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Relation of regional cortical thickness and surface area
with general cognitive abilities in psychosis-risk

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Relation of regional cortical thickness and surface area with general cognitive abilities in psychosis-risk

By

Ryan Guest
Bachelor of Arts, Boston College, 2016

Advisor: Elaine Walker, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
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Abstract

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with general cognitive abilities in psychosis-risk
By Ryan Guest

Individuals with schizophrenia largely demonstrate moderate to severe deficits in cognition. Still, there exists incredible heterogeneity in cognitive abilities, as one-fifth are comparable to controls. Recent research has begun to explain differences in general cognition among schizophrenia through variation in gray matter volume. However, volume is the product of both cortical thickness (CT) and surface area (SA), two indices that differ in developmental timing, genetic influences, and underlying cytoarchitecture. Thus, involving cortical volume may obscure finer associations between structure and cognition. As cognitive deficits present early before the onset of psychosis, this question should be examined among youth at clinical high risk for psychosis (CHR-P) who are thought to be in the prodromal phase of illness and are less impacted by additional confounds (e.g. anti-psychotic use). In the present study, 645 participants (449 at CHR-P, 205 healthy controls) from the North American Prodromal Longitudinal Study (NAPLS2) completed an extensive cognitive battery and had undergone structural MRI scans at their initial assessment. Both CT and SA were extracted from 34 regions bilaterally (68 in total), and subcortical volume in eight regions (16 in total) were also derived. Multivariate linear regression was used to determine the association between regional cortical morphometry and general cognitive performance, adjusting for age, age-squared, sex, and the interaction between diagnostic group and morphometry. Results demonstrate that greater widespread SA and subcortical volumes predicted better general cognitive performance and that this pattern was largely shared across groups. In contrast, greater thickness among frontal and occipital regions predicted better cognitive performance in CHR-P, whereas no association was found among controls except for the lateral orbitofrontal cortex where increased thinning related to better performance. Overall, these results underline the importance of more minute measures of the cortex to examine cognition and how variation in performance may be shared across groups as well as group-specific. Results suggest that abnormal neurodevelopmental processes underlying CT in CHR-P may uniquely contribute to poorer cognitive performance. Future studies may investigate how increased cortical thinning associated with conversion to psychosis among CHR-P may relate to cognitive impairments.

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Introduction

Over the last few decades, studies of individuals with schizophrenia have consistently found on average moderate to large impairments in cognition across domains (Heinrichs & Zakzanis, 1998). These detrimental impairments are apparent at the first psychotic episode (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Zhang et al., 2019) and even among anti-psychotic-naïve adults (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014). There is heterogeneity in cognitive performance among individuals with schizophrenia spectrum disorders as one-fifth of adults with schizophrenia demonstrate "near normal" cognitive abilities (Allen, Goldstein, & Warnick, 2003) and, albeit rare, others present with superior intellect (MacCabe et al., 2012). Data-driven approaches to subgroup individuals with schizophrenia based on current cognitive symptoms have yielded fairly consistent results, with subgroups stratified based on severity of impairments, rather than domain-specific differences (Carruthers, Gurvich, Sumner, van Rheenen, & Rossell, 2019). The origins of these varying cognitive impairments remain a vital interest. The present study aims to determine how variation in general cognitive performance can be explained by distinct indices of the cortex among individuals at imminent risk for psychosis.

Neurocognitive impairments are observed before the onset of illness—during the prodrome or at-risk period. Adolescents and young adults who later develop schizophrenia demonstrate stable cognitive deficits through the transition from prodrome to frank psychosis (Carrión et al., 2018). Thus, cognitive deficits associated with psychotic disorders need to be explored among people at ultra-high risk (UHR) or clinical high risk for psychosis (CHR-P); both are similar symptom-based designations for people who may be within the prodromal phase

of a psychotic disorder (Fusar-Poli et al., 2013). Ultimately about one-third of youth at CHR-P develop psychosis within three years (Fusar-Poli et al., 2013), and those at-risk exhibit mild to moderate cognitive impairments regardless of clinical outcome (Seidman et al., 2016). Thus, efforts have focused on characterizing trajectories of cognitive decline *a posteriori* by comparing measures thought to estimate preserved cognitive abilities against those assessing current intellectual functioning (Weickert et al., 2000). This has further classified the heterogeneity of the course of people with schizophrenia as they can exhibit stable, deteriorated, or compromised abilities through early development (Kremen et al., 2008; Dickinson et al., 2020).

Cortical thickness (CT) and surface area (SA), two distinct indices of gray matter that compose its volume, may differentially contribute to observed cognitive deficits in psychosis. In voxel-based morphometry (VBM) with surface-based approaches, cortical volume is measured as the product of CT and SA at each cortical region of interest (Winkler et al., 2010). Each are influenced by different genetic factors (Grasby et al., 2020). SA may represent the number of cortical columns situated in the cortex, while CT includes the density and positioning of neurons and their connections as well as surrounding glial cells (Tadayon, Pascual-Leone, & Santarnecchi, 2020; Narr et al., 2007). The two indices of cortex follow similar, normative trajectories across infancy into adulthood, with each exhibiting an inverted-U pattern across the first few decades of life (Raznahan et al., 2011). Both increase in area or thickness across infancy and childhood, peaking between the ages of 8 and 10, and are followed by a decrease into adulthood. During this decrease in adolescence and early adulthood, SA demonstrates a gradual decrease over time versus CT (Tamnes et al., 2017). Ultimately gray matter volume more strongly correlates with SA rather than CT (Winkler et al., 2010). Still, CT alters gray matter

volume, as changes in volume in late adulthood (Storsve et al., 2014) and in adolescence (Schnack et al., 2015; Tamnes et al., 2017) is primarily driven by ongoing changes in CT. SA contraction may contribute to volumetric changes too in late adolescence alongside changes in CT (Schnack et al., 2015). These distinct indices of cortex are both fundamentally tied to function. SA expansion may allow greater capacity for information processing, whereas CT may relate to increased density and support of interneuronal connections between columns and, during some periods of development, the efficiency and the stability of connections may improve with cortical thinning (Tadayon et al., 2020). Age-related cortical thinning within some regions is assumed to be the consequence of synaptic pruning (Tadayon et al., 2020) as well as myelination (Seldon, 2005).

