the activation of the STG and differential COMT effects on activation of the IFG and insula. Differences in error processing and genetic effects on the regions that process errors may be a defining feature of schizophrenia compared to healthy people with poor cognition.

## Cognitive Deficits and Neural Deviations as Diagnostic Classifiers for Schizophrenia

Cognitive deficits have been a central focus of schizophrenia research, partly because they are common in the disorder and partly because they have such wide-reaching impacts on daily function and prognostic outcome[5, 6]. Cognitive deficits have been thought to be the defining feature of schizophrenia that differentiates it from other disorders involving psychosis. Some researchers propose that schizophrenia is a “disorder of cognition”, and should be defined as such[280]. Others suggest that psychotic symptoms in schizophrenia are a direct consequence of cognitive dysfunction that appears early in adolescence and continues to decline up to, and

slightly after the first psychotic break[281]. Researchers of this mind cite that Kraeplin and Bleuler, two of the most influential figures in psychiatric disorder classification, agreed with this concept. Kraeplin based the original dementia praecox/manic depression dichotomy on the presence or absence of cognitive decline, whereas Bleuler conceptualized schizophrenia as a disorder of thought rather than one defined by delusions and hallucinations.

Cognitive impairment is an attractive feature to distinguish schizophrenia from other psychotic disorders, especially due to pervasive deficits that are often on the magnitude of .5-2 standard deviations below healthy controls[10]. This approach, however, is problematic. While cognitive deficits are generally thought to be the most severe in schizophrenia compared to other psychoses, cognitive deficits are more similar than different across psychotic disorders. Cognitive measures alone, as shown in Supplement Table 3.1 from Study 1, do not distinguish psychosis groups. Verbal Fluency and Digit Sequencing tests from the BACS and antisaccade error rate were the only measures that differentiated the schizophrenia-like group from other psychosis groups, but other psychosis groups also showed deviations when compared to healthy controls. Such a pattern describes a continuum of cognitive deficits rather than discrete profiles of cognitive impairment in disorders of psychosis. If a continuum of cognitive deficits implies diagnostic specificity, then the question becomes where is the cutoff? How cognitively impaired does someone have to be to fall into a schizophrenia diagnosis versus a schizoaffective diagnosis, two diagnoses which seem to have similar scores on most cognitive measures in Study 1.

Better diagnostic specificity may be achieved through the consideration of cognitive measures in conjunction with measures of brain structure. Study 1 showed shared deviations in general cognitive ability and structural deviations in schizophrenia-like and schizoaffective-like

groups, but distinct deviations between the two groups related to more specific cognitive abilities and brain structure. Such distinctions confirm the need to consider schizophrenia and schizoaffective disorders as separate entities. Additionally, all psychosis groups showed similar deficits in spatial working memory, but only the schizophrenia-like group showed concomitant deficits in brain structure. Better distinction between psychosis groups in Study 1 was likely due to the multivariate nature of the analyses. The cognitive variates in our CCAs, which are characterized by a number of cognitive measures and their relation to brain structure, are far less variable within group than individual BACS measures (Figure 6.1a vs. b), a battery frequently used to assess neuropsychological function in schizophrenia[282]. One can see from the density curves in Figure 6.1 that the bipolar-like group also was better differentiated from the other two psychosis groups using the CCA cognitive variates over BACS measures alone.

Although Study 1 was able to identify some specificity of cognitive and structural brain deviations to particular psychotic disorders, distributions in Figure 6.1 make it abundantly clear that there is heterogeneity within each psychotic disorder when they are defined by DSM symptomatology. There is substantial overlap, even among schizophrenia, the psychosis group supposedly defined by cognitive impairment, and healthy people. One way to leverage this heterogeneity is to use biomarkers to classify individuals rather than DSM defined symptoms. The Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, on which data from Study 1 is based, has capitalized on heterogeneity by grouping psychiatric disorders into “biotypes” using many biomarkers, some of which are cognitive[283]. This approach seems promising in that more distinct groups arise from the use of cognition with multiple types of neural measures rather than symptoms. In our Study 1 analysis, biotype classification greatly improved the distinction between psychosis groups using the CCA method (Figure 6.2). Caution

is warranted, however, given that some cognitive measures used in the CCAs went into biotype construction (antisaccade error rate and latency and BACS composite).

Good classifiers in psychiatry not only have to differentiate one disorder from the other, but have to differentiate people with the disorder from healthy controls. Although uncommonly reported in the literature, there are healthy individuals who perform just as poorly as people with schizophrenia on cognitive tasks that do not display signs of psychosis and are unlikely to develop psychosis. Healthy people with poor cognition show similar neural disruptions as people with schizophrenia in terms of activation of the prefrontal cortex during cognitive tasks[112, 113], connectivity within the FPN, and connectivity between the FPN and DMN[27]. Similarities between healthy people and people with schizophrenia make a harder case for the use of cognition as a central classifier for the disorder.

Results of Studies 2 and 3 support this observation by using a sample of healthy people with LCC. The resting-state analysis from Study 2 demonstrated that there were no detectable schizophrenia-specific disruptions in connectivity of the FPN and DMN and replicated results in the literature related to each group[34, 90, 106]. Study 3 showed only weak support for schizophrenia-specific disruptions. The schizophrenia and LCC groups did not differ in terms of antisaccade behavior, with each group making a substantial number of errors. When comparing the schizophrenia group to the LCC group, there also were no detectable differences in neural responses to correct antisaccade trials and only differences in activation of one region, the STG, during antisaccade errors. Deficits in error processing have long been documented in the schizophrenia literature, but primarily in the form of reduced error related negativity (ERN)[284-286], as measured by EEG, and reduced error-related activation of the ACC, as measured by fMRI[241, 269, 270]. We replicated fMRI findings in the ACC activation during both correct and error

trials, although this reduction also was present in the LCC group. The STG is not generally mentioned in studies of error related processing although it, along with the insula, are modulated by prior outcomes and may contribute to the assessment and selection of future behaviors[275]. Polli and colleagues[287], however, have shown that immediate error-related adjustments in performance during an antisaccade task are preserved in schizophrenia. People with schizophrenia showed intact error correction and post-error slowing. It could be that immediate responses are intact but that the information communicated by the error cannot be maintained throughout the task to bias more controlled responses, a feature suggested to be the role of the STG and insula. While this particular deficit may be specific to schizophrenia, future research needs to explore the details of this hypothesis before it can be used a classifier for schizophrenia.

## The Role of Genetics in Identifying Schizophrenia-specific Deficits in Cognition and Associated Brain Circuitry

There are similar cognitive deficits and associated brain disruptions in a large number of healthy individuals who are unlikely to develop a psychotic disorder. Multiple measures of cognitive-related phenomena help address the problem of differentiation as seen in Study 1, but another source is genetics. Considering genetic effects on brain function can serve two purposes: 1. Further refine mechanisms behind why groups are different or 2. Provide evidence of divergent mechanisms that underlie disruptions that are similar. The use of genetics in Study 3 pointed to the latter. Both schizophrenia and LCC groups showed under activation of the R IFG and insula compared to the HCC group, but the effect of COMT on IFC/insula activation was different for the LCC group than for the schizophrenia group. In the LCC group, the COMT Val allele was associated with higher levels of activation in the IFG/Insula (about at the same level as the HCC group); in the schizophrenia group, it was associated with lower levels of activation.

Higher levels of activation in this region were generally associated with good cognitive performance, as seen in the HCC group. Furthermore, the Val allele is often associated with larger responses to errors (ERN), which tend to have beneficial effects on cognitive performance. In spite of having both qualities, the LCC group had poor cognitive performance regardless of genotype. The paring of a seemingly beneficial brain patterns with poor behavioral performance could point to sub-groups of healthy people with LCC, indicating heterogeneity even within one of the more extreme tails of the healthy distribution. While gene x diagnosis interactions are interesting, those identified in Study 3 are considered preliminary. The number of individuals in each group were small. Replication of these patterns are needed in larger samples, but our results provide interesting questions that could drive future hypothesis testing.

We found no significant effects of RGS4 and Akt genotype on task-based activation. These genes are less frequently studied than COMT, but there was sufficient evidence to support their effect on cognition and brain function (See Table 2.1). Absence of evidence deos not indicate absence of effect. Our sample sizes were small and these genes may have more subtle effects than COMT, especially since they impact more downstream processes that could be mediated by other molecules under genetic control. It could also be that effects may depend on interaction with COMT genotype[148, 288] which could not be assessed with the current sample size.

There were no detectable gene effects on connectivity measures of either the FPN or DMN networks in the resting-state analysis. Previous literature has found gene effects on both the FPN and DMN, although results are mixed. The COMT Val allele has been associated with both increased[289] and decreased[290] prefrontal connectivity within the FPN. For the DMN, the Val allele has been associated with increased connectivity [291] and inverted U patterns when considered with variation in the DRD2 receptor gene[292]. There also is evidence that the effect of

COMT genotype on resting state connectivity changes from adolescence to adulthood[293] and may be affected by gender[294], neither of which could be explored in this sample. Effects of the two other genes of interest, RGS4 and Akt, on connectivity are sparse and are restricted to connectivity during working memory performance[295, 296]. Again, restrictions in sample size may account for the lack of genetic effects on connectivity measures.

Studies report associations between SNP variation and cognitive-related neuroimaging measures using candidate approaches, but methods utilizing gene networks may be more informative. It is likely that genetic effects on neuroimaging measures are pleiotropic, with many loci of importance, each contributing a small effect. SNPs contributing to cognitive ability have been identified using neuroimaging measures as quantitative traits in GWAS studies[297], but such studies only identify SNP associations and fail to address SNP/SNP interactions or the mechanisms that underlie associations. GWAS "hits", however, can provide a start to gene network construction through the use of large scale genetic databases, which contain data related to expression, regulatory motifs, and microRNAs[298]. Models of gene x gene interactions can then be data-derived or based on *apriori* information using Bayesian methods. These methods have their downsides, including inclusion bias of specific genes; there are some regions of the genome that are more well-studied than others and these factors are more heavily represented in available databases. Consideration of gene networks also requires denser genotyping for each individual, which drives up cost and reduces feasibility for smaller projects like Studies 2 and 3.

## Future Directions

While the results of Studies 1-3 shed light on the specificity of cognitive deficits and their neural underpinnings in schizophrenia, there are still questions that warrant further investigation. In Study 1, we identified schizophrenia-specific disruptions in the relationship between cortical

gray matter structure and cognition compared to other psychosis groups, but there are other relevant regions that lie outside the cortex. These include the basal ganglia, thalamus, amygdala, hippocampus, and cerebellum, all of which significantly contribute to cognitive functioning and are known to be disrupted in psychosis[152-154, 299]. Although important, they were not considered in Study 1 because we were interested in how the four structural measures (GMV, CT, CSA, and LGI) together were related to cognition, and only cortical measures would have measures for all four. Furthermore, the sample size available would not warrant the addition of more variables than were already included in the analysis. When larger samples become available, as will be the case at the end of the second iteration of the B-SNIP project, subcortical measures should be considered for further investigation.

Another possibility is exploring other aspects of brain structure like white matter integrity as measured by diffusion tenor imaging (DTI). There seems to be evidence for differences in gray matter deficits across psychosis groups [63], although the evidence is unclear for differences in white matter[300-302]. It could be that cognitive impairment in bipolar disorder is more a consequence of disruptions in white matter in the absence of extreme disruptions in gray matter structure, whereas cognitive impairment in schizophrenia is a consequence of disruptions in both. If considered jointly, gray matter and white matter alterations may provide further insights into the etiology of cognitive deficits in different psychotic disorders given that white matter has a distinct developmental pattern from that of gray matter[47].

In Studies 2 and 3 we found similar functional brain disruptions in healthy people with LCC and people with schizophrenia. The two groups either did not differ from each other or differed in terms of severity when compared to the HCC group. This was especially true for the resting-state analysis in Study 2. Study 2, however, addressed a static measure of network

connectivity, in which voxel-wise correlations of BOLD signals are considered over the entire time course. While a necessary first step in any resting-state analysis, this method assumes that the strength of connections and spatial characteristics of a network are constant across time, even though the statistical interdependence, or functional connectivity, among regions can change from moment to moment[303, 304]. SZ and LCC groups could differ in terms of dynamic connectivity. The most common way to analyze more "dynamic" forms of functional connectivity is to conduct a sliding time-window correlation for each individual. This can be based on regions within a single network or across multiple networks defined in the overall group. The resulting covariance matrices are fed into a k-means clustering algorithm to assess the frequency and structure of reoccurring functional connectivity patterns or "brain states"[305]. More focus on the fluctuations in connectivity, or brain states, rather than a time-course average, may identify more subtle differences between people with schizophrenia and healthy people with LCC. There is evidence that people with schizophrenia transition less often to particular brain states when compared to more typical healthy comparison groups and have different dynamic connectivity patterns than those seen in bipolar disorder[306]. Dynamic connectivity methods, however, are still not standard and there are added difficulties in defining and interpreting brain states, particularly when psychiatric groups are the subject of interest.

The benefit of looking at more than one snapshot of brain function also could apply to the task-based analysis. In Study 3, the response amplitude to a particular stimulus was estimated, but regions may rise and fall at different rates. Further information about the shape of the hemodynamic response, rather than amplitude alone, may further differentiate people with schizophrenia from healthy people with LCC. More information also could be gleaned from looking at the stages of cognitive processing, including preparation, execution, and evaluation

(especially after errors) although a slower event-related design would be needed in order to conduct such an analysis with fMRI.

## Conclusions about Cognitive Deficits in Schizophrenia

Cognitive deficits and associated disruptions in brain function and structure continue to be sources of significant dysfunction in schizophrenia. The use of multiple MRI modalities in addition to the use of multiple comparison groups as in the three studies described can help further differentiate which disruptions are specific to schizophrenia and which are present in other psychosis groups or the healthy population. Understanding these differences could provide better insight into the mechanisms behind cognitive impairment in this disorder. This understanding could lead to more targeted trajectories for behavioral and pharmacological remediation of cognitive deficits in a number of different populations including people with schizophrenia.