Among individuals with schizophrenia, global reductions in CT and SA are apparent in both hemispheres, particularly in frontal and temporal areas (van Erp et al., 2018). These cortical differences may underlie the psychopathology or development of schizophrenia, particularly as it relates to deficits in cognition among individuals with schizophrenia. There is evidence suggesting that widespread aberrations in gray matter thinning underlie overall poor cognitive performance in schizophrenia, with less impaired individuals exhibiting comparable CT to healthy controls (HC; Cobia, Csernansky, & Wang, 2011). Gray matter volume and thickness in distributed areas of the brain has been shown to relate to better general cognitive abilities in adults with and without psychosis (Rodrigue et al., 2018). Similar findings are exhibited longitudinally in schizophrenia too (Kubota et al., 2015). Rodrigue et al. (2018) found a relation between SA and general cognition, with smaller SA in frontal and parietal areas predicting better performance among adults with and without psychosis.

Some more specific cognitive functions pertinent to global cognitive abilities have been investigated in samples of people with schizophrenia. Ehrlich et al. (2012) found that performance on working memory was positively correlated with CT in temporal regions among individuals with schizophrenia; in contrast, performance in this domain was positively associated with CT frontal areas among healthy individuals. The authors then speculated that inefficiency among areas in the prefronal cortex lead to compensatory changes in other brain regions (e.g. temporal cortices). In contrast, Rodrigue et al. (2018) note that performance on tasks related to working memory was positively associated with cortical volume and SA in the frontal and temporal regions. It appears that the connection with working memory was primarily driven by individuals with affective psychosis (e.g. bipolar disorder with psychotic features). This pattern of findings suggests that alterations in typical brain-cognition associations among people with schizophrenia may reflect disruptions in general cognitive abilities in addition to more specific observed deficits (e.g. working memory).

To date, we have a limited understanding of the correlates of CT and SA in individuals at risk for psychosis. In CHR-P samples, it has not been established that reductions in gray matter are present at baseline when compared to healthy individuals (Cannon et al., 2015), although there is some suggestion that CT, but not SA, is reduced among CHR-P youth in fronto-temporal-parietal areas (del Re et al., 2020). Rather, there is evidence that declines from baseline levels of regional CT are greater in CHR-P youth who convert to psychosis (Cannon et al., 2015). But, like groups of people with psychosis (Brugger & Howes, 2017; Alnæs et al., 2019), there is likely significant variability among CHR-P in brain morphometry. These findings are consistent with the assumption of etiological and neurobiological variability among patients with

schizophrenia and other psychoses. It is plausible that variations in gray matter volume and other MRI-derived measures of the cortex explain variability in cognitive performance among individuals at risk. Koutsouleris and colleagues have begun to investigate this topic, relying on a small sample of anti-psychotic-naïve adults at UHR (Koutsouleris et al., 2010; Koutsouleris, et al., 2012). Poor performance on a measure of cognitive set-shifting was related to less GMV near the ventromedial prefrontal cortex and greater GMV in the cerebellum; in contrast, performance among healthy individuals positively associated with GMV in the insular cortices (Koutsouleris et al., 2010). In this same sample using multivariate analysis methods, cognitive performance across measures was directly correlated with GMV in structures in the prefrontal, temporal, and limbic regions of the brain as well as subcortical structures. Again, brain-cognition associations differed from patterns found among healthy individuals, as performance, especially on measures relying on verbal ability, was positively related to cortical and subcortical GMV across the cortex (Koutsouleris et al., 2012). Taken together, the findings suggest differential patterns are beginning to emerge among individuals at-risk for psychosis. Still, in the absence of distinguishing between CT and SA, important relations may be obscured by volumetric approaches to determining associations.

The present study utilizes structural neuroimaging and extensive cognitive data collected from at-risk and healthy adolescents and adults from the second phase of the North American Prodromal Longitudinal Study (NAPLS2) to determine the relations between brain morphometry and cognition during this particularly critical phase of illness. Rather than depend on regional gray matter volume that may muddle the association between structure and function, we will examine how two different MRI cortical measurements that comprise volume, CT and SA, relate

to patterns of cognitive performance. The cognition functioning will be limited to general cognitive abilities rather than by subdomain since schizophrenia for the most part impacts cognition broadly rather than any specific domain (Dickinson, Iannone, Wilk, & Gold, 2004). To complement these sets of analyses, the relative contribution of regional subcortical gray matter volume to cognition will be determined as these structures likely support general cognition in addition to cortical structures. It is predicted that CT, but not SA, will directly contribute to observed general cognitive performance, which would align with previous findings about the absence of a clear association between cognitive deficits and cortical SA in schizophrenia (Jessen et al., 2019; van Rheenen et al., 2018). This cortical thinning may not be simply limited to frontal regions but also include temporal and parietal cortices of the brain; thus, consistent with noted differences between CHR-P and HC (del Re et al., 2020). Subcortical volumes similarly may directly contribute to general cognitive performance too. Volume in subcortical regions among schizophrenia tend to be reduced (van Erp et al., 2016), and certain regions have subsequently been positively related to short-term memory (Koshiyama et al., 2018) and executive functioning skills (Fan et al., 2019). Overall, an investigation into the brain-cognition association with CT and SA among individuals at CHR-P will greatly clarify the potential causes of variations in cognitive function at this early stage of illness. Since these cognitive deficits demonstrated in schizophrenia may correlate with attenuated positive symptoms and negative symptoms (Hegde et al., 2013) as well as anti-psychotic dosage (Kawai et al, 2006; Vila-Badalia et al., 2020), potential confounds may also be identified.

Method

In short, NAPLS2 aims to overall determine the relative risk of conversion to psychosis among help-seeking individuals deemed at CHR-P and ultimately define the pathophysiology underlying symptoms of early psychosis. This study provides a comprehensive and detailed data set with previous investigations into the genetic susceptibility to schizophrenia among CHR-P (Perkins et al., 2019), observed cognitive deficits (Seidman et al., 2016), associated inflammatory biomarkers and hormonal changes (Cullen et al., 2020; Perkins et al., 2015), and excessive cortical thinning across time (Cannon et al., 2015). Consequently, the protocol and background of each methodology are described at length elsewhere: the recruitment and clinical information of the entire NAPLS2 cohort (Addington et al., 2015), the selection and administration of cognitive measures (Seidman et al., 2016), and the collection and processing of structural MRI scans (Cannon et al., 2015; Chung et al., 2019). The following sections thus present procedures in brief.

Participants

Six hundred and fifty-four adolescents and young adults (449 individuals at CHR-P, 205 HCs) from the larger NAPLS2 consortium had been administered the neurocognitive battery and had structural MRI scans collected at baseline. Participants were recruited at hospitals and universities from across the United States and Canada between 2009 and 2012; sites include Emory University (Atlanta, GA), Yale University (New Haven, CT), Harvard Medical School at Beth Israel Deaconess Medical Center (Boston, MA), University of North Carolina at Chapel Hill, Zucker Hillside Hospital (Glen Oaks, NY), University of California at San Diego, University of California at Los Angeles, and University of Calgary (Calgary, Canada).

Institutional review boards at each respective site approved the study and its protocol. Informed consent was given by each adult participant and, in the case of a minor, informed consent was provided by the parent or legal guardian and written assent was given by the child.

Clinical high risk for psychosis was evaluated by the Criteria of Psychosis-Risk Syndromes as specified by the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan, Walsh, & Woods, 2010) in addition to the presence of schizotypal personality disorder before adulthood. The SIPS and its psychosis-risk criteria is a well-validated nineteen-item instrument, comparable to other screening tools developed in parallel (Fusar-Poli et al., 2016) and widely used in research and clinical settings (de Pablo, Estradé, Cutroni, Andlauer, & Fusar-Poli, 2021). Most at-risk individuals in NAPLS2 (93%) met attenuated positive symptom syndrome, a psychosis-risk syndrome that consists of recent or worsening subthreshold symptoms that are frequent (at least an average of once per week for the previous month) and distressing yet do not categorically meet the criteria for psychosis as insight is retained (Addington, et al., 2015). A comparison sample of age- and gender-matched healthy participants did not meet any psychosis-risk syndrome, were not currently prescribed any psychiatric medication, and did not have any first-degree relative with a psychotic disorder. Subjects in both groups had never met for a psychotic episode, current or in the past, did not meet for substance dependence as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994), and did not have an intellectual disability (consistently measured IQ < 70) or central nervous system disorder (e.g. epilepsy).

Materials and Procedure

Neurocognition

The constructed NAPLS2 battery consisted of the majority of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) alongside selected subtests from achievement and intelligence tests, the Wechsler Abbreviated Scale of Intelligence (WASI; Weschler, 1999) and the fourth edition of the Wide Range Achievement Test (WRAT4; Wilkinson & Robertson, 2006). The former consensus battery measures seven cognitive domains: speed of processing, verbal learning, working memory, reasoning and problem-solving, visual learning, attention and vigilance, and social cognition. Each depend on at least one cognitive measure for its assessment, with the first three domains listed relying on more than one. The measure under social cognition, the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Managing Emotions subtest, was excluded based on limitations with its use among adolescents and children (Seidman et al., 2016). Additional measures in the NAPLS2 battery (e.g. olfactory identification, auditory perception) were excluded from these analyses.

A composite score of performance on all neurocognitive measures was calculated via principal component analysis (Guest, in preparation). This score explained 43% of the performance across included neuropsychological tests among those who had cognitive data available (N = 914). The largest loadings were held by two instruments from the MCCB and the two subtests from WASI: Letter Number Sequence (0.76), WASI Block Design subtest (0.74), WASI Vocabulary subtest (0.74), and Brief Assessment of Cognition in Schizophrenia Symbol Coding (0.71). The composite score additionally strongly correlated with current IQ as measured

by the WASI, $r(914) = 0.78$, $p < .001$. A composite score was selected, as opposed to the current IQ measure, since it is a robust index of performance on measures in a plethora of domains and likely better captures participants' overall cognitive ability.

Image Collection and Processing

T1-weighted structural brain scans were acquired on either Siemens or GE 3T MRI scanners at each respective site. The scanning protocol was optimized for each respective scanner manufacturer in accordance to Alzheimer's Disease Neuroimaging Initiative (ADNI) Protocol (http://adni.loni.usc.edu). The voxel dimensions were 1 x 1 x 1.2 mm. All scans were processed at a single site (Yale University) using FreeSurfer version 5.2 (http://surfer.nmr.mgh.harvard.edu/; Dale, Fischl, & Sorreno, 1999; Fischl et al., 2004). CT (mm) and SA (mm^2) were extracted from thirty-four regions in each hemisphere (68 regions in total) using the gyrus-based Desikan-Killiany atlas (Desikan et al., 2006). Volume in eight subcortical regions (16 regions in total) were additionally derived based on automatic segmentation in FreeSurfer (Fischl et al., 2002). All cortical measurements were adjusted for site.