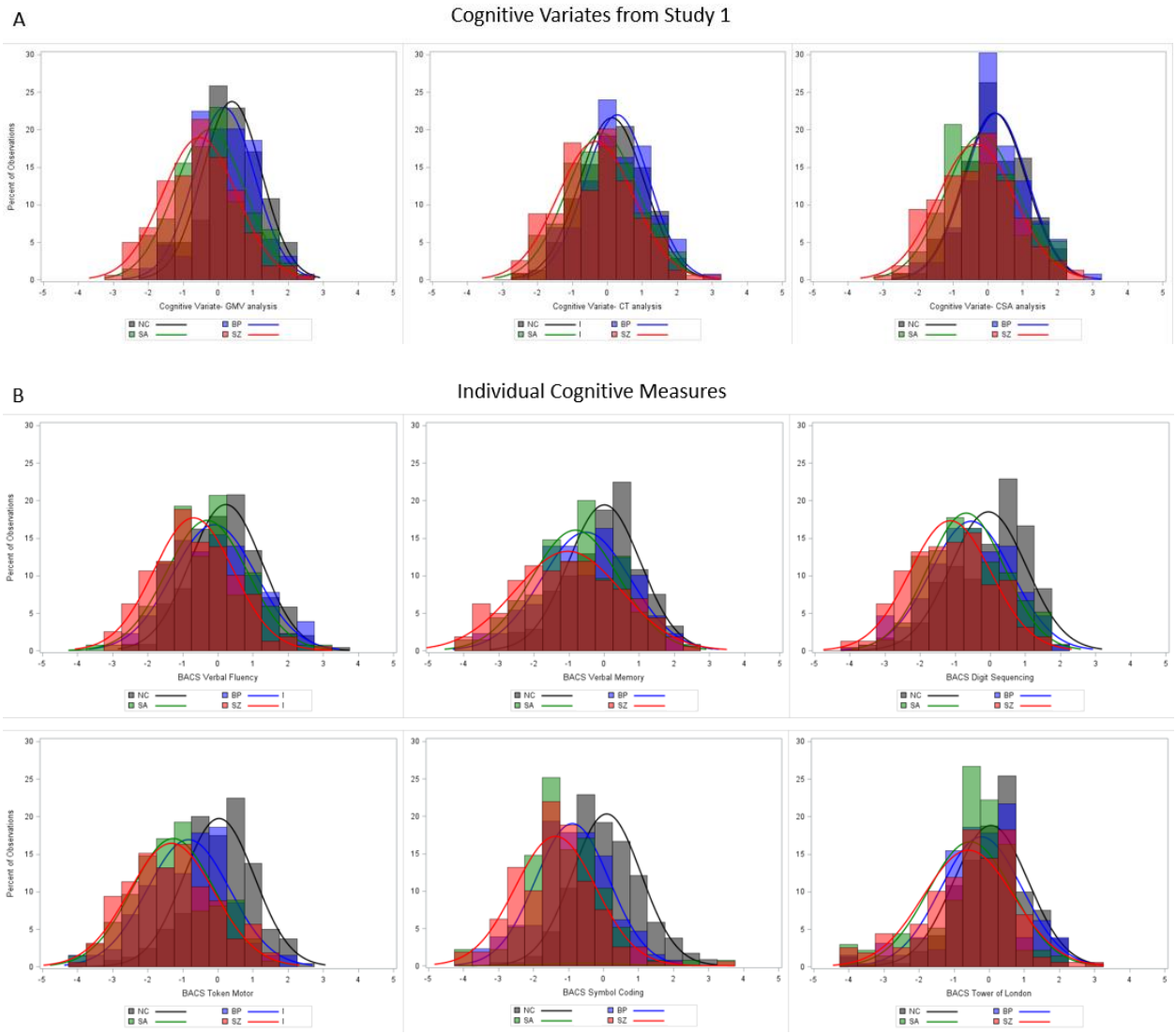



**Figure 6.1** *Group Distinctions with Cognition and Structure vs. Cognition Alone*. Panel A shows the distribution of each group on the latent cognitve variate from the first pair of the CCA (in percent of observations). Groups are notated by color. A density function is also plotted for each group in the same color. Panel B shows the same but for individual BACS measures. In Panel A, consideration of multiple cognitve measurs and their relationship to brain strcutre results in narrower distributions and clearer distnctions among psychosis groups than in Panel B. In both panels, there is substantial overalp across all groups. BACS = Brief Assessment of Cognition in Schizophrenia; HC = healthy controls; BP = bipolar-like; SA = schizoaffective-like; SZ = schizophrenia-like.

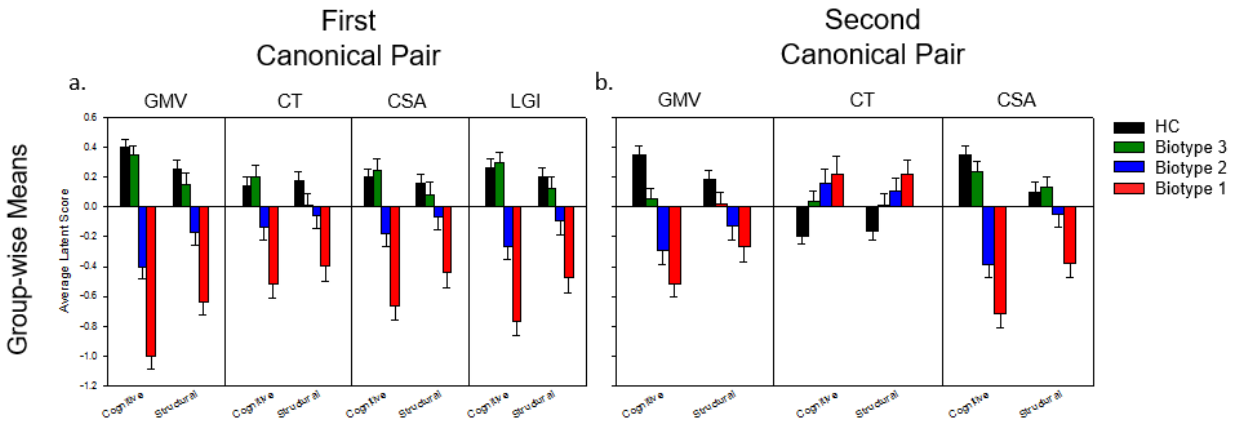



**Figure 6.2** *Study 1 Results by Biotype Classification*. Bars show average score on the cognitve and latent variates for each significant CCA pair. For comparison see Figure 3.2 which is the same information plotted by Schizo-Bipolar Scale. GMV = gray matter volume; CT = cortical thickness; CSA = cortical surface area; LGI = local gyrification index; HC = healthy control

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# APPENDIX A

# SUPPLEMENT-STRUCTURE

## Method Supplement

### Participants

Inclusion criteria for all participants were as follows: age between 18 and 60 years old, English proficiency, premorbid IQ above 70 (as measured by the WRAT), no known history of head trauma or neurological disorders, and no substance abuse within the last month and/or substance dependence within the last 6 months. Healthy controls reported no personal or immediate family history of psychotic disorders and/or recurrent depression. Individuals with psychosis were stable and a majority were receiving consistent drug therapies from 4 weeks prior to study participation. There were 19 psychosis individuals who were unmedicated (i.e. reported no use of any psychotropic medications). Further details of recruitment procedures and clinical characterization of patient samples have been outlined elsewhere (Ivleva, Bidesi et al. 2013; Tamminga, Ivleva et al. 2013). Thirty-three participants were missing gyrification measures, therefore gyrification analyses were based on 645 individuals rather than 678.

### Cognitive Assessment

Cognitive tests that did not yield scores based on normative data (DPX and AS) were normed to the healthy sample who did not have elevated Cluster A personality disorder traits (within 1 symptom of disorder). See Supplement Table 3.1 for descriptive data.

### MRI Structural Processing

Scans were collected on 3-T scanners across sites with protocols standardized according to the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (http://www.loni.ucla.edu/ADNI). Structural MRI data were converted to nifti format and visually inspected for scanner artifacts and neurobiological abnormalities. Structural measures were obtained using a standard pipeline in Freesurfer v5.1 (Fischl 2012) as implemented in Nanda et al. (2014) and Padmanabhan et al. (Padmanabhan, Tandon et al. 2015). Images were run through autorecon1 and remaining non-brain tissue was removed manually if necessary. Images were then run through the remainder of the pipeline (autorecon2 and 3). Gray matter volume (GMV), cortical thickness (CT), cortical surface area (CSA), and local gyrification index (LGI) measures were then extracted from 68 cortical regions using the standard cortical parcellation (Disikan-Killany Atlas) available in Freesurfer (Fischl, van der Kouwe et al. 2004; Desikan, Ségonne et al. 2006) (see Supplement Table 3.2).

**CCA**

CCA is a data-driven, multivariate procedure that identifies the relationship between two sets of variables, criterion and predictor variables, by maximizing correlations across and within sets. This type of analysis is preferred when measures of the criterion and predictor variables are related both within and between sets and when the relationship between sets is non-directional (Lambert, Wildt et al. 1988). This is in direct contrast to other multivariate techniques like redundancy analysis, which instead maximizes variance of the criterion set predicted by the predictor set and assumes direct statistical dependence of one set on the other (Lambert, Wildt et al. 1988). CCA was determined to be more suitable to evaluate relationships between cognition and brain structure because there are meaningful correlations within each variable set (across

cognitive measures and across brain regions) and directional relationships between cognition and brain structure would not be appropriate.

For the CCA, all cognitive measures included were adjusted for age, sex, and race. All structural measures (for each ROI) included were adjusted for the same variables plus intracranial volume (ICV) when relations with parameters were significant (Hamm, Ethridge et al. 2014). Cognitive and structural measures were standardized before insertion into the CCA to avoid violations of normality. Visual inspection of individual measure distributions did not indicate any significant violations of normality or heteroscedasticity, although normality is not strictly required for CCA.

The simultaneous nature of this analysis negates the need for multiple comparison correction within each CCA analysis. Multiple testing across CCA analyses, however, were accounted for using Bonferroni correction. Threshold for significance was set at $p = .0125$ (.05/4 CCA analyses). In addition to the requirement of Bonferroni-corrected significance, we additionally conducted a resampling procedure using a jackknife method to ensure the stability of CCA latent pairs. A delete-2 jackknife procedure(Lee 2007) was performed (random sampling without replacement) with 10,000 replicates. The CCA was then conducted on each replicate. Only variates that reached significance in the original analysis and variates in which the loadings of the individual measures did not include "0" in the 99% confidence interval in the delete-2 jackknife procedure were considered for further interpretation.

**Schizo-Bipolar Scale**

Fifteen (5 from each diagnostic group) of the 423 individuals with psychosis included in the canonical correlation analysis had not been assigned Schizo-Bipolar Scale scores and were not included in further analyses. Psychosis groups were constructed using the Schizo-Bipolar

Scale (SBS). The SBS ranges from 0-9 and reflects the proportion of non-affective psychosis symptoms and manic symptoms in relation to total illness duration as well as which mood symptoms (manic vs. depressive) are predominant when present. Assignment of SBS scores was performed by trained clinical raters across all B-SNIP sites. Intraclass Correlation Coefficients (ICCs) as well as other psychometric details of the SBS can be found in Keshavan et al. (Keshavan, Morris et al. 2011). Breakdown of SBS groups by DSM IV diagnosis are in Supplement Table 3.3.

## Results Supplement

### Jackknife Results

CCA latent pairs were retained for further analysis if their correlation was significant ($p \leq .0125$, see Supplement Table 3.4) and if the loadings of individual variables was stable, as determined by the jackknife analysis. All pairs except the third pair in the GMV analysis reached these criteria. Jackknifed parameters estimates were similar to original estimates and did not include zero in the 99% confidence limit interval (see Supplement Table 3.5 and Supplement Figure 3.1).

### Psychosis Continuum Analysis

Pairwise comparisons between groups on cognitive and structural latent variates were conducted on those measures that were significant for the omnibus effect. Results of these pairwise comparisons are reported without multiple testing corrections. A comparison of results without and with multiple testing correction using a Hochberg procedure(Hochberg 1988) are presented in Supplement Table 3.6.

Associations between latent variate scores and anti-psychotic medication and symptoms sub-scales are listed in Supplement Table 3.7. There were four significant associations after

Bonferroni correction: the cognitive variate in the first pair of the CT (PANSSpos) and GMV (PANSSneg) analyses, the structural variate in the first pair of the CSA analysis (PANSSpos), and the structural variate in the second pair of the CT analysis (CPZ daily dose). All significant symptom associations were negative, with more severe symptomatology associated with lower scores on latent variates. Effect sizes for significant symptom associations, however, were small (ranging between $\eta^2 = .02$ and $\eta^2 = .03$). Larger daily CPZ doses were associated with higher latent scores on the CT structural variate (thinner cortex). The effect size, like those for symptoms, was small ($\eta^2 = .02$).