Clinical Information

As indicated previously, trained clinicians and research staff administered the SIPS to all participants in order to determine if an individual meets for a psychosis-risk syndrome or psychosis. Alongside this greater aim, the measure quantifies the severity of symptoms in domains relevant to psychosis: positive symptoms (five items in total), negative symptoms (six total), disorganized symptoms (four total), and general symptoms (four total). Each is rated on a six-point scale; from *Absent* to *Severe and Psychotic* for all five positive symptom ratings and from *Absent* to *Extreme* for the remaining items. Both the total of all positive symptoms (i.e.

Unusual Though Content, Suspiciousness, Grandiosity, Perceptual Abnormalities, and Disorganized Communication) and the total of all negative symptoms (i.e. Social Anhedonia, Avolition, Expression of Emotion, Experience of Emotions and Self, Ideational Richness, and Occupational Functioning) for each participant were calculated for these analyses. Additional information about medication history, racial and ethnic identities, biological sex, and other demographic variables were collected.

Statistical Analyses

All analyses were conducted using R version 4.0.3 (R Core Team, 2020) and whole-brain visualizations were created using the *ggseg* package in R (Mowinkel & Vidal-Piñeiro, 2020). Descriptive statistics for each diagnostic group were computed. Multivariate linear regression was used to estimate general cognitive performance from site-corrected cortical morphometry at each brain region. Models included all participants and were adjusted for biological sex, age, age^2, diagnostic group (CHR-P vs. HC), and the interaction between brain structure and diagnostic group. The interaction term was added to determine whether the relation between structure and cognition among adolescents and young adults at CHR-P differed from healthy participants. CHR-P served as the reference for diagnostic group; thus, the brain structure variable represented the relation between structure and cognition for CHR-P participants. Additional covariates were considered: anti-psychotic medication lifetime use, total positive symptoms, and total negative symptoms.

For each model, residuals plots were reviewed and variance inflation factor (VIF) was calculated to ensure assumptions for multivariate linear regression (e.g. homoscedasticity, normally distributed errors) were met. A calculated VIF greater than 10 would strongly indicate

multicollinearity (Bowerman & O'Connell, 1990). Studentized deleted residuals were computed alongside Cook's distance to identify the influence of potential outliers in the model; a Cook's distance greater than 1 would require closer inspection (Cook & Weisberg, 1982). Furthermore, the plots of residuals were compared between models with and without age^2 to ensure that its addition is necessary and better fits the data. The Benjamini-Hochberg method was applied to control for false discovery rate (FDR) within each set of models ($q < .05$; Benjamini & Hochberg, 1995).

Results

The demographic and clinical information is presented in Table 1. Calculated VIF for the regional cortical measure in each model did not indicate any multicollinearity; continuous covariates also remained low. Cook's distance was calculated for each point within each model; none reached the designated threshold. Similarly, six participants appeared to be potential outliers across models based on studentized deleted residuals but were still retained in the analyses due to their limited effect on the overall models. Based on these diagnostic statistics, assumptions for multivariate linear regression were met. Correlations between general cognitive performance and average morphometry across the regions of interest are presented in Table 2, along with potential confounds such as history of anti-psychotic use and symptoms. As none of the cortical morphometry variables significantly correlated with any potential confounds, regression models did not adjust for these.

Cortical Thickness

See Table 3 for the standardized beta values and *p*-values for each significant regional CT predictor and its associated interaction term. Three regions in the frontal lobe significantly and

positively predicted general cognitive performance among individuals at CHR-P: precentral gyrus, paracentral gyrus, and lateral orbitofrontal cortex. The precentral gyrus demonstrated an effect bilaterally. The other two were lateralized, with the right paracentral gyrus and left lateral orbitofrontal cortex as the only significant predictors. Likewise, some regions outside of the frontal lobe predicted cognitive performance. Greater CT of lateral occipital areas in both hemispheres significantly predicted better general cognition. Cortical thickness in other areas of the brain (e.g. cingulate, temporal) did not correlate with general cognitive ability. Thus, among adolescents and adults at CHR-P, increased CT in specific regions in the frontal and occipital cortices notably contributed to better general cognitive performance.

Next, the interaction terms for each model where regional CT was a significant predictor was examined. In the majority of cases (five out of six significant linear regression models), there was a significant interaction between regional thickness and diagnostic group: left precentral, right paracentral, left lateral orbitofrontal, and bilateral lateral occipital. This therefore indicates that healthy participants did not demonstrate the same association between CT and general cognition at those regions. No interaction between regional CT and diagnostic group was found for the right precentral. See Figure 1 for the marginal effects of CT in the above regions on general cognitive performance between diagnostic groups.

To further characterize these relations between cognitive performance and CT among typically developing controls, the analyses were repeated with HC as the reference group. Greater CT in the left lateral orbitofrontal cortex associated with worse cognitive performance among healthy individuals ($\beta = -0.16$, $p = .02$), in contrast to CHR-P individuals who demonstrated a positive association between the two variables. In all other regression models, the

right paracentral (β = -0.01, *p* = .86), left precentral (β = -0.10, *p* = .14), and bilateral lateral occipital (left: β = -0.04, *p* = .55, right: β = -0.12, *p* = .06) did not associate with general cognitive abilities.

Cortical SA

In total, greater cortical SA in thirty-four brain regions significantly predicted better general cognitive performance; all were widespread across cortical areas of the brain. See Table 4 for the standardized beta values and *p*-values for each significant regional cortical SA predictor and its associated interaction term. In the frontal cortex, six regions, largely bilateral, were positively associated with general cognitive performance: bilateral medial orbitofrontal, bilateral pars triangularis, right pars opercularis, bilateral precentral, bilateral superior frontal, and right paracentral.

Additionally, general cognitive performance was positively associated with SA of the lateral portions of the temporal lobe, with bilateral inferior temporal, bilateral middle temporal, and bilateral superior temporal, and left entorhinal directly associated with cognition. In the parietal cortices, bilateral precuneus, right superior parietal, and right postcentral additionally were found to be positively associated with performance. Likewise, all regions within the occipital lobe and the insula bilaterally predicted cognitive performance. Lastly, the bilateral posterior cingulate and left rostral anterior cingulate cortex predicted better cognitive performance in CHR-P.

Overall, greater widespread cortical SA predicted better cognitive performance among CHR-P. Among these thirty-four regions, only one interaction term was significant: left pars triangularis (β = -0.44, *p* = .05) that resides near the inferior frontal gyrus. None of the other

interaction terms were significant (all *p*'s > .05). This linear regression was repeated with HC as the reference group to characterize the potential relation among the comparison group. This region did not predict general cognitive abilities in the HC group (β = 0.07, *p* = .22). Thus, altogether this indicates that the association among HCs did not significantly deviate from the association between cortical SA and cognition in almost all of these widespread brain regions.

Subcortical Volume

Lastly, the relation of subcortical volumes in these regions with general cognitive performance was examined. The volumes of the majority of subcortical structures predicted general cognitive performance. These included the bilateral hippocampi, bilateral ventral diencephalon (e.g. hypothalamus, mammillary bodies), bilateral thalami, bilateral putamen, bilateral amygdala, right pallidum, and right caudate. See Table 5 for the standardized beta values and *p*-values for each significant regional subcortical volume predictor and its associated interaction term. Overall, greater subcortical volume in the above regions predicted better cognitive performance among individuals at CHR-P. Only volume in the left pallidum and left caudate were not significantly related with cognitive performance. Tests of the interactions indicated that the relation of regional subcortical volume with general cognition did not differ by diagnostic group, as no interaction term was significant (all *p*'s > .05). See Figure 2 for a visualization of significant regions across the brain for each set of cortical features.

Discussion

The purpose of this study was to elucidate the connection between brain structure and cognition among CHR-P individuals by utilizing two morphometric indices of the cortex. Rather than depending on global measures of gray matter volume, two separate indices, CT and SA,

were used to determine whether they differentially predicted general cognitive abilities in CHR-P and HC. As research on brain-cognition relations is rapidly accumulating, especially in clinical research, it is important to understand the implications of utilizing alternative morphometrics.

The present results indicate that increased CT in several prefrontal and occipital areas of the brain were significant predictors of better cognitive performance in CHR-P youth. The pattern of findings overlaps with regions where CT was predictive of general cognitive abilities in multivariate analyses of data from people with and without psychosis (Rodrigue et al., 2018). Specifically, previous research showed that general cognition was associated with larger gray matter volume and CT, but smaller SA. In contrast, HC differed from participants at CHR-P in that the correlation between these structures and cognitive performance were negligible, with the exception of the lateral portion of the orbitofrontal cortex, where thinning was related to better cognitive performance. Normative cortical thinning may increase the efficiency and stability of connections between neurons, as thickness has been inversely associated with crystallized intelligence among healthy adult populations (Tadayon et al., 2020). In contrast, greater cortical thinning seen in psychosis has been posited to reflect an abnormal neurodevelopmental process that disrupts connections and interferes with the capabilities of neurons to process information. Thus, in CHR-P and psychosis, greater thickness at times may relate to a better capacity to function and process information.

Overall, the differential associations between CT and cognitive function for the CHR-P and HC groups illustrates how cortical morphometry that differentiates CT from SA may uniquely reveal deficits associated with CHR-P. One of these regions, the lateral portion of the left orbitofrontal cortex, plays a strong role in decision-making, reward, and semantic processing

(Kahnt et al., 2012). Thinning in this region has been associated with more cognitively impaired subgroups of individuals with schizophrenia (van Rheenen et al., 2018) and with more severe negative symptoms in schizophrenia (Walton et al., 2018). It is of interest that this region demonstrates greater functional connectivity among adjacent regions in the frontal cortex (i.e. prefrontal cortex, motor), parietal-temporal areas, and lateral areas in the occipital cortex (Kahnt et al., 2012; Zald et al., 2014). Previous research notes that thickness within this prefrontal region may relate to structural and functional connectivity in schizophrenia specifically. The integrity of white matter in the inferior fronto-occipital fasciculus, connecting the orbitofrontal cortex to parietal and occipital areas of the cortex, has been positively associated with thickness in the left lateral orbitofrontal region in schizophrenia among men, and only marginally significant among both males and females (Liu, et al., 2014). Similarly, thickness in the right lateral orbitofrontal cortex in schizophrenia patients was positively associated with white matter integrity in the thalamo-orbitofrontal pathway (Kubota et al., 2013). Other significant regions from the results include lateral occipital areas and other frontal regions involved in motor function. For these latter regions, namely CT in the precentral gyrus and its medial junction with the post-central gyrus (paracentral gyrus), recent research suggest that activity in these areas in conjunction with fronto-parietal networks and subcortical structures may underlie general psychomotor slowing demonstrated in schizophrenia, explaining some cognitive findings (Osborne, et al., 2020).

It is to be expected that there would be some similar morphometric influences on cognition for healthy and at-risk individuals as a function of shared neurodevelopmental processes. Interestingly, however, these were chiefly within the contribution of cortical SA, where expansion predicted better cognitive performance across diagnostic groups. These areas

were widespread throughout the cortex, but excluded medial temporal areas and inferior parietal lobules. This is in contrast to findings reported by Rodrigue et al. (2018) that found smaller SA related to better cognitive performance among individuals with and without psychosis. However, previous research has shown that larger SA relates to general cognitive abilities (Grasby et al., 2020), in both crystallized and fluid forms of intelligence (Tadayon et al., 2020). Larger SA may reflect expansion due to the proliferation of progenitor neurons in early neurodevelopment (radial unit hypothesis) that subsequently has long-lasting impacts in adulthood for overall cognitive abilities (Rakic et al., 2009). Providing support for this theory, a meta-analysis using data from samples that had been genotyped and scanned, revealed that genetic factors underlying total SA, but not average CT, were involved in the regulation of progenitor neurons and also associated with both educational attainment and general cognition (Grasby et al., 2020). Lastly, in addition to examining cortical regions, the present study included supplemental analyses which revealed that numerous subcortical volumes (particularly among regions in the right hemisphere) predicted better cognitive functioning in all participants.