**Supplement Table 3.1 List of Cognitive Assessments, Domain of Cognition Assessed, and Group-Wise Comparison of Normed Means**

| | | SZ-like | | SAD-like | | BP-like | | HC | | ANOVA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Assessment | Cognitive Domain | Mean | SD | Mean | SD | Mean | SD | Mean | SD | F (3, 659) | p | Post hoc[c] |
| **WRAT Reading Subtest** | Premorbid IQ | 96.6 | 16.1 | 98.7 | 15.5 | 103.7 | 13.7 | 104.5 | 13.7 | 11.8 | <.0001 | SZ, SAD < HC, BP |
| **BACS**[a] | | | | | | | | | | | | |
| TOL | Executive Function | -.59 | 1.3 | -.54 | 1.2 | -.22 | 1.2 | .06 | 1.1 | 12.6 | <.0001 | SZ < BP, HC<br>SAD < HC |
| Digit Sequencing | Working Memory | -1.1 | 1.2 | -.68 | 1.1 | -.54 | 1.2 | -.05 | 1.1 | 31.4 | <.0001 | SZ < SAD, BP < HC |
| Symbol Coding | Attention/ Processing Speed | -1.4 | 1.2 | -1.1 | 1.0 | -.88 | 1.04 | .09 | .98 | 74.9 | <.0001 | SZ < BP < HC<br>SAD < HC |
| Verbal Memory | Verbal Memory | -1.0 | 1.5 | -.80 | 1.2 | -.51 | 1.3 | .02 | 1.0 | 25.6 | <.0001 | SZ < BP < HC<br>SAD < HC |
| Verbal Fluency | Processing Speed | -.69 | 1.1 | -.30 | 1.2 | -.10 | 1.2 | .23 | 1.0 | 22.8 | <.0001 | SZ < SAD, BP < HC |
| TMT | Motor Speed | -1.3 | 1.2 | -1.3 | 1.2 | -.83 | 1.2 | .04 | 1.0 | 62.0 | <.0001 | SZ, SAD < BP < HC |
| **WMS Spatial Span**[a] | | | | | | | | | | | | |
| Forward Span | Working Memory | -.33 | 1.0 | -.4 | 1.0 | -.47 | 1.1 | .03 | .95 | 8.9 | <.0001 | SZ, SAD, BP < HC |
| Backward Span | Working Memory | -.58 | 1.1 | -.56 | .97 | -.54 | .98 | .11 | .91 | 24.9 | <.0001 | SZ, SAD, BP < HC |
| **DPX**[b] | | | | | | | | | | | | |
| Correct RT | Response Speed | .70 | 1.3 | .43 | 1.2 | .33 | .97 | -.11 | .97 | 18.6 | <.0001 | HC < BP < SZ<br>HC < SAD |
| D-Prime | Signal Detection | -.67 | 1.4 | -.54 | 1.2 | -.45 | 1.1 | .11 | .85 | 19.6 | <.0001 | SZ, SAD, BP < HC |
| BX-AY | Goal Maintenance/ Inhibition | .02 | 1.2 | .03 | 1.1 | .02 | 1.0 | -.01 | .90 | .06 | .98 | |
| **Antisaccades**[b] | | | | | | | | | | | | |
| Error Rate | Inhibition/ Working Memory | 1.6 | 1.8 | .87 | 1.6 | .78 | 1.6 | -.11 | .99 | 44.6 | <.0001 | HC < BP, SAD < SZ |
| Correct RT | Response Speed | .62 | 1.4 | .27 | 1.3 | .34 | 1.2 | -.01 | .98 | 8.9 | <.0001 | HC < BP, SZ |

WRAT = Wide Range Achievement Test; BACS = Brief Assessment of Cognition in Schizophrenia; TOL = Tower of London; TMT = Token Motor Task; WMS= Weshler Memory Scale; DPX = Dot Probe Task; RT = Reaction Time; HC= Healthy Controls; BP= Bipolar; SAD= Schizoaffective; SZ= Schizophrenia

[a]Means were calculated on z-scores and based on respective test norms.

[b]Means were calculated on z-scores and based on the study-wide healthy comparison sample without any elevated Cluster A traits.

[c]Post hoc tests were performed using Tukey's-Kramer. Comparisons listed were significant at p< .05.

**Supplement Table 3.2 List of Lobes and their Subdivisions**

| Lobe | Component Sub-regions (Right and Left) in Each Canonical Correlation Analysis |
|---|---|
| Frontal | Caudal middle frontal, rostral middle frontal, medial orbitofrontal, lateral orbitofrontal, frontal pole, pars opercularis, pars orbitalis, pars triangularis, superior frontal, precentral, and paracentral regions |
| Parietal | Inferior parietal, superior parietal, supramarginal, precuneus, and postcentral regions |
| Temporal | Bank of superior temporal sulcus, inferior temporal, middle temporal, superior temporal, fusiform, entorhinal, parahippocampal, transverse temporal, temporal pole, and insula regions |
| Occipital | Cuneus, lingual, pericalcarine, and lateral occipital regions |
| Cingulate | Caudal anterior cingulate, isthmus cingulate, rostral anterior cingulate, and posterior cingulate regions |

**Supplement Table 3.3 Schizo-Bipolar Scale Groups by DSM IV Diagnosis**

| | | DSM Diagnosis | | |
|---|---|---|---|---|
| | | BP | SAD | SZ |
| Schizo-Bipolar Scale (SBS) | BP-like | 126 | 3 | 0 |
| | SAD-like | 22 | 90 | 23 |
| | SZ-like | 0 | 18 | 141 |

Cells show N of DSM diagnoses in each of the groups determined by the SBS. Individuals with a DSM diagnosis of schizoaffective disorder were more likely to fall into SBS groups that were not consistent with their DSM diagnosis. DSM = Diagnostic and Statistical Manual; BP= Bipolar; SAD= Schizoaffective; SZ= Schizophrenia

**Supplement Table 3.4 Significance of CCA Variate Pairs**

| CCA | Canonical Correlation | Squared Canonical Correlation | Eigenvalue | Wilk's Lambda | F(num df, den df) | p- value |
|---|---|---|---|---|---|---|
| GMV | | | | | | |
| Pair 1 | .54 | .29 | .41 | .14 | 1.4 (952, 8243.7) | < .001 |
| Pair 2 | .46 | .22 | .28 | .19 | 1.2 (871, 768.1) | < .001 |
| Pair 3 | .43 | .18 | .23 | .25 | 1.1 (792, 7112.1) | .008 |
| CT | | | | | | |
| Pair 1 | .56 | .31 | .45 | .15 | 1.3 (952, 8243.7) | < .001 |
| Pair 2 | .49 | .24 | .32 | .22 | 1.1 (871, 768.1) | .01 |
| CSA | | | | | | |
| Pair 1 | .54 | .29 | .40 | .15 | 1.3 (952, 8243.7) | < .001 |
| Pair 2 | .46 | .21 | .27 | .21 | 1.2 (871, 768.1) | .002 |
| LGI | | | | | | |
| Pair 1 | .54 | .3 | .42 | .15 | 1.2 (952, 7791) | < .001 |

Table shows results for significant variate pairs of each CCA analysis. CCA = canonical correlation analysis; GMV = Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis.

**Supplement Table 3.5a Jackknife results-Cognitive Variables**

| | Pair 1-GMV | | | | Pair 2-GMV | | | | Pair 3- GMV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| WRAT | .7591 | .7589 | > .001 | .74651, .77059 | -.0174 | -.0178 | > .001 | -.06051, .02884 | -.051 | -.048 | > .001 | -.10911, .07923 |
| BACS- Tower of London | .6277 | .6275 | > .001 | .60927, .64394 | .2484 | .2477 | > .001 | .20367, .2906 | .2721 | .2648 | > .001 | -.22477, .3141 |
| BACS- Digit Sequencing | .4961 | .496 | > .001 | .47284, .51933 | .3911 | .3901 | > .001 | .34559, .43235 | -.2834 | -.2722 | > .001 | -.33528, .3341 |
| BACS- Symbol Coding | .5528 | .5527 | > .001 | .53183, .57546 | .4094 | .4087 | > .001 | .3644, .45341 | .3351 | .3252 | > .001 | -.28971, .39345 |
| BACS- Verb Mem | .5535 | .5533 | > .001 | .5403, .56669 | -.0366 | -.0368 | > .001 | -.06935, -.00755 | .0939 | .0909 | > .001 | -.08113, .13023 |
| BACS- Verb Fluency | .4895 | .4893 | > .001 | .47152, .50736 | .251 | .2505 | > .001 | .2127, .28087 | .093 | .0901 | > .001 | -.06508, .14952 |
| BACS- Token Motor Task | .3865 | .3864 | > .001 | .36947, .40308 | .0135 | .0135 | > .001 | -.02288, .05467 | -.1483 | -.1436 | > .001 | -.20485, .13714 |
| Spatial Span-Forward | .0139 | .0141 | > .001 | -.01151, .03901 | .5619 | .5609 | > .001 | .52511, .59587 | .244 | .2379 | > .001 | -.16342, .30857 |
| Spatial Span-Backward | .1666 | .1667 | > .001 | .14127, .19017 | .4746 | .4736 | > .001 | .4327, .50656 | .1706 | .1667 | > .001 | -.09157, .24122 |
| DPX-Correct RT | -.2179 | -.2179 | > .001 | -.24159, -.19176 | -.3167 | -.3162 | > .001 | -.36642, -.25381 | .4241 | .4105 | .001 | -.41679, .48637 |
| DPX- D-Prime | .0999 | .1 | > .001 | .07943, .11993 | .2823 | .2818 | > .001 | .25178, .31471 | -.0192 | -.0173 | > .001 | -.07172, .05893 |
| DPX- AX-BY | -.0446 | -.0446 | > .001 | -.06297, -.02811 | .0876 | .0874 | > .001 | .05792, .11481 | -.0891 | -.0866 | > .001 | -.13211, .05902 |
| Antisaccade ER | -.4037 | -.4037 | > .001 | -.43007, -.37687 | -.5196 | -.5186 | > .001 | -.55353, -.4833 | .196 | .1892 | > .001 | -.192, .26597 |
| Antisaccade Correct RT | -.2549 | -.2547 | > .001 | -.27648, -.23444 | -.2435 | -.2433 | > .001 | -.2877, -.19536 | .0346 | .0347 | > .001 | -.06576, .12276 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5a Jackknife results-Cognitive Variables cont.**

| | Pair 1-CT | | | | Pair 2-CT | | | | Pair 1-CSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| WRAT | .7199 | .7226 | > .001 | .71009, .73681 | .1861 | .1106 | > .001 | .06774, .15082 | .6945 | .69428 | > .001 | .67491, .71505 |
| BACS- Tower of London | .1667 | .2838 | > .001 | .26241, .30707 | .0182 | .1027 | > .001 | .06346, .14393 | .478 | .4778 | > .001 | .4575, .50028 |
| BACS- Digit Sequencing | .3227 | .4123 | > .001 | .39488, .43286 | .2063 | .0908 | > .001 | .05807, .12302 | .3304 | .33039 | > .001 | .30087, .36418 |
| BACS- Symbol Coding | -.1252 | .1706 | > .001 | .15187, .19204 | .0157 | -.1089 | > .001 | -.14143, -.07526 | .4261 | .42587 | > .001 | .40149, .45081 |
| BACS- Verb Mem | -.0056 | .2443 | > .001 | .22615, .26476 | -.0589 | -.0664 | > .001 | -.09633, -.03359 | .4012 | .40093 | > .001 | .37965, .42081 |
| BACS- Verb Fluency | -.092 | .227 | > .001 | .20882, .24929 | -.3984 | -.2447 | > .001 | -.26847, -.21572 | .2459 | .24569 | > .001 | .22454, .27057 |
| BACS- Token Motor Task | .4112 | .316 | > .001 | .29817, .33351 | -.0595 | -.1996 | > .001 | -.22441, -.17553 | .2207 | .22056 | > .001 | .19953, .24069 |
| Spatial Span-Forward | -.3509 | -.2664 | > .001 | -.28437, -.24529 | .2236 | .1864 | > .001 | .16112, .21218 | -.2124 | -.21219 | > .001 | -.24097, -.17876 |
| Spatial Span-Backward | -.4536 | -.2502 | > .001 | -.27036, -.22708 | .0489 | .1143 | > .001 | .0783, .15101 | -.1933 | -.19317 | > .001 | -.22143, -.16416 |
| DPX-Correct RT | .0972 | -.0116 | > .001 | -.04229, .02333 | .8319 | .6177 | > .001 | .60277, .63419 | -.1104 | -.11035 | > .001 | -.13049, -.08882 |
| DPX- D-Prime | -.1286 | .0031 | > .001 | -.01661, .02747 | .4566 | .2444 | > .001 | .22101, .26535 | .1249 | .12491 | > .001 | .10161, .152 |
| DPX- AX-BY | -.0937 | .0035 | > .001 | -.01755, .024 | -.3449 | -.2937 | > .001 | -.3107, -.27608 | -.1943 | -.19414 | > .001 | -.21262, -.17349 |
| Antisaccade ER | -.0654 | -.1134 | > .001 | -.13431, -.09438 | .1838 | .2646 | > .001 | .23613, .29207 | -.1722 | -.17212 | > .001 | -.19871, -.14451 |
| Antisaccade Correct RT | -.0087 | -.017 | > .001 | -.03555, .00067 | .0996 | .2401 | > .001 | .21297, .26243 | -.1037 | -.10348 | > .001 | -.12698, -.08163 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5a Jackknife results-Cognitive Variables cont.**

| | Pair 2-CSA | | | | Pair 1-LGI | | | |
|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| WRAT | .4034 | .4024 | > .001 | .34511, .44806 | .742 | .7419 | > .001 | .72953, .75703 |
| BACS- Tower of London | .4324 | .4314 | > .001 | .39886, .45888 | .5952 | .595 | > .001 | .5796, .61176 |
| BACS- Digit Sequencing | .6133 | .612 | > .001 | .56062, .65589 | .4305 | .4304 | > .001 | .41448, .45186 |
| BACS- Symbol Coding | .5069 | .5059 | > .001 | .46526, .54175 | .5052 | .505 | > .001 | .48946, .5212 |
| BACS- Verb Mem | .1913 | .1909 | > .001 | .13149, .23972 | .4268 | .4266 | > .001 | .40988, .44318 |
| BACS- Verb Fluency | .3523 | .3516 | > .001 | .30726, .3917 | .3909 | .3909 | > .001 | .37156, .41129 |
| BACS- Token Motor Task | .0843 | .0842 | > .001 | .02659, .13826 | .2463 | .2464 | > .001 | .22714, .26314 |
| Spatial Span-Forward | .7497 | .7483 | > .001 | .70203, .78845 | -.088 | -.088 | > .001 | -.10901, -.06539 |
| Spatial Span-Backward | .5714 | .5704 | > .001 | .5091, .6253 | -.0579 | -.0577 | > .001 | -.07788, -.03267 |
| DPX-Correct RT | -.1597 | -.1595 | > .001 | -.19736, -.12557 | -.0499 | -.0499 | > .001 | -.07038, -.03035 |
| DPX- D-Prime | .4568 | .456 | > .001 | .41878, .49229 | .0853 | .0854 | > .001 | .06049, .10599 |
| DPX- AX-BY | -.035 | -.0352 | > .001 | -.08869, .01678 | -.1219 | -.122 | > .001 | -.14534, -.0983 |
| Antisaccade ER | -.4017 | -.4007 | > .001 | -.46181, -.33681 | -.1641 | -.164 | > .001 | -.18358, -.14378 |
| Antisaccade Correct RT | -.177 | -.1768 | > .001 | -.22737, -.12955 | -.1547 | -.1547 | > .001 | -.17707, -.13625 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables**