It is also important to note that previously reported trends in CT and SA were observed in the present study. Global cortical SA across regions of interest remained uncorrelated with global CT but strongly correlated with global subcortical volume, with greater SA related to greater volume. In contrast, global CT only weakly correlated with subcortical volume, in the same direction as SA and subcortical volume. These findings between global SA and CT align with previous research between the two (Winkler et al., 2010). Age-related trends across groups were noted as age inversely correlated with both global CT and global subcortical volume. For the latter, age weakly correlated with subcortical volume. Age and surface area were ultimately

uncorrelated. The association between cortical CT and age followed previous patterns in adolescence and early adulthood (Tamnes et al., 2017; Raznahan et al., 2011). As these morphometric variables likely share non-linear associations with age, a linear correlation may not adequately assess the relation within this age range.

Overall, the findings of the present study further support the relations between morphometry and cognition and the importance of distinctions between indices of brain structure. Noteworthy strengths of the study include the large samples of CHR-P and HC which afforded the required statistical power to investigate connections between brain regions and cognition. This is in contrast to previous studies that relied on a limited number of at-risk participants (Koutsouleris et al., 2012; Koutsouleris et al., 2010). Also, the large battery of cognitive measures provided the breadth needed to tap general cognitive functioning, as well as specific cognitive functions previously shown to be impaired in schizophrenia. Likewise, the decomposition of volume into CT and SA provided a clearer picture of how regional gray matter is related to cognition. Finally, the focus on individuals at CHR-P, rather than diagnosed patients, may provide a clearer understanding of associations, as they are not likely confounded by extraneous variables (e.g. increased lifetime anti-psychotic use, duration of untreated psychosis) that may impact cortical structures and/or cognitive performance after the onset of illness. This overall provides a necessary understanding of structure-cognition association during initial presentation of deficits among individuals who are at imminent risk for psychosis.

There still remains limitations regarding the present study. The present focus was on general cognitive functioning, rather than domain-specific cognition (e.g. working memory, language). Domain-specific associations with regional CT or SA may be obscured due to the

indexing of performance across all measures. However, a broad cognitive impairment may be more central to psychosis than any specific one (Dickinson et al., 2004). Likewise, there may be selective enrollment; at-risk individuals who choose and are able to participate in research may demonstrate better cognitive abilities than the larger at-risk population due to selection bias (Kline et al., 2019) or selected exclusionary criteria in NAPLS2 (e.g. intellectual disability). Additionally, our findings resulted from univariate analyses that considers each regional cortical index separately and therefore may explain minimal variation in cognition. It is possible that cortical regional patterns contribute to overall cognition, so multivariate approaches that identify patterns of brain morphometry may provide additional insights. Alongside this, a longitudinal study of the association between cortical indices and cognition among CHR-P would greatly expand our findings. It is noted that progressive changes in CT in right prefrontal regions predict conversion to psychosis (Cannon et al., 2015) and it would be pertinent to examine whether thinning within these regions contribute to cognition. To note, these regions did not overlap with our CT findings. Lastly, we limited ourselves to CT and SA of regional gray matter and had not considered how the integrity of white matter and functional connectivity may impact gray matter and contribute to overall cognitive performance. Networks of regions, such as the parieto-frontal integration network (Jung & Haier, 2007) may better explain variation in intelligence; people with schizophrenia may demonstrate marked dysconnectivity within networks that leads to impaired cognition (Cole, Anticevic, Repovs, & Barch, 2011). Clearly, there are many issues that will benefit from attention in future studies of brain morphometrics and cognition.

In conclusion, our findings contribute to the identification of shared and disease-specific cortical underpinnings of cognitive functioning in both psychosis-risk and healthy development.

The CHR-P paradigm—the period when individuals present with attenuated psychotic symptoms and cognitive impairments—and the separation of volume into CT and SA granted us the finer capability to quantify the regional contributions to overall cognition.

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Table 1

Demographic and clinical information for each subsample.

	Entire sample (N = 654)	
	CHR-P (N = 449)	**HC (N = 205)**
Age in years, M ± SD (range)	18.6 ± 4.0 (12 – 35)	20.3 ± 4.6 (12 – 34)
Sex, N (%)		
Male	272 (61%)	109 (53%)
Female	177 (39%)	96 (47%)
Race, N (%)		
White (European)	268 (60%)	114 (56%)
Black (e.g. African, African Caribbean)	65 (14%)	38 (18%)
Interracial	50 (11%)	19 (9%)
Other	66 (15%)	34 (17%)
Ethnicity, N (%)		
Hispanic/Latino	81 (18%)	35 (17%)
Non-Hispanic/Latino	368 (82%)	170 (83%)
SIPS Positive Item Total, M ± SD (range)	12.0 ± 4.0 (0 – 24)	0.9 ± 1.5 (0 – 8)
SIPS Negative Item Total, M ± SD (range)	11.7 ± 6.2 (0 – 30)	1.1 ± 2.2 (0 – 14)
Current IQ, M ± SD (range)	104.0 ± 15.0 (62 – 136)	111.0 ± 14.3 (72 – 139)
Lifetime antipsychotic dosage in CPZ equivalent units, M ± SD (range)	12741 ± 113794 (0 – 2231125)	–

Note. No HC participant reported any usage of anti-psychotic medication. Due to missingness, sample size was reduced for SIPS Negative Items in CHR-P (N = 446) and history of anti-psychotic use in CHR-P (N = 445) and in HC (N = 202). Abbreviations: clinical high risk for psychosis, CHR-P; healthy control, HC; Structured Interview for Psychosis-Risk Syndromes, SIPS; chlorpromazine, CPZ;

Table 2

Correlations between morphometric variables, general cognitive performance, and disease-related potential covariates (N = 654, unless noted otherwise).