| | Pair 1-GMV | | | | Pair 2-GMV | | | | Pair 3- GMV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Left caudal middle frontal | .3334 | .3331 | > .001 | .31668, .34955 | .1143 | .114 | > .001 | .07094, .14866 | -.2114 | -.2054 | > .001 | -.26752, .17368 |
| Left frontal pole | .2374 | .2372 | > .001 | .22604, .24806 | .0234 | .0234 | > .001 | .00617, .03959 | -.0578 | -.0559 | > .001 | -.0741, .05084 |
| Left lateral orbitofrontal | .2167 | .2165 | > .001 | .20103, .23084 | .168 | .1675 | > .001 | .13454, .19567 | -.2061 | -.1996 | > .001 | -.24389, .19423 |
| Left medial orbitofrontal | .1686 | .1685 | > .001 | .15068, .18297 | .2753 | .2746 | > .001 | .2479, .29527 | -.1932 | -.1864 | > .001 | -.22463, .19787 |
| Left paracentral | -.1326 | -.1326 | > .001 | -.14591, -.11849 | -.0704 | -.0702 | > .001 | -.09383, -.04787 | -.1134 | -.1103 | > .001 | -.14293, .09256 |
| Left pars opercularis | .2184 | .2182 | > .001 | .20417, .23069 | .1736 | .1732 | > .001 | .15128, .19201 | .0065 | .0061 | > .001 | -.03797, .05365 |
| Left pars orbitalis | .197 | .1969 | > .001 | .17958, .21327 | .072 | .0717 | > .001 | .02831, .11102 | -.3825 | -.37 | > .001 | -.40501, .37665 |
| Left pars triangularis | .218 | .2179 | > .001 | .19734, .23543 | .3778 | .3769 | > .001 | .35859, .39235 | -.0018 | -.001 | > .001 | -.04651, .04351 |
| Left pre-central | .3136 | .3134 | > .001 | .29625, .33231 | .2414 | .2408 | > .001 | .19857, .27736 | -.32 | -.3091 | > .001 | -.35939, .31919 |
| Left rostral middle frontal | .2034 | .2034 | > .001 | .18605, .2193 | .2813 | .2806 | > .001 | .24214, .31084 | -.2924 | -.2825 | > .001 | -.33111, .29146 |
| Left superior frontal | .3153 | .3152 | > .001 | .29759, .33126 | .3175 | .3165 | > .001 | .28346, .34301 | -.2542 | -.2453 | > .001 | -.28785, .26085 |
| Right caudal middle frontal | .0042 | .0042 | > .001 | -.01481, .0195 | .263 | .2624 | > .001 | .22466, .2899 | -.2413 | -.2337 | > .001 | -.28459, .22777 |
| Right frontal pole | -.0401 | -.0401 | > .001 | -.05351, -.02802 | .0979 | .0978 | > .001 | .0763, .11495 | -.0797 | -.0775 | > .001 | -.1056, .06629 |
| Right lateral orbitofrontal | .1646 | .1645 | > .001 | .14429, .18173 | .3066 | .3058 | > .001 | .2638, .33563 | -.3078 | -.298 | > .001 | -.35042, .29101 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables**

| | Pair 1-GMV | | | | Pair 2-GMV | | | | Pair 3- GMV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right medial orbitofrontal | .06 | .06 | > .001 | .0431, .07517 | .3142 | .3134 | > .001 | .28988, .33189 | -.1451 | -.1402 | > .001 | -.18372, .14525 |
| Right paracentral | .1921 | .1919 | > .001 | .18026, .2034 | .1636 | .1632 | > .001 | .14573, .17943 | .0363 | .0351 | > .001 | -.02622, .06745 |
| Right pars opercularis | .3658 | .3655 | > .001 | .35018, .38001 | .2396 | .239 | > .001 | .21076, .26401 | -.1364 | -.1316 | > .001 | -.17611, .14044 |
| Right pars orbitalis | .3825 | .3822 | > .001 | .36572, .39937 | .2435 | .2429 | > .001 | .20042, .2743 | -.2744 | -.2657 | > .001 | -.31306, .2557 |
| Right pars triangularis | .2984 | .2983 | > .001 | .28577, .31197 | .1201 | .1197 | > .001 | .08827, .14402 | -.2116 | -.2044 | > .001 | -.23332, .20981 |
| Right pre-central | .3371 | .3369 | > .001 | .32028, .35272 | .2594 | .2587 | > .001 | .22553, .28494 | -.183 | -.1766 | > .001 | -.22377, .19047 |
| Right rostral middle frontal | .2521 | .252 | > .001 | .2366, .26656 | .2469 | .2462 | > .001 | .21806, .26789 | -.173 | -.1673 | > .001 | -.20829, .16307 |
| Right superior frontal | .3447 | .3445 | > .001 | .32671, .36239 | .2636 | .2627 | > .001 | .21614, .29952 | -.3973 | -.3839 | .001 | -.42721, .39595 |
| Left inferior parietal | .1926 | .1925 | > .001 | .17656, .21032 | .161 | .1606 | > .001 | .11311, .19882 | -.3909 | -.378 | > .001 | -.41418, .38441 |
| Left post-central | .2084 | .2083 | > .001 | .19238, .22699 | .2043 | .2038 | > .001 | .16644, .23533 | -.2684 | -.2588 | > .001 | -.30394, .27902 |
| Left precuneus | -.0122 | -.0121 | > .001 | -.03128, .00756 | .378 | .377 | > .001 | .34646, .40047 | -.2279 | -.2201 | > .001 | -.2668, .23778 |
| Left superior parietal | .4828 | .4825 | > .001 | .47235, .49271 | .1127 | .1122 | > .001 | .08866, .13602 | -.0371 | -.0351 | > .001 | -.05951, .0502 |
| Left supramarginal | -.0942 | -.094 | > .001 | -.11144, -.07787 | .3045 | .3039 | > .001 | .28261, .32212 | -.1293 | -.1252 | > .001 | -.1728, .12229 |
| Right inferior parietal | .15 | .15 | > .001 | .12869, .17033 | .4021 | .4012 | > .001 | .36805, .4275 | -.247 | -.238 | > .001 | -.29268, .26234 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables**

| | Pair 1-GMV | | | | Pair 2-GMV | | | | Pair 3- GMV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right post-central | .1842 | .1841 | > .001 | .16955, .20224 | .073 | .0726 | > .001 | .04124, .10407 | -.2706 | -.2613 | > .001 | -.29161, .27325 |
| Right precuneus | .0368 | .0368 | > .001 | .02069, .05322 | .2765 | .2758 | > .001 | .24405, .30235 | -.2691 | -.26 | > .001 | -.30092, .27062 |
| Right superior parietal | .4157 | .4154 | > .001 | .40427, .42686 | .0697 | .0694 | > .001 | .04484, .09294 | -.1186 | -.1143 | > .001 | -.1382, .1189 |
| Right supramarginal | .23 | .2298 | > .001 | .21467, .24374 | .0931 | .0927 | > .001 | .05328, .12808 | -.3407 | -.3297 | > .001 | -.36573, .32615 |
| Left bank of STS | .0217 | .0217 | > .001 | .00382, .04175 | .263 | .2624 | > .001 | .2212, .2986 | -.3781 | -.3652 | > .001 | -.40406, .3853 |
| Left entorhinal | .1789 | .1788 | > .001 | .16225, .19203 | .1685 | .168 | > .001 | .14177, .19501 | -.1887 | -.1821 | > .001 | -.2123, .19306 |
| Left fusiform | .1715 | .1714 | > .001 | .15428, .18797 | .3174 | .3166 | > .001 | .29079, .33695 | -.1483 | -.1429 | > .001 | -.18529, .16161 |
| Left inferior temporal | -.071 | -.071 | > .001 | -.09271, -.05188 | .3684 | .3677 | > .001 | .34152, .38462 | -.0096 | -.0094 | > .001 | -.06057, .04829 |
| Left insula | .1324 | .1325 | > .001 | .11288, .15311 | .3254 | .3244 | > .001 | .28413, .35637 | -.3403 | -.3282 | > .001 | -.37376, .36047 |
| Left middle temporal | .2332 | .2331 | > .001 | .21263, .2518 | .2625 | .2618 | > .001 | .21663, .3035 | -.363 | -.3508 | > .001 | -.40288, .3621 |
| Left parahippocampal | .1015 | .1015 | > .001 | .08669, .11616 | .2127 | .2121 | > .001 | .18861, .23155 | .0023 | .0027 | > .001 | -.03585, .04672 |
| Left superior temporal | -.0137 | -.0137 | > .001 | -.03032, .00362 | .3075 | .3068 | > .001 | .2775, .33016 | -.1963 | -.1895 | > .001 | -.23757, .2029 |
| Left temporal pole | .1981 | .1979 | > .001 | .18274, .21172 | .0255 | .0254 | > .001 | -.00646, .05413 | -.1523 | -.1483 | > .001 | -.19834, .11453 |
| Left transverse temporal | .2013 | .2012 | > .001 | .1863, .21535 | .1915 | .1909 | > .001 | .17146, .21003 | .0386 | .0381 | > .001 | -.00938, .07152 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables**

| | Pair 1-GMV | | | | Pair 2-GMV | | | | Pair 3- GMV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right bank of STS | .0318 | .0319 | > .001 | .01643, .04767 | .2702 | .2696 | > .001 | .25217, .28807 | -.0922 | -.0885 | > .001 | -.12106, .10797 |
| Right entorhinal | .0365 | .0364 | > .001 | .02401, .04785 | .0466 | .0464 | > .001 | .02809, .06568 | -.1037 | -.1001 | > .001 | -.1258, .09656 |
| Right fusiform | -.0235 | -.0234 | > .001 | -.04066, -.00675 | .3089 | .3082 | > .001 | .28558, .33054 | -.1517 | -.1461 | > .001 | -.18928, .16638 |
| Right inferior temporal | .2136 | .2135 | > .001 | .19607, .2316 | .2774 | .2766 | > .001 | .25007, .29948 | -.1716 | -.1655 | > .001 | -.2076, .17984 |
| Right insula | .0005 | .0006 | > .001 | -.01818, .02136 | .3121 | .3112 | > .001 | .27215, .34303 | -.3451 | -.3331 | > .001 | -.37656, .36009 |
| Right middle temporal | .2567 | .2566 | > .001 | .23598, .27616 | .383 | .3821 | > .001 | .34342, .41497 | -.2812 | -.2715 | > .001 | -.32807, .29059 |
| Right parahippocampal | .1096 | .1096 | > .001 | .09194, .12684 | .3326 | .3317 | > .001 | .31532, .34863 | -.0147 | -.0136 | > .001 | -.05285, .03696 |
| Right superior temporal | .1659 | .1657 | > .001 | .15189, .17886 | .1646 | .1642 | > .001 | .13613, .18716 | -.1678 | -.1623 | > .001 | -.20445, .16094 |
| Right temporal pole | .0823 | .0822 | > .001 | .0687, .09544 | -.0151 | -.0151 | > .001 | -.04323, .01275 | -.2339 | -.2267 | > .001 | -.25834, .21492 |
| Right transverse temporal | .239 | .2389 | > .001 | .22766, .25167 | .133 | .1325 | > .001 | .10931, .15506 | -.1456 | -.1405 | > .001 | -.16412, .15489 |
| Left cuneus | .2781 | .2781 | > .001 | .26007, .29512 | .2961 | .2952 | > .001 | .26992, .3186 | -.1666 | -.1605 | > .001 | -.20574, .17155 |
| Left lateral occipital | .072 | .072 | > .001 | .05225, .09269 | .408 | .407 | > .001 | .37558, .43041 | -.2145 | -.2071 | > .001 | -.25995, .21235 |
| Left lingual | .2185 | .2185 | > .001 | .20011, .23701 | .2918 | .291 | > .001 | .26689, .31644 | -.177 | -.1703 | > .001 | -.20521, .20027 |
| Left pericalcarine | .2083 | .2082 | > .001 | .1898, .22538 | .3766 | .3757 | > .001 | .35801, .39322 | -.0008 | -.0003 | > .001 | -.04815, .04445 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables**