	1	2	3	4	5	6	7	8
1. Age in years	–							
2. SIPS Positive Total	**-0.14***	–						
3. SIPS Negative Total	**-0.12***	**0.64***	–					
4. Lifetime anti-psychotic use	**-0.08***	**0.17***	0.18	–				
5. Global cortical surface area	-0.07	-0.04	0.00	-0.02	–			
6. Global cortical thickness	**-0.47***	0.00	0.03	0.04	0.01	–		
7. Global subcortical volume	**-0.12***	-0.01	0.07	-0.02	**0.76***	**0.17***	–	
8. General cognitive performance	**0.36***	**-0.21***	**-0.23***	**-0.13***	**0.16***	**0.12***	**0.13***	–

Note. * $p < .05$ Missingness reduced the sample size for SIPS Negative Items in CHR-P (N = 446) and history of anti-psychotic use in CHR-P (N = 445) and in HC (N = 202). Abbreviations: Structured Interview for Psychosis-Risk Syndromes, SIPS;

Table 3

Standardized beta values and associated unadjusted p-values for regional cortical thickness predicting general cognition for CHR-P and interaction terms (brain region x diagnostic group; reference group: CHR-P) are presented for each hemisphere. Regions are organized by cortical area.

	Left hemisphere				Right hemisphere			
Brain region	**Brain region (β)**	**p-value**	**Brain region x group (β)**	**p-value**	**Brain region (β)**	**p-value**	**Brain region x group (β)**	**p-value**
Frontal								
Paracentral	—	—	—	—	0.17	< 0.001	-1.37	0.017
Precentral	0.13	0.001	-2.08	0.002	0.14	0.001	-1.05	0.114
Lateral orbitofrontal	0.11	0.008	-2.03	< 0.001	—	—	—	—
Occipital								
Lateral occipital	0.12	0.007	-1.23	0.034	0.12	0.006	-1.87	0.002

Table 4.

Standardized beta values and associated unadjusted p-values for regional SA predicting general cognition for CHR-P and interaction terms (brain region x diagnostic group; reference group: CHR-P) are presented for each hemisphere. Regions are organized by cortical area.

	Left hemisphere				Right hemisphere			
Brain region	**Brain region (β)**	**p-value**	**Brain region x group (β)**	**p-value**	**Brain region (β)**	**p-value**	**Brain region x group (β)**	**p-value**
Cingulate								
Posterior cingulate	0.14	0.001	-0.02	0.925	0.19	< 0.001	0.07	0.758
RA cingulate	0.15	< 0.001	-0.04	0.827	—	—	—	—
Frontal								
Paracentral	—	—	—	—	0.15	0.001	0.09	0.671
Pars opercularis	—	—	—	—	0.17	< 0.001	0.01	0.960
Medial orbitofrontal	0.14	0.001	-0.02	0.943	0.17	< 0.001	-0.10	0.721
Pars triangularis	0.21	< 0.001	-0.44	0.049	0.16	< 0.001	-0.10	0.630
Precentral	0.15	0.001	-0.05	0.881	0.16	< 0.001	-0.18	0.565
Superior frontal	0.18	< 0.001	0.00	0.995	0.17	< 0.001	0.10	0.721
Insula								
Insula	0.18	< 0.001	0.13	0.603	0.16	< 0.001	-0.15	0.556
Occipital								
Cuneus	0.20	< 0.001	-0.15	0.577	0.18	< 0.001	-0.05	0.840
Lateral occipital	0.15	0.001	0.08	0.778	0.17	< 0.001	0.27	0.295
Lingual	0.15	< 0.001	0.08	0.744	0.14	0.001	0.05	0.848
Pericalcarine	0.16	< 0.001	-0.07	0.732	0.16	< 0.001	-0.14	0.536
Parietal								
Postcentral	—	—	—	—	0.15	0.001	0.26	0.341
Superior parietal	—	—	—	—	0.16	< 0.001	0.10	0.730

Precuneus	0.16	< 0.001	0.27	0.284	0.15	0.001	0.36	0.162
Temporal								
Entorhinal	0.20	< 0.001	-0.25	0.129	—	—	—	—
Inferior temporal	0.15	< 0.001	0.08	0.757	0.20	< 0.001	-0.26	0.251
Middle temporal	0.18	< 0.001	0.01	0.970	0.16	< 0.001	0.19	0.478
Superior temporal	0.19	< 0.001	-0.02	0.956	0.17	< 0.001	0.10	0.751

Abbreviations: rostral anterior, RA;