| | Pair 1-GMV | | | | Pair 2-GMV | | | | Pair 3- GMV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right cuneus | .1874 | .1873 | > .001 | .1715, .20075 | .2456 | .2449 | > .001 | .22861, .2615 | .0215 | .0213 | > .001 | -.01487, .0526 |
| Right lateral occipital | .3464 | .3461 | > .001 | .32986, .36153 | .2554 | .2547 | > .001 | .22599, .27991 | -.1633 | -.1577 | > .001 | -.20354, .16011 |
| Right lingual | .2067 | .2067 | > .001 | .18904, .2239 | .3287 | .3278 | > .001 | .30641, .34908 | -.0546 | -.0515 | > .001 | -.09137, .09276 |
| Right pericalcarine | .102 | .102 | > .001 | .084, .11871 | .3771 | .3762 | > .001 | .3596, .39351 | .0788 | .077 | > .001 | -.04063, .11654 |
| Left caudal anterior cingulate | -.0579 | -.0577 | > .001 | -.0724, -.04533 | .1418 | .1414 | > .001 | .11703, .16019 | -.1656 | -.16 | > .001 | -.18919, .16108 |
| Left isthmus cingulate | .1393 | .1393 | > .001 | .11888, .16211 | .3937 | .3927 | > .001 | .36665, .41821 | -.1786 | -.1718 | > .001 | -.22073, .19801 |
| Left posterior cingulate | .177 | .177 | > .001 | .16464, .19116 | .1166 | .1162 | > .001 | .09362, .13446 | -.0946 | -.0912 | > .001 | -.12179, .10164 |
| Left rostral anterior cingulate | .2289 | .2288 | > .001 | .21485, .24125 | .175 | .1744 | > .001 | .15444, .19195 | -.1072 | -.1031 | > .001 | -.13237, .1179 |
| Right caudal anterior cingulate | .2268 | .2267 | > .001 | .21299, .24097 | .1821 | .1815 | > .001 | .15963, .20339 | -.1341 | -.1292 | > .001 | -.15989, .1493 |
| Right isthmus cingulate | .129 | .129 | > .001 | .11369, .14676 | .1659 | .1653 | > .001 | .12746, .20186 | -.3187 | -.3076 | > .001 | -.34153, .32879 |
| Right posterior cingulate | .1388 | .1388 | > .001 | .12624, .1527 | .0621 | .0617 | > .001 | .03629, .08632 | -.0875 | -.0837 | > .001 | -.12498, .10955 |
| Right rostral anterior cingulate | .3297 | .3295 | > .001 | .31335, .34466 | .2332 | .2325 | > .001 | .20777, .25343 | -.126 | -.1215 | > .001 | -.15788, .12921 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 1-CT | | | | Pair 2-CT | | | | Pair 1-CSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Left caudal middle frontal | .3483 | .4178 | > .001 | .40283, .43221 | -.0762 | -.2572 | > .001 | -.28162, -.23246 | -.3919 | -.05524 | > .001 | -.07182, -.03982 |
| Left frontal pole | .0572 | .214 | > .001 | .20436, .22504 | .2591 | -.049 | > .001 | -.06726, -.03065 | .0771 | -.05763 | > .001 | -.06766, -.04705 |
| Left lateral orbitofrontal | -.0642 | .1265 | > .001 | .10903, .14413 | .0327 | -.2646 | > .001 | -.28667, -.2447 | -.0723 | -.38365 | > .001 | -.39698, -.36662 |
| Left medial orbitofrontal | -.0401 | .1797 | > .001 | .16757, .19105 | .1017 | -.1218 | > .001 | -.14019, -.1025 | .0708 | -.35418 | > .001 | -.37063, -.33952 |
| Left paracentral | -.0936 | .3156 | > .001 | .29672, .33317 | -.3545 | -.3221 | > .001 | -.34011, -.30307 | -.2914 | -.06119 | > .001 | -.0722, -.04897 |
| Left pars opercularis | -.1722 | .0516 | > .001 | .03327, .0677 | .0767 | -.2842 | > .001 | -.2973, -.27213 | -.0077 | -.11646 | > .001 | -.1296, -.10139 |
| Left pars orbitalis | .1996 | .2695 | > .001 | .25176, .2886 | .1307 | -.2761 | > .001 | -.29799, -.25374 | .1011 | -.3128 | > .001 | -.32714, -.30043 |
| Left pars triangularis | -.0106 | .1649 | > .001 | .14547, .18428 | -.2964 | -.3584 | > .001 | -.37375, -.34222 | .0662 | .00359 | > .001 | -.01678, .02596 |
| Left pre-central | .0514 | .2116 | > .001 | .19591, .22731 | .0704 | -.2769 | > .001 | -.29181, -.26201 | -.1998 | -.09444 | > .001 | -.11131, -.07572 |
| Left rostral middle frontal | -.188 | .2211 | > .001 | .20588, .23707 | -.3233 | -.2475 | > .001 | -.26718, -.22843 | -.3098 | -.32151 | > .001 | -.33748, -.3035 |
| Left superior frontal | .0874 | .3041 | > .001 | .28817, .3206 | -.2858 | -.2736 | > .001 | -.29546, -.25066 | -.3605 | -.37091 | > .001 | -.38537, -.3529 |
| Right caudal middle frontal | .046 | .4831 | > .001 | .46424, .50027 | -.203 | -.3387 | > .001 | -.36692, -.30939 | -.0552 | -.39167 | > .001 | -.40428, -.37769 |
| Right frontal pole | .1702 | .2535 | > .001 | .23891, .26763 | -.1012 | -.222 | > .001 | -.24064, -.20472 | -.0576 | .077 | > .001 | .0652, .08887 |
| Right lateral orbitofrontal | -.0729 | .185 | > .001 | .16293, .20573 | -.1088 | -.3686 | > .001 | -.38874, -.34461 | -.384 | -.18464 | > .001 | -.20269, -.16382 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 1-CT | | | | Pair 2-CT | | | | Pair 1-CSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right medial orbitofrontal | .0645 | .0809 | > .001 | .06789, .09453 | .329 | -.1756 | > .001 | -.19176, -.16095 | -.3544 | .0709 | > .001 | .05517, .08761 |
| Right paracentral | .1335 | .3189 | > .001 | .30605, .33249 | .2162 | -.1891 | > .001 | -.20736, -.16862 | -.0612 | -.29114 | > .001 | -.30446, -.27693 |
| Right pars opercularis | -.228 | .0277 | > .001 | .00423, .05065 | -.2093 | -.4591 | > .001 | -.47552, -.44419 | -.1165 | -.00774 | > .001 | -.02511, .00952 |
| Right pars orbitalis | .1068 | .1838 | > .001 | .1599, .20679 | -.1823 | -.45 | > .001 | -.46662, -.43281 | -.3131 | .10106 | > .001 | .08161, .12275 |
| Right pars triangularis | .0002 | .2629 | > .001 | .24322, .28313 | .0104 | -.3563 | > .001 | -.37692, -.33401 | .0034 | .06623 | > .001 | .05316, .08097 |
| Right pre-central | .0119 | .3029 | > .001 | .28365, .32203 | -.0849 | -.36 | > .001 | -.38122, -.34067 | -.0945 | -.19964 | > .001 | -.21744, -.18037 |
| Right rostral middle frontal | -.0177 | .2981 | > .001 | .27763, .31638 | -.0261 | -.3309 | > .001 | -.35175, -.3093 | -.3218 | -.30953 | > .001 | -.32474, -.29385 |
| Right superior frontal | .0254 | .3751 | > .001 | .35544, .39385 | .4076 | -.3489 | > .001 | -.37189, -.32517 | -.3712 | -.3602 | > .001 | -.3752, -.33937 |
| Left inferior parietal | .0339 | .066 | > .001 | .04577, .08644 | -.5705 | -.3928 | > .001 | -.40579, -.37977 | -.0462 | -.30033 | > .001 | -.315, -.28425 |
| Left post-central | -.017 | .0617 | > .001 | .04831, .07492 | -.0019 | -.1113 | > .001 | -.12819, -.09618 | -.2296 | -.0172 | > .001 | -.03347, .00563 |
| Left precuneus | .085 | .2584 | > .001 | .24191, .27441 | -.1455 | -.2885 | > .001 | -.30897, -.26907 | -.2331 | -.35207 | > .001 | -.36557, -.33477 |
| Left superior parietal | -.6397 | .0637 | > .001 | .05063, .07765 | .1097 | -.1971 | > .001 | -.21089, -.1853 | -.094 | -.07977 | > .001 | -.09588, -.06216 |
| Left supramarginal | -.092 | -.0837 | > .001 | -.10233, -.06475 | .0725 | -.3423 | > .001 | -.35804, -.32863 | .008 | .00017 | > .001 | -.01182, .0138 |
| Right inferior parietal | .1107 | .2587 | > .001 | .24728, .27177 | .3174 | -.1322 | > .001 | -.15222, -.11309 | -.3006 | -.04611 | > .001 | -.06573, -.02304 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 1-CT | | | | Pair 2-CT | | | | Pair 1-CSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right post-central | .0756 | .3284 | > .001 | .3183, .34037 | .3382 | -.0141 | > .001 | -.03702, .00437 | -.0173 | -.22936 | > .001 | -.2442, -.21311 |
| Right precuneus | .0622 | .3151 | > .001 | .30255, .32849 | .1517 | -.1866 | > .001 | -.20749, -.16607 | -.3524 | -.23287 | > .001 | -.24683, -.21691 |
| Right superior parietal | .5003 | .368 | > .001 | .35729, .38101 | .1343 | -.1195 | > .001 | -.14184, -.09771 | -.0799 | -.09389 | > .001 | -.10958, -.0777 |
| Right supramarginal | .0466 | .2411 | > .001 | .22485, .25818 | -.1496 | -.2786 | > .001 | -.30009, -.25974 | .0001 | .00805 | > .001 | -.00531, .02488 |
| Left bank of STS | -.0403 | .047 | > .001 | .02774, .06802 | -.1632 | -.3679 | > .001 | -.38225, -.355 | -.1024 | -.05392 | > .001 | -.07077, -.03481 |
| Left entorhinal | .0141 | -.0154 | > .001 | -.03024, .00243 | -.28 | -.2256 | > .001 | -.24085, -.20903 | -.0421 | .03615 | > .001 | .02099, .0504 |
| Left fusiform | .0921 | .0274 | > .001 | .01196, .04614 | -.2672 | -.2532 | > .001 | -.27053, -.23581 | -.4235 | .00861 | > .001 | -.00805, .02942 |
| Left inferior temporal | -.2249 | -.0677 | > .001 | -.08155, -.05197 | .2579 | -.1745 | > .001 | -.19388, -.15308 | -.2678 | .05788 | > .001 | .03956, .07436 |
| Left insula | -.0023 | .1715 | > .001 | .1552, .18767 | .0164 | -.2054 | > .001 | -.22583, -.17958 | -.2165 | .00149 | > .001 | -.01469, .0199 |
| Left middle temporal | .0335 | -.1628 | > .001 | -.18135, -.14384 | .0337 | -.3455 | > .001 | -.36303, -.32807 | -.2654 | -.22332 | > .001 | -.24215, -.20551 |
| Left parahippocampal | .0736 | .1351 | > .001 | .11718, .15223 | -.199 | -.2251 | > .001 | -.2464, -.20165 | -.1601 | -.0978 | > .001 | -.11142, -.08355 |
| Left superior temporal | -.1546 | -.0147 | > .001 | -.03054, .00212 | .0873 | -.2754 | > .001 | -.29256, -.25845 | -.0397 | -.18207 | > .001 | -.19666, -.16477 |
| Left temporal pole | -.0011 | .0559 | > .001 | .03965, .07138 | .0185 | -.2503 | > .001 | -.26434, -.23352 | .0061 | .25741 | > .001 | .24284, .26916 |
| Left transverse temporal | .1154 | .2048 | > .001 | .19219, .21773 | .0243 | -.1614 | > .001 | -.17894, -.14288 | .0082 | .10276 | > .001 | .0882, .11755 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 1-CT | | | | Pair 2-CT | | | | Pair 1-CSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right bank of STS | .0189 | .0727 | > .001 | .06041, .08681 | .0428 | -.1682 | > .001 | -.18802, -.15103 | -.054 | -.10225 | > .001 | -.1171, -.08365 |
| Right entorhinal | -.148 | -.2902 | > .001 | -.30244, -.27897 | .2671 | -.0109 | > .001 | -.03257, .01437 | .0362 | -.04212 | > .001 | -.05537, -.02712 |
| Right fusiform | -.0524 | -.0609 | > .001 | -.07383, -.04656 | -.0546 | -.1671 | > .001 | -.18244, -.1499 | .0086 | -.42311 | > .001 | -.43813, -.40774 |
| Right inferior temporal | .1222 | -.0692 | > .001 | -.08197, -.05491 | .3748 | -.0988 | > .001 | -.11915, -.07841 | .0579 | -.26756 | > .001 | -.28403, -.25133 |
| Right insula | .2956 | .2373 | > .001 | .22162, .25373 | .0415 | -.2552 | > .001 | -.27414, -.2334 | .0013 | -.21627 | > .001 | -.22978, -.19972 |
| Right middle temporal | -.3533 | -.2544 | > .001 | -.27298, -.23472 | -.4171 | -.3448 | > .001 | -.36285, -.32365 | -.2235 | -.26517 | > .001 | -.2854, -.24424 |
| Right parahippocampal | -.0992 | -.1621 | > .001 | -.1746, -.15045 | .1857 | -.0791 | > .001 | -.09737, -.05853 | -.0979 | -.15993 | > .001 | -.17655, -.14214 |
| Right superior temporal | .0326 | .0495 | > .001 | .03025, .07018 | -.0781 | -.3439 | > .001 | -.36284, -.32531 | -.1823 | -.03971 | > .001 | -.05156, -.0253 |
| Right temporal pole | .1646 | .1507 | > .001 | .13601, .16543 | -.0973 | -.2278 | > .001 | -.24239, -.21007 | .2576 | .00603 | > .001 | -.00542, .01974 |
| Right transverse temporal | .0061 | -.0701 | > .001 | -.08297, -.05684 | .0558 | -.1428 | > .001 | -.15947, -.12756 | .1028 | .00822 | > .001 | -.00501, .02237 |
| Left cuneus | .0938 | .2197 | > .001 | .2077, .23135 | -.0543 | -.149 | > .001 | -.16649, -.13302 | -.1708 | -.13535 | > .001 | -.15407, -.11523 |
| Left lateral occipital | .3377 | .2718 | > .001 | .26024, .28373 | .7465 | -.1145 | > .001 | -.13467, -.09339 | -.1848 | -.34651 | > .001 | -.36511, -.32595 |
| Left lingual | -.0715 | -.0658 | > .001 | -.07933, -.0506 | .0396 | -.2183 | > .001 | -.23551, -.20211 | .0414 | .011 | > .001 | -.01071, .03356 |
| Left pericalcarine | -.0827 | -.0688 | > .001 | -.08299, -.05523 | -.309 | -.2201 | > .001 | -.23795, -.20541 | .0425 | .07017 | > .001 | .05157, .08992 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 1-CT | | | | Pair 2-CT | | | | Pair 1-CSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right cuneus | -.0004 | .1799 | > .001 | .16942, .18981 | .0276 | .0353 | > .001 | .0201, .04956 | -.1355 | -.17069 | > .001 | -.18946, -.15125 |
| Right lateral occipital | -.3812 | .0234 | > .001 | .01193, .0358 | -.3914 | -.1234 | > .001 | -.14028, -.10845 | -.3468 | -.07227 | > .001 | -.08681, -.05678 |
| Right lingual | .1546 | .1735 | > .001 | .16177, .1839 | -.0284 | -.0633 | > .001 | -.08226, -.0485 | .0109 | .04147 | > .001 | .02016, .06284 |
| Right pericalcarine | -.1312 | -.0569 | > .001 | -.06885, -.04577 | .2401 | .0143 | > .001 | -.00229, .02956 | .0702 | .04251 | > .001 | .02219, .06278 |
| Left caudal anterior cingulate | -.0099 | .1346 | > .001 | .1224, .14867 | -.0858 | -.1165 | > .001 | -.13213, -.09958 | .0275 | -.07421 | > .001 | -.08834, -.06116 |
| Left isthmus cingulate | -.056 | .0899 | > .001 | .07572, .10634 | .0366 | -.1735 | > .001 | -.19516, -.15248 | .0033 | -.01398 | > .001 | -.02876, .00259 |
| Left posterior cingulate | .0545 | .1944 | > .001 | .18054, .20928 | .0261 | -.1937 | > .001 | -.21267, -.17466 | -.2224 | .01114 | > .001 | -.0024, .02392 |
| Left rostral anterior cingulate | -.0967 | .0134 | > .001 | .00176, .02884 | .0988 | -.0818 | > .001 | -.09966, -.06284 | -.2147 | -.26292 | > .001 | -.27423, -.2524 |
| Right caudal anterior cingulate | -.0394 | .1725 | > .001 | .15748, .18661 | -.0217 | -.2071 | > .001 | -.22396, -.18917 | -.0744 | .0275 | > .001 | .01145, .04546 |
| Right isthmus cingulate | .0627 | .1164 | > .001 | .10181, .13175 | -.1742 | -.2475 | > .001 | -.26283, -.23027 | -.0141 | .00335 | > .001 | -.0099, .01794 |
| Right posterior cingulate | -.1808 | .1375 | > .001 | .12021, .15458 | -.1082 | -.2871 | > .001 | -.30486, -.26852 | .011 | -.22221 | > .001 | -.23455, -.20878 |
| Right rostral anterior cingulate | .2277 | .2401 | > .001 | .22192, .25719 | -.2285 | -.2931 | > .001 | -.30942, -.27635 | -.2632 | -.21452 | > .001 | -.23032, -.19792 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 2-CSA | | | | Pair 1-LGI | | | |
|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Left caudal middle frontal | .1726 | .0598 | > .001 | .02808, .09199 | .1382 | .1381 | > .001 | .12488, .15107 |
| Left frontal pole | .1102 | .0096 | > .001 | -.00626, .02489 | .1392 | .1391 | > .001 | .12949, .1478 |
| Left lateral orbitofrontal | .139 | .2485 | > .001 | .22389, .27362 | .1213 | .1212 | > .001 | .10774, .13403 |
| Left medial orbitofrontal | .2509 | .113 | > .001 | .07756, .14811 | .1299 | .1298 | > .001 | .11798, .14291 |
| Left paracentral | .1829 | -.0678 | > .001 | -.08789, -.0498 | -.0148 | -.0148 | > .001 | -.02579, -.00531 |
| Left pars opercularis | .265 | .123 | > .001 | .101, .14597 | -.1159 | -.1158 | > .001 | -.12949, -.10128 |
| Left pars orbitalis | .3468 | .1808 | > .001 | .15854, .20279 | -.2083 | -.2081 | > .001 | -.22215, -.19765 |
| Left pars triangularis | .1816 | .4046 | > .001 | .38393, .4221 | -.2626 | -.2624 | > .001 | -.27359, -.25097 |
| Left pre-central | .312 | .2286 | > .001 | .19871, .25568 | -.0331 | -.0331 | > .001 | -.04368, -.02317 |
| Left rostral middle frontal | .2062 | .2645 | > .001 | .24128, .28623 | .1805 | .1805 | > .001 | .17074, .18952 |
| Left superior frontal | .2522 | .284 | > .001 | .25784, .30863 | .1268 | .1268 | > .001 | .11804, .13533 |
| Right caudal middle frontal | .0599 | .1722 | > .001 | .14491, .19661 | -.0344 | -.0344 | > .001 | -.04611, -.02177 |
| Right frontal pole | .0096 | .1098 | > .001 | .08907, .12608 | -.1422 | -.1422 | > .001 | -.15477, -.12901 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 2-CSA | | | | Pair 1-LGI | | | |
|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right lateral orbitofrontal | .2491 | .1386 | > .001 | .11552, .16326 | -.0964 | -.0964 | > .001 | -.10953, -.08253 |
| Right medial orbitofrontal | .1133 | .2501 | > .001 | .2247, .27221 | -.099 | -.0989 | > .001 | -.11041, -.08784 |
| Right paracentral | -.068 | .1826 | > .001 | .15464, .21005 | -.208 | -.2078 | > .001 | -.22273, -.19464 |
| Right pars opercularis | .1232 | .2643 | > .001 | .24427, .282 | .2885 | .2884 | > .001 | .27547, .30154 |
| Right pars orbitalis | .1812 | .3459 | > .001 | .32162, .36689 | -.2593 | -.2592 | > .001 | -.27272, -.24588 |
| Right pars triangularis | .4056 | .1811 | > .001 | .15934, .19989 | -.0689 | -.0689 | > .001 | -.08085, -.05707 |
| Right pre-central | .2293 | .3113 | > .001 | .29041, .33135 | -.0716 | -.0715 | > .001 | -.08461, -.05912 |
| Right rostral middle frontal | .2651 | .2057 | > .001 | .1747, .23652 | -.1363 | -.1362 | > .001 | -.14906, -.12377 |
| Right superior frontal | .2847 | .2516 | > .001 | .21917, .28658 | .0559 | .0558 | > .001 | .04254, .06771 |
| Left inferior parietal | .4164 | .1452 | > .001 | .12225, .16771 | .0144 | .0144 | > .001 | .00052, .02808 |
| Left post-central | .2014 | .2909 | > .001 | .27028, .31005 | -.0577 | -.0576 | > .001 | -.06984, -.04806 |
| Left precuneus | .2357 | .2879 | > .001 | .26636, .31055 | -.0636 | -.0635 | > .001 | -.07534, -.05129 |
| Left superior parietal | .2624 | .3617 | > .001 | .34356, .37996 | -.0659 | -.0659 | > .001 | -.07738, -.05497 |
| Left supramarginal | .061 | .1691 | > .001 | .15255, .18694 | .1004 | .1003 | > .001 | .08753, .1129 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 2-CSA | | | | Pair 1-LGI | | | |
|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Right inferior parietal | .1454 | .4153 | > .001 | .39543, .43385 | .0138 | .0138 | > .001 | .0005, .02712 |
| Right post-central | .2916 | .2009 | > .001 | .17737, .22375 | -.1898 | -.1897 | > .001 | -.20156, -.17945 |
| Right precuneus | .2887 | .235 | > .001 | .21103, .2594 | -.0368 | -.0368 | > .001 | -.05109, -.02493 |
| Right superior parietal | .3627 | .2616 | > .001 | .24506, .27935 | -.1288 | -.1287 | > .001 | -.14075, -.11692 |
| Right supramarginal | .1697 | .0606 | > .001 | .03875, .08323 | .167 | .167 | > .001 | .15487, .18058 |
| Left bank of STS | .2843 | .2076 | > .001 | .18959, .22564 | .1719 | .1718 | > .001 | .15575, .18544 |
| Left entorhinal | -.1598 | .2064 | > .001 | .18691, .22264 | .1701 | .17 | > .001 | .15701, .18701 |
| Left fusiform | .2442 | .361 | > .001 | .34162, .37834 | .1137 | .1136 | > .001 | .10245, .1249 |
| Left inferior temporal | .2178 | .2345 | > .001 | .21055, .25469 | .1132 | .1132 | > .001 | .10267, .12337 |
| Left insula | .1881 | .2098 | > .001 | .18646, .23125 | .0425 | .0425 | > .001 | .02715, .05703 |
| Left middle temporal | .3514 | .2283 | > .001 | .20544, .25076 | .1314 | .1313 | > .001 | .12087, .14114 |
| Left parahippocampal | .2848 | .1458 | > .001 | .11858, .16957 | -.2535 | -.2533 | > .001 | -.26483, -.23934 |
| Left superior temporal | .1252 | .2397 | > .001 | .22066, .25724 | .1189 | .1189 | > .001 | .10696, .13308 |
| Left temporal pole | -.0266 | .0841 | > .001 | .06172, .11342 | .1492 | .1492 | > .001 | .13771, .16311 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 2-CSA | | | | Pair 1-LGI | | | |
|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Left transverse temporal | .1071 | .2531 | > .001 | .23489, .26948 | .1494 | .1493 | > .001 | .13465, .16396 |
| Right bank of STS | .2081 | .2837 | > .001 | .26828, .30172 | .0611 | .0611 | > .001 | .04676, .07515 |
| Right entorhinal | .207 | -.1594 | > .001 | -.17746, -.14155 | .2054 | .2053 | > .001 | .19211, .21917 |
| Right fusiform | .3621 | .2436 | > .001 | .21922, .26643 | .1881 | .1881 | > .001 | .17472, .20136 |
| Right inferior temporal | .2351 | .2173 | > .001 | .19677, .2394 | .1992 | .1992 | > .001 | .18744, .21058 |
| Right insula | .2105 | .1875 | > .001 | .1668, .20772 | .2124 | .2123 | > .001 | .19952, .22592 |
| Right middle temporal | .2287 | .3506 | > .001 | .32823, .37277 | .0935 | .0935 | > .001 | .0811, .10565 |
| Right parahippocampal | .1462 | .2841 | > .001 | .26565, .30206 | .1816 | .1815 | > .001 | .16785, .19514 |
| Right superior temporal | .2404 | .1249 | > .001 | .10055, .14549 | .0621 | .0621 | > .001 | .047, .07681 |
| Right temporal pole | .0844 | -.0265 | > .001 | -.04269, -.00885 | .1835 | .1834 | > .001 | .16949, .19687 |
| Right transverse temporal | .2539 | .1067 | > .001 | .08647, .12487 | .074 | .074 | > .001 | .05789, .08925 |
| Left cuneus | .3012 | .3163 | > .001 | .27506, .35443 | -.1447 | -.1445 | > .001 | -.15959, -.13148 |
| Left lateral occipital | .2462 | .3147 | > .001 | .27806, .35344 | -.0858 | -.0857 | > .001 | -.09982, -.07189 |
| Left lingual | .4804 | .426 | > .001 | .40298, .44332 | -.054 | -.054 | > .001 | -.06955, -.04066 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.5b Jackknife results-Structural Variables cont.**

| | Pair 2-CSA | | | | Pair 1-LGI | | | |
|---|---|---|---|---|---|---|---|---|
| | Original Loading | Jackknife Estimate | Std. Error | 99% CLM | Original Loading | Jackknife Estimate | Std. Error | 99% CLM |
| Left pericalcarine | .4354 | .4082 | > .001 | .39032, .42766 | -.0451 | -.045 | > .001 | -.0594, -.03112 |
| Right cuneus | .3172 | .3004 | > .001 | .26325, .3367 | -.0798 | -.0797 | > .001 | -.09468, -.06624 |
| Right lateral occipital | .3156 | .2455 | > .001 | .21041, .28288 | -.0577 | -.0576 | > .001 | -.07142, -.04499 |
| Right lingual | .4272 | .4791 | > .001 | .45736, .49789 | -.0216 | -.0215 | > .001 | -.03465, -.00917 |
| Right pericalcarine | .4094 | .4342 | > .001 | .41302, .45215 | -.0682 | -.0681 | > .001 | -.08219, -.05519 |
| Left caudal anterior cingulate | .2746 | .0632 | > .001 | .03951, .08465 | .1031 | .1031 | > .001 | .09266, .11242 |
| Left isthmus cingulate | .0732 | .1965 | > .001 | .17561, .21667 | -.0075 | -.0075 | > .001 | -.02092, .00513 |
| Left posterior cingulate | .0704 | .1658 | > .001 | .14524, .18253 | .1081 | .1081 | > .001 | .09681, .11778 |
| Left rostral anterior cingulate | .2609 | .0954 | > .001 | .07096, .11635 | .1062 | .1061 | > .001 | .09299, .11798 |
| Right caudal anterior cingulate | .0634 | .2738 | > .001 | .25241, .2927 | .106 | .1058 | > .001 | .09401, .11715 |
| Right isthmus cingulate | .1972 | .0728 | > .001 | .04467, .10153 | .0779 | .0779 | > .001 | .06414, .09183 |
| Right posterior cingulate | .1663 | .0703 | > .001 | .02531, .11162 | .1751 | .1749 | > .001 | .16217, .18629 |
| Right rostral anterior cingulate | .0957 | .2603 | > .001 | .23618, .28295 | .0672 | .0672 | > .001 | .05496, .07795 |

Estimates from the CCA analyses on the original sample with estimates, standard error, and 99% confidence intervals from the jackknife procedure. Jackknife estimates and confidence limits are based on 10,000 replicates samples of leave two observations out.

**Supplement Table 3.6 Effects of Multiple Testing Corrections**

| | Pair-wise Comparisons | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HC vs. BP-like | | HC vs. SAD-like | | HC vs. SZ-like | | BP-like vs. SAD-like | | BP-like vs. SZ-like | | SZ-like vs. SAD-like | |
| **Cognitive Variates** | Raw | Adj. | Raw | Adj. | Raw | Adj. | Raw | Adj. | Raw | Adj. | Raw | Adj. |
| Pair 1 GMV | .03[a] | .93[a] | < .001 | < .001 | < .001 | < .001 | < .001 | .02 | < .001 | < .001 | .01[a] | .43[a] |
| Pair 1 CT | .16 | .93 | .008[a] | .38[a] | < .001 | < .001 | < .001 | .02 | < .001 | < .001 | .10 | .93 |
| Pair 1 CSA | .70 | .93 | < .001 | .02 | < .001 | < .001 | < .001 | .03 | < .001 | < .001 | .17 | .93 |
| Pair 1 LGI | .55 | .93 | < .001 | .01 | < .001 | < .001 | .006[a] | .27[a] | < .001 | < .001 | .03[a] | .93[a] |
| Pair 2 GMV | < .001 | < .001 | < .001 | .03 | < .001 | < .001 | .07 | .93 | .40[a] | .93[a] | .005[a] | .25[a] |
| Pair 2 CT | .17 | .93 | .03[a] | .93[a] | < .001 | < .001 | .52 | .93 | .001[a] | .07[a] | .01[a] | .43[a] |
| Pair 2 CSA | < .001 | < .001 | < .001 | .003 | < .001 | < .001 | .46 | .93 | .27 | .93 | .06 | .93 |
| **Structural Variates** | Raw | Adj. | Raw | Adj. | Raw | Adj. | Raw | Adj. | Raw | Adj. | Raw | Adj. |
| Pair 1 GMV | .68 | .93 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | < .001 | .39 | .93 |
| Pair 1 CT | .42 | .93 | < .001 | .01 | < .001 | < .001 | < .001 | .004 | < .001 | < .001 | .51 | .93 |
| Pair 1 CSA | .61 | .93 | .004[a] | .17[a] | < .001 | .02 | .04[a] | .93[a] | .009[a] | .40[a] | .66 | .93 |
| Pair 1 LGI | .60 | .93 | < .001 | .008 | < .001 | < .001 | .004[a] | .17[a] | < .001 | .03 | .69 | .93 |
| Pair 2 GMV | .10 | .93 | .08 | .93 | < .001 | < .001 | .93 | .93 | .02[a] | .85[a] | .03[a] | .93[a] |
| Pair 2 CT | .15 | .93 | .03[a] | .93[a] | < .001 | .04 | .53 | .93 | .10 | .93 | .31 | .93 |