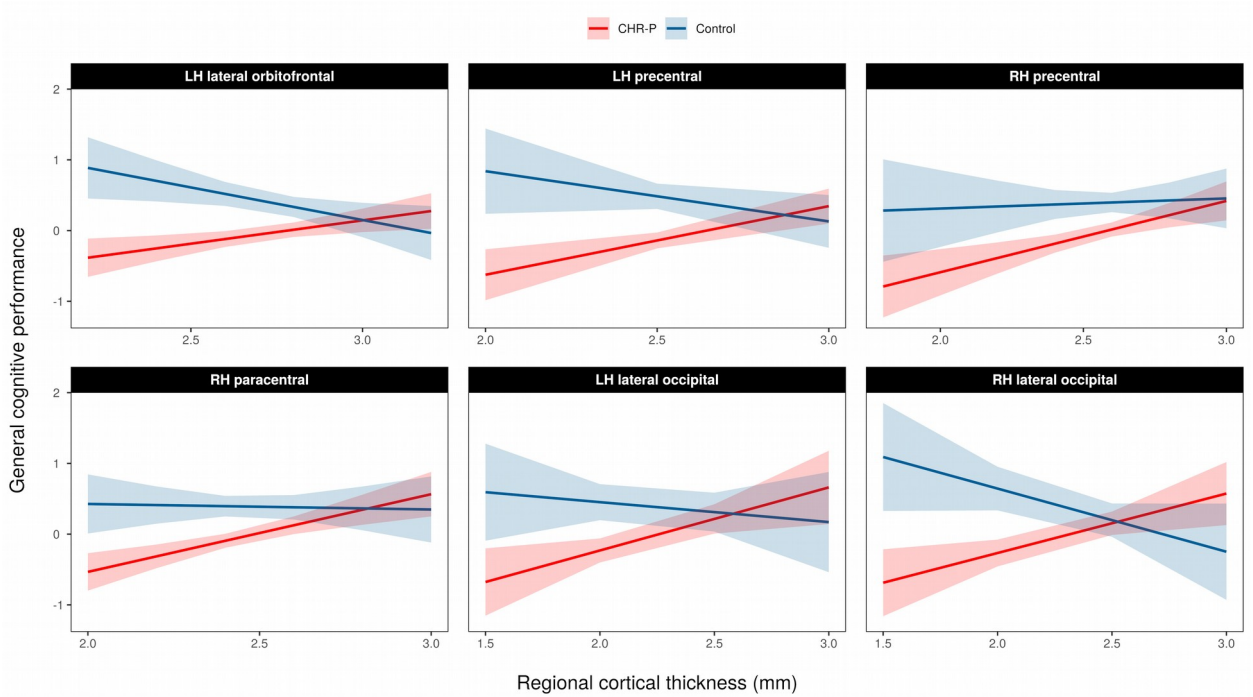
Table 5

The standardized beta values and associated unadjusted p-values for regional subcortical volume predicting general cognition for CHR-P and interaction terms (brain region x diagnostic group; reference group: CHR-P) are presented for each hemisphere. Regions are organized by cortical area.

	Left hemisphere				Right hemisphere			
Brain region	**Brain region (β)**	**p-value**	**Brain region x group (β)**	**p-value**	**Brain region (β)**	**p-value**	**Brain region x group (β)**	**p-value**
Subcortical								
Amygdala	0.14	0.001	0.09	0.734	0.17	< 0.001	0.16	0.526
Caudate	—	—	—	—	0.13	0.002	0.04	0.876
Hippocampus	0.13	0.003	0.06	0.857	0.20	< 0.001	-0.20	0.542
Pallidum	—	—	—	—	0.16	< 0.001	0.04	0.865
Putamen	0.18	< 0.001	0.03	0.906	0.19	< 0.001	0.22	0.450
Thalamus proper	0.16	< 0.001	0.01	0.978	0.19	< 0.001	-0.07	0.819
Ventral diencephalon	0.15	< 0.001	0.18	0.575	0.18	< 0.001	0.07	0.832

Figure 1.

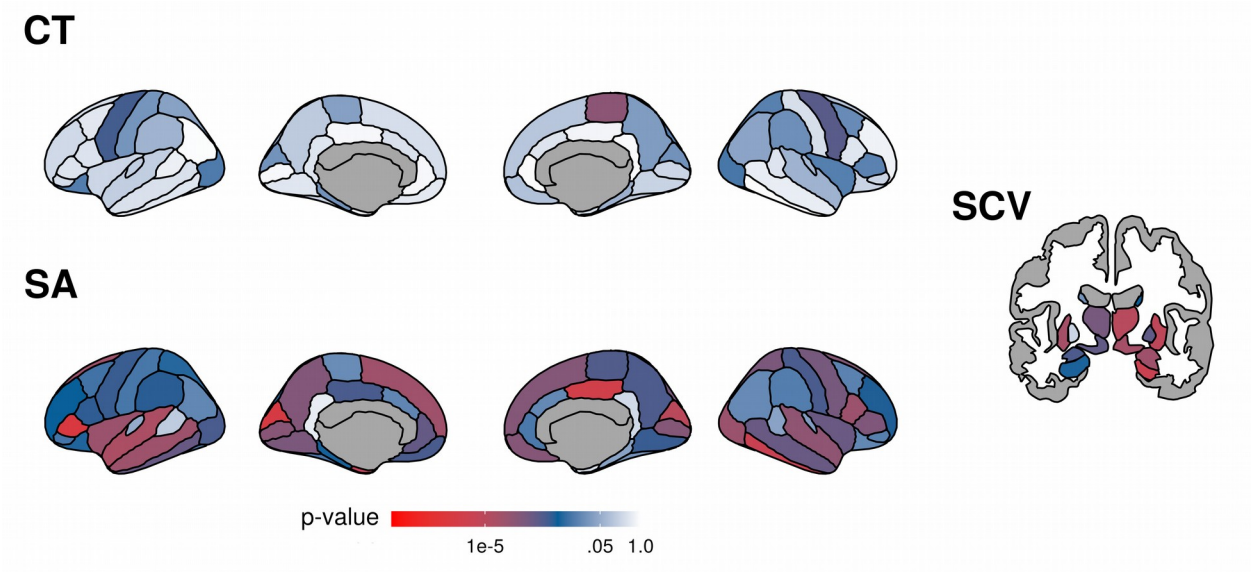
Marginal effects of the interaction between cortical thickness and diagnostic group (CHR-P versus HC) in the prediction of general cognitive performance.



Abbreviations: clinical high risk for psychosis, CHR-P;

Figure 2.

The results of linear regression models of cognitive performance with cortical thickness, surface area, and subcortical volume as predictors are displayed (N = 654). Associated p-values of each cortical morphometric variable are plotted. The corpus callosum and other non-cortical areas for each set are shaded gray.



Abbreviations: cortical thickness, CA; surface area, SA; subcortical volume, SCV;