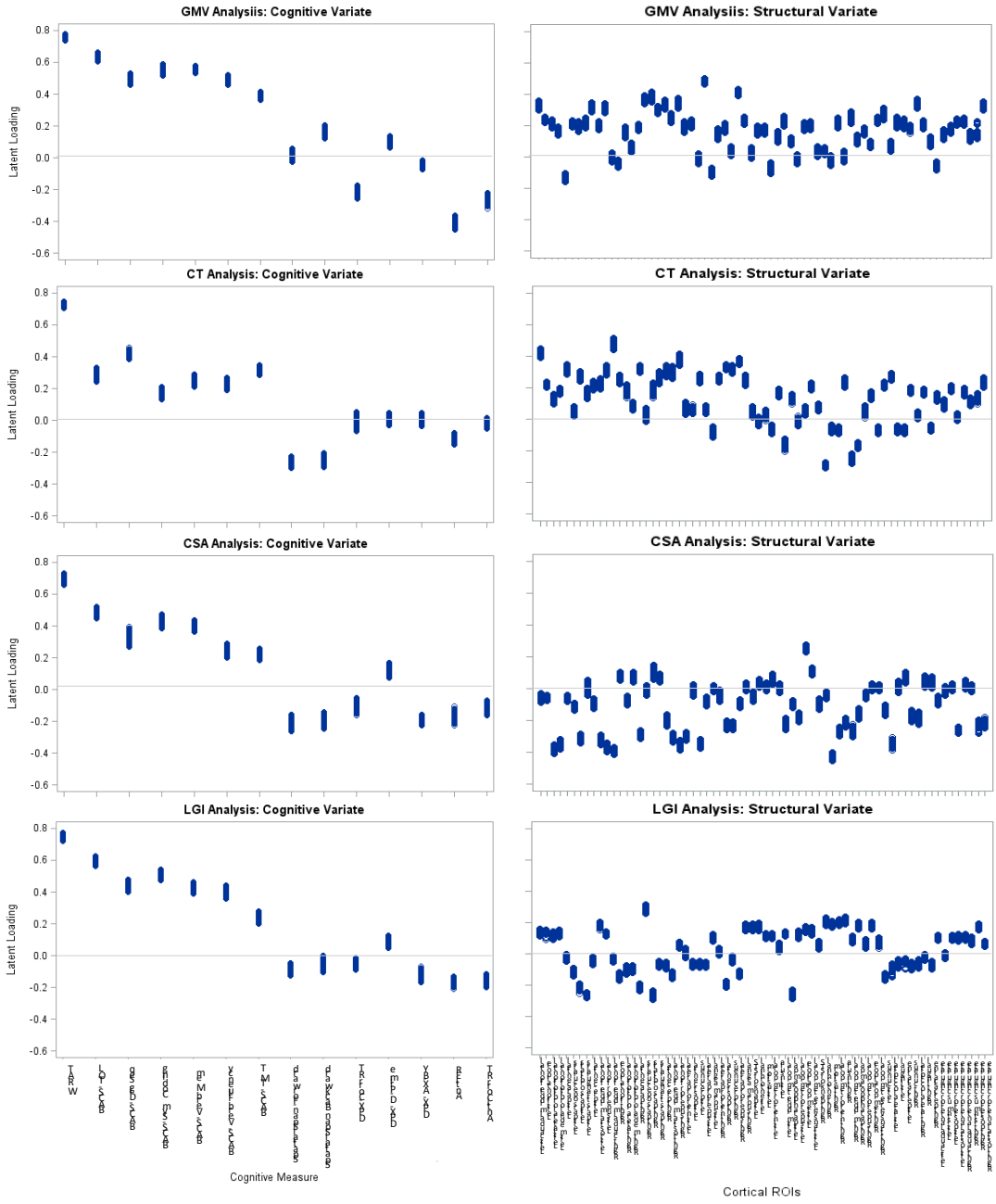
Raw and adjusted p-values for pair-wise comparisons. Adjusted p-values were obtained with Hochberg's correction. P-values for the cognitive and structural variate in Pair 2 CSA are not reported because the omnibus effect failed to reach significance. HC= Healthy Controls; BP= Bipolar; SAD= Schizoaffective; SZ= Schizophrenia.
[a]Comparison was not significant after Hochberg correction.

**Supplement Table 3.7 Symptom and Anti-Psychotic Medication Effects on CCA Latent Variables**

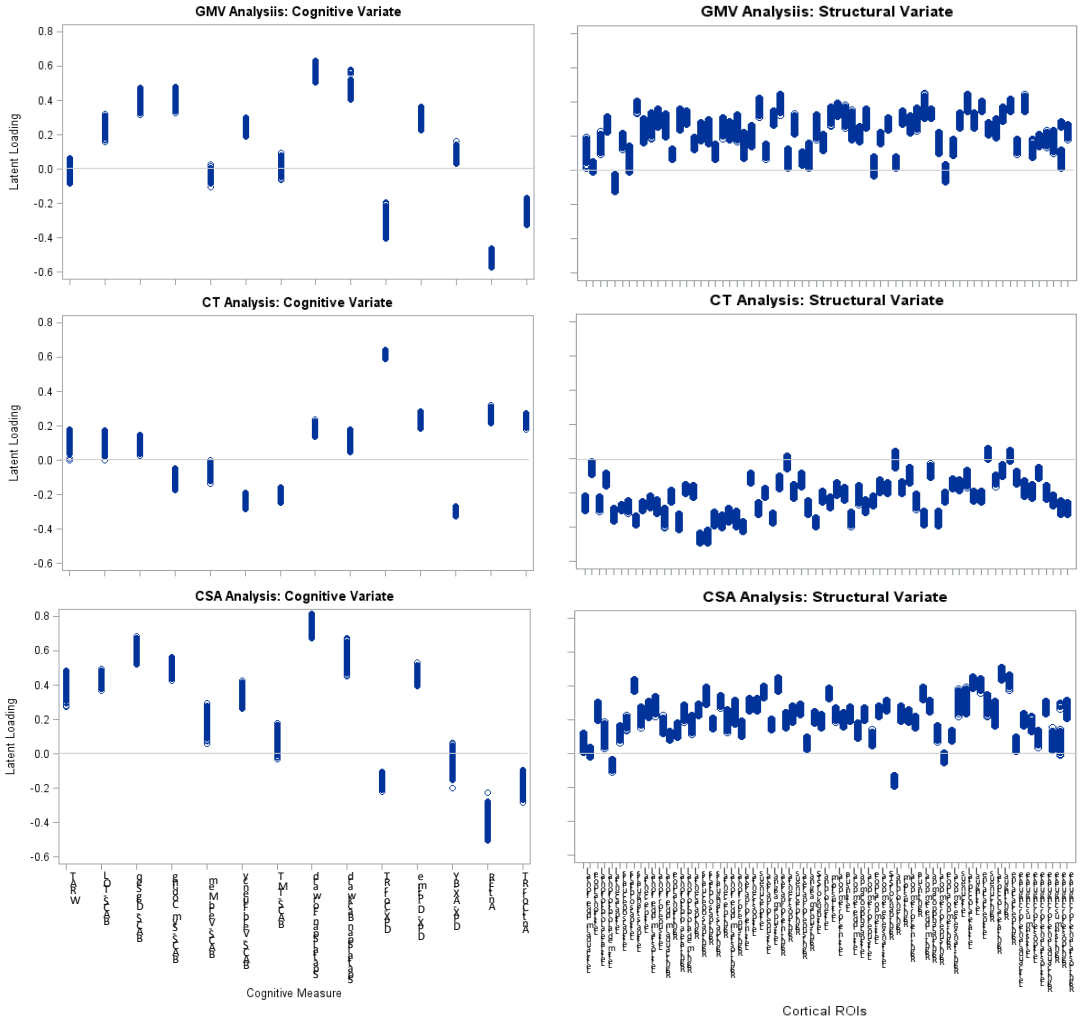
| | PANSS Total | | | PANSS pos | | | PANSS neg | | | YMRS | | | MADRS | | | CPZ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cognitive Variates** | β | p | $\eta^2$ | β | p | $\eta^2$ | β | p | $\eta^2$ | β | p | $\eta^2$ | β | p | $\eta^2$ | β | p | $\eta^2$ |
| Pair 1 GMV | -0.009 | .005 | 0.02 | -0.026 | .005 | 0.02 | -0.035 | <.001[a] | 0.03 | < 0.001 | .95 | < 0.01 | 0.005 | .38 | < 0.01 | < 0.001 | .01 | 0.02 |
| Pair 1 CT | -0.007 | .02 | 0.01 | -0.031 | .001[a] | 0.03 | -0.019 | .04 | 0.01 | -0.007 | .40 | < 0.01 | 0.008 | .17 | < 0.01 | < 0.001 | .02 | 0.02 |
| Pair 1 CSA | -0.006 | .05 | 0.01 | -0.021 | .02 | 0.01 | -0.020 | .04 | 0.01 | < 0.001 | .95 | < 0.01 | 0.006 | .29 | < 0.01 | < 0.001 | .05 | 0.01 |
| Pair 1 LGI | -0.007 | .04 | 0.01 | -0.018 | .06 | 0.01 | -0.024 | .01 | 0.02 | < 0.001 | 1.00 | < 0.01 | 0.006 | .25 | < 0.01 | < 0.001 | .04 | 0.02 |
| Pair 2 GMV | 0.001 | .78 | < 0.01 | 0.004 | .62 | < 0.01 | -0.008 | .39 | < 0.01 | 0.004 | .65 | < 0.01 | 0.005 | .37 | < 0.01 | < 0.001 | .65 | < 0.01 |
| Pair 2 CT | 0.004 | .27 | < 0.01 | < 0.001 | 1.00 | < 0.01 | 0.025 | .01 | 0.02 | -0.020 | .02 | 0.01 | < 0.001 | .93 | < 0.01 | < 0.001 | .03 | 0.02 |
| Pair 2 CSA | -0.003 | .35 | < 0.01 | -0.009 | .30 | < 0.01 | -0.012 | .17 | < 0.01 | -0.008 | .29 | < 0.01 | 0.003 | .50 | < 0.01 | < 0.001 | .87 | < 0.01 |
| Pair 3 GMV | 0.002 | .57 | < 0.01 | 0.019 | .04 | 0.01 | 0.004 | .68 | < 0.01 | -0.001 | .93 | < 0.01 | -0.009 | .10 | 0.01 | < 0.001 | .12 | 0.01 |
| **Structural Variates** | | | | | | | | | | | | | | | | | | |
| Pair 1 GMV | -0.007 | .02 | 0.01 | -0.030 | .00 | 0.02 | -0.026 | .01 | 0.02 | -0.002 | .78 | < 0.01 | -0.002 | .68 | < 0.01 | < 0.001 | .17 | 0.01 |
| Pair 1 CT | -0.008 | .02 | 0.01 | -0.028 | .00 | 0.04 | -0.018 | .07 | < 0.01 | 0.003 | .72 | < 0.01 | -0.003 | .53 | < 0.01 | < 0.001 | .13 | < 0.01 |
| Pair 1 CSA | -0.007 | .02 | 0.01 | -0.036 | <.001[a] | 0.02 | -0.009 | .35 | 0.01 | 0.006 | .49 | < 0.01 | -0.001 | .87 | < 0.01 | < 0.001 | .94 | 0.01 |
| Pair 1 LGI | -0.008 | .01 | 0.02 | -0.022 | .014 | 0.02 | -0.018 | .05 | 0.01 | -0.006 | .44 | < 0.01 | 0.001 | .90 | < 0.01 | < 0.001 | .83 | < 0.01 |
| Pair 2 GMV | -0.003 | .28 | < 0.01 | -0.009 | .32 | < 0.01 | -0.020 | .02 | 0.01 | -0.002 | .84 | < 0.01 | -0.002 | .68 | < 0.01 | < 0.001 | .18 | 0.01 |
| Pair 2 CT | -0.006 | .07 | 0.01 | -0.013 | .15 | 0.01 | -0.002 | .82 | < 0.01 | -0.015 | .08 | 0.01 | -0.014 | .01 | 0.02 | 0.001 | .002[a] | 0.03 |
| Pair 2 CSA | -0.004 | .16 | < 0.01 | -0.017 | .06 | 0.01 | -0.012 | .17 | < 0.01 | -0.007 | .35 | < 0.01 | -0.010 | .06 | 0.01 | < 0.001 | .16 | 0.01 |
| Pair 3 GMV | 0.002 | .57 | < 0.01 | 0.021 | .02 | 0.01 | 0.002 | .80 | < 0.01 | -0.008 | .33 | < 0.01 | -0.010 | .06 | 0.01 | < 0.001 | .88 | < 0.01 |

**Supplement Figure 3.1** *Results of the Jackknife Procedure.* Plots show distribution of canonical loadings of individual measures across the 10,000 jackknife replicates for CCA pair 1, pair 2, and pair 3. Reference lines are placed at zero to distinguish which individual measures included zero within the 99% confidence limits and those that did not. This along with the information located in Supplement Tables 5a-b were used to select CCA pairs for further interpretation and analysis. WRAT = Wide Range Achievement Test; BACS = Brief Assessment of Cognition in Schizophrenia; TOL = Tower of London; Dig Seq = Digit Sequencing, Sym Coding = Symbol Coding; Verb Memory = Verbal Memory; Verb Fluency = Verbal Fluency; TMT = Token Motor Task; DPX = Dot Probe Task; Anti = Antisaccade; ER = Error Rate; Corr RT = Correct Reaction Time

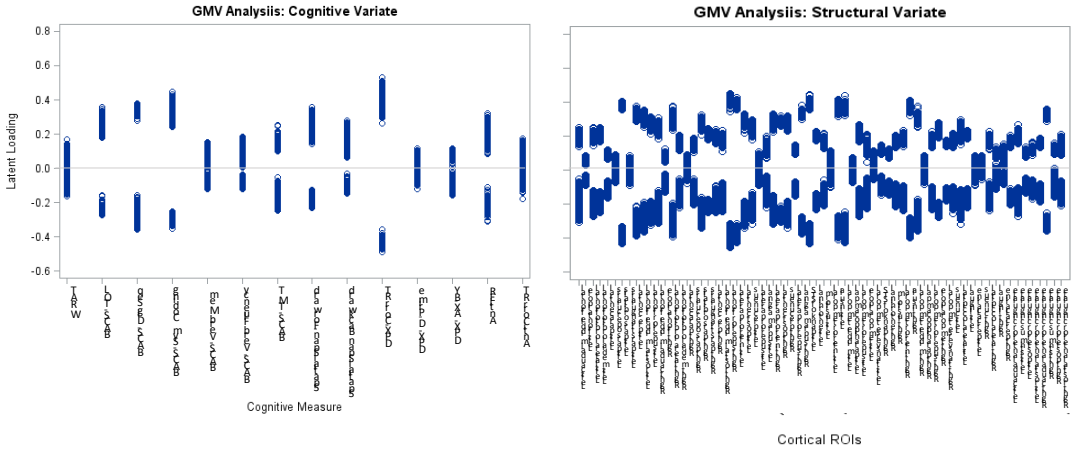
# CCA Pair 1

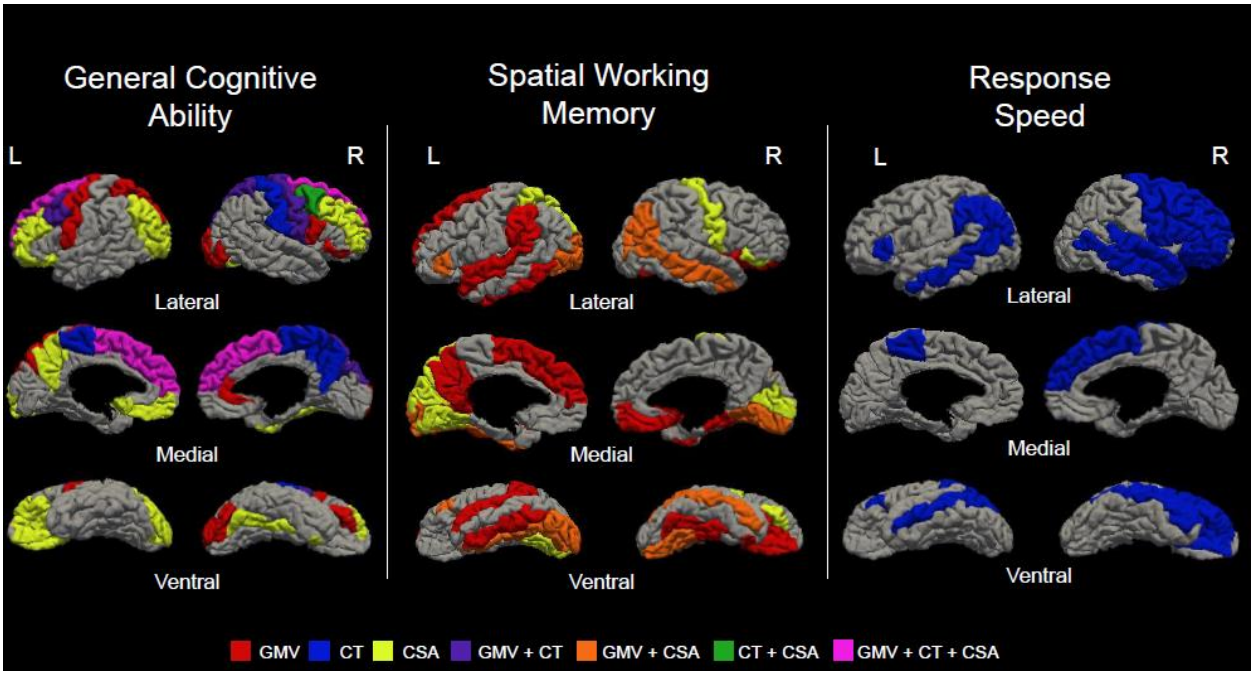

GMV Analysiis: Cognitive Variate
GMV Analysiis: Structural Variate
CT Analysis: Cognitive Variate
CT Analysis: Structural Variate
CSA Analysis: Cognitive Variate
CSA Analysis: Structural Variate
LGI Analysis: Cognitive Variate
LGI Analysis: Structural Variate
Latent Loading
Cognitive Measure
Cortical ROIs

# CCA Pair 2




# CCA Pair 3






**Supplement Figure 3.2** *Spatial Pattern of Structural Loadings.* Images show brain regions associated with particular cognitive abilities based on loadings obtained from the CCAs. Colors show regions with a loading greater than .3 and -.3 (moderate effect) in one or more of the CCA pairs. Regions with loadings above .3 in singular CCAs are in primary colors (red, blue, yellow); regions with loadings above .3 in multiple CCAs are a mixture of the primary colors used for the singular analyses (purple, orange, green). Pink regions loaded highest in GMV, CT, and CSA analyses. General cognitive ability was associated with frontal and parietal regions. Overlap in brain regions was seen in GMV and CT analyses (purple regions) and GMV, CT, and CSA analyses (pink regions). Regions unique to one analysis were primarily found in the CSA analysis (yellow regions). Spatial working memory was associated with regions distributed throughout the cortex with frontal and temporal regions overlapping across GMV and CSA analyses (orange). Response speed was associated with regions in frontal/temporal cortex particularly in the right hemisphere and select parietal regions in the left hemisphere.

# APPENDIX B

# SUPPLEMENT-CONNECTIVITY

## Method Supplement

### HCC and LCC Grouping

SPAN tasks used to divide healthy people into LCC and HCC groups included the reading span (R-SPAN), operation span (O-SPAN), and symmetry span (Sym-SPAN) [251]. Composite scores for each task were converted to a total index score and compared to established norms [251]. Comparison participants with index scores in the upper quartile (above 75%) were included in the high cognitive control group (HCC; N=28), and comparison participants with index scores in the lower quartile (below 25%) were included in the low cognitive control group (LCC; N=30). Comparison participants scoring between the $25^{th}$ and $75^{th}$ percentile were excluded from the study. Schizophrenia (SZ) participants also completed the SPAN tasks, but were not further subdivided into groups, nor excluded for scoring between the $25^{th}$ and $75^{th}$ percentile.

### Preprocessing

Preprocessing steps included removal of non-brain material (BET [313]), motion correction (MCFLIRT, [314]), smoothing (full-width half-maximum [FWHM]= 4 mm), grand-mean intensity normalization, and high-pass temporal filtering (.01 Hz). Each participant's resting state scan was then registered to their respective structural image (FLIRT, [314, 315]), transformed to MNI152 standardized space, and resampled to a 2 mm isotropic voxel grid.

## Dual Regression

Step one of the dual regression performs a spatial regression between the group-level ICA network and each participant's preprocessed and denoised data. Results of this step returns a time course for each participant that is associated with regions encompassed in the group-level network. The second step is a temporal regression between subject-specific time courses extracted from the first regression and every other voxel in the brain. This step is used to construct a spatial map for each participant that corresponds to regions of the brain that are temporally correlated with the group-level network. After transforming values to Z-scores, voxel-wise values index how strongly it is connected to the group-level network as a whole.

**Supplement Table 4.1** Correlations between Symptom Ratings and Connectivity Measures

| | PANSS pos (r) | PANSS neg (r) | PANSS gen (r) |
|---|---|---|---|
| **DMN** | | | |
| R. Cuneus | -.03 | .02 | .05 |
| **lFPN** | | | |
| L. Inferior Temporal Gyrus | .04 | .10 | .17 |
| R. Insula | .20 | .18 | .08 |

[a]Table shows Pearson correlation coefficients between connectivity values in the schizophrenia group and PANSS sub-test scores (n = 25) for clusters that showed a graded pattern across the HCC, LCC, and schizophrenia groups. No correlation coefficients were significant at $p < .05$. pos = positive; neg = negative; gen = general; PANSS = Positive and Negative Symptom Scale; DMN= default mode network; lFPN = left frontal parietal network.

# APPENDIX C

# SUPPLEMENT-ACTIVATION

## Method Supplement

### Participant Classification

Healthy comparison groups were constructed based on SPAN scores. SPAN tasks have good test-retest reliability [211], predict performance on both higher order and lower order cognitive control tasks [88, 212], including antisaccades [25, 88, 107]. Using established norms [316], comparisons subjects with composite scores in the upper quartile (above 75%) were included in the high cognitive control group (HCC), whereas comparisons subjects with composite scores in the lower quartile (below 25%) were included in the low cognitive control group (LCC). Schizophrenia (SZ) subjects also completed the SPAN tasks, but were not further subdivided into groups. SPAN scores in the SZ and LCC group were not significantly different ($t$ (44) = 0.68, $p$ = 0.49). HCC (n=21) and LCC (n= 27). The HCC (n= 21) and LCC (n= 27) group were matched to the SZ group for age, gender and handedness.

### Scan Parameters

The structural scan was a T1–weighted 3D FSPGR, repetition time (TR)= 8.1, echo time (TE) = 3.1, flip angle = 20°, field of view (FOV) = 240 mm × 240 mm, matrix size = 256 × 256, 150 axial slices, in-slice resolution = 0.94 × 0.94 mm, slice thickness = 1.2 mm. The functional scans were two T2*-weighted gradient echo EPI sequences, repetition time (TR) = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm, matrix size = 64 × 64, 33 interleaved oblique

slices, in-slice resolution = 3.4 × 3.4 mm, slice thickness = 4 mm, slice gap = 0 mm, scan time = 5:26, 158 volumes plus 4 initial dummy scans to allow for magnet stabilization.

DNA Processing and Genotyping

Saliva samples were air incubated for 2 hours. PrepIT solution was then added to the sample and vortexed to ensure mixing. Samples were incubated on ice for 10 minutes and centrifuged at room temperature for 5 minutes at 15,000 × *g* to remove impurities. A 100% ethanol solution was added to the sample, which was centrifuged for another 2 minutes at 15,000 × *g* to isolate DNA. A 70% ethanol wash was applied to the DNA and then dissolved with TE solution. DNA was incubated overnight and vortexed to ensure rehydration. Remaining DNA was stored at -20º C.

Single nucleotide polymorphism (SNP) competitive allele-specific PCR primers (KASP assays) were designed by and ordered from LGC Genomics. The SNP of interest was rs4680 (COMT). The COMT SNP had two possible alleles, A or G, resulting in three potential genotypes (AA-Met/Met, AG-Met/Val, GG-Val/Val). PCR and endpoint genotyping were done on a Roche 480 LightCycler following the standard PCR protocol provided by LGC Genomics. Roche LightCycler 480 Software was used for allele determination.

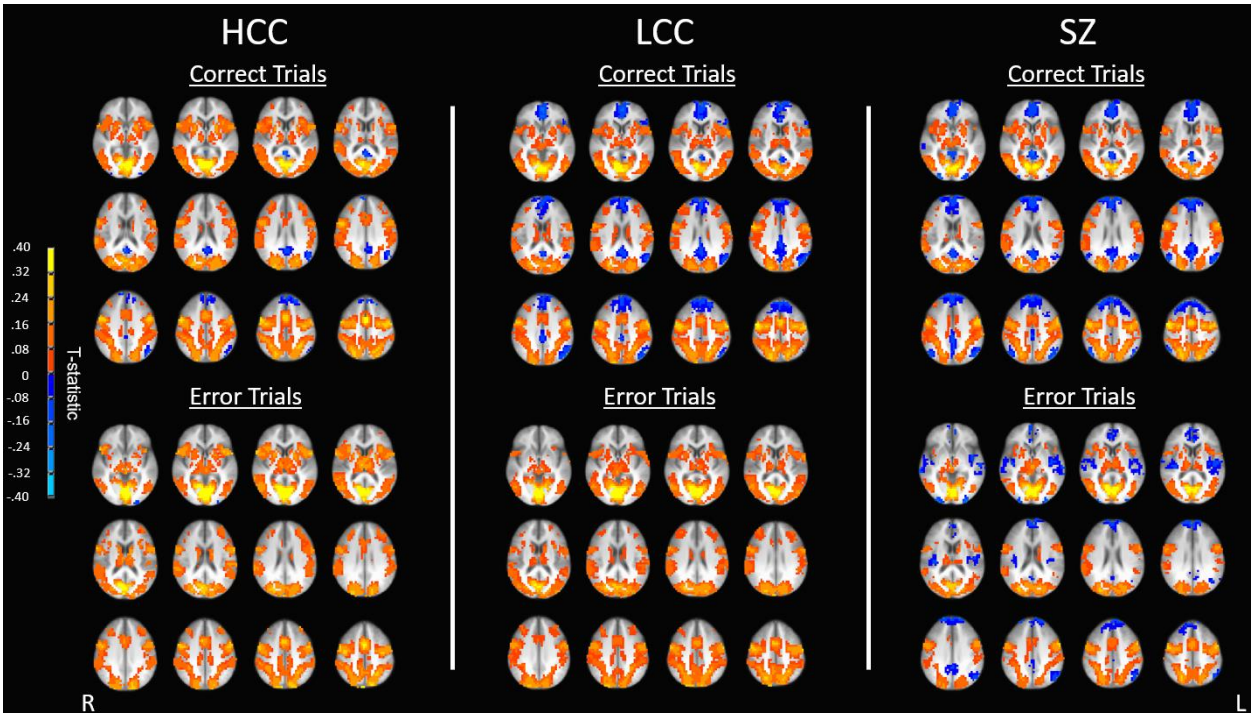
Imaging Preprocessing

Three-dimensional datasets were created from individual DICOM files for each antisaccade run. Preprocessing of functional images included despiking, slice timing correction, registration to a representative volume for movement, alignment of functional data to anatomy, smoothing with a 4mm full-width at half-maximum (FWHM) Gaussian filter, and scaling each voxel to a mean of 100. One 4D file was created for each subject by concatenating the two preprocessed antisaccade runs.

**Supplement Table 5.1** Correlations between Symptom Ratings, CPZ Daily Dose and STG/Insula Activation during Error Trials

| | PANSS pos | PANSS neg | PANSS gen | CPZ Daily Dose Equivalent |
|---|---|---|---|---|
| Right STG/Insula | .06 | .14 | -.0006 | -.27 |
| Left STG/Insula | -.16 | .31 | -.05 | -.11 |

[a]Table shows Pearson correlation coefficients between activation values in the schizophrenia group and PANSS sub-test scores (n = 20) and CPZ daily dose equivalent (n=10) for clusters that showed schizophrenia-specific deficits in activation during antisaccade error trials. No correlation coefficients were significant at $p < .05$. pos = positive; neg = negative; gen = general; PANSS = Positive and Negative Symptom Scale; CPZ = chlorpromazine; STG = superior temporal gyrus.




**Supplement Figure 5.1** *Antisaccade Activation for Correct and Error Trials*. Maps show significant BOLD % signal change or correct trials (top) and error trials (bottom) for each of the three groups (HCC, LCC, SZ). Warm colors indicate positive activation related to correct and error trials, cool colors indicated task-induced deactivations related to correct and error trials. Activations are shown on an anatomical image averaged across all subjects in talairach space (z = 0 to z = 44). HCC = high cognitive control; LCC = low cognitive control; SZ = schizophrenia.