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Cingulate gyrus neuroanatomy in schizophrenia subjects and their non-psychotic siblings

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Abstract

Background and methods: In vivo neuroimaging studies have provided evidence of decreases in the gray matter volume of the cingulate gyrus in subjects with schizophrenia as compared to healthy controls. To investigate whether these changes might be related to heritable influences, we used high-resolution magnetic resonance imaging and labeled cortical mantle distance mapping to measure gray matter volume, as well as thickness and the area of the gray/white interface, in the anterior and posterior segments of the cingulate gyrus in 28 subjects with schizophrenia and their non-psychotic siblings, and in 38 healthy control subjects and their siblings.
Results: There was a significant effect of group status on posterior cingulate cortex (PCC) gray matter volume ($p=0.02$). Subjects with schizophrenia and their non-psychotic siblings showed similar reductions of gray matter volume (~10%) in the PCC compared to healthy control subjects and their siblings. In turn, trend level effects of group status were found for thickness ($p=0.08$) and surface area ($p=0.11$) of the PCC. In the combined group of schizophrenia subjects and their siblings, a direct correlation was observed between PCC gray matter volume and negative symptoms. However, the reduction in PCC gray matter volume in schizophrenia subjects and their siblings was proportionate to an overall reduction in whole cerebral volume, i.e., the effect of group on the volume of the PCC became non-significant when cerebral volume was included as a covariate ($p=0.4$). There was no significant effect of group on anterior cingulate cortex volume, thickness, or area.
Conclusions: Our findings suggest that decreases in the gray matter volume of the PCC occur in schizophrenia subjects and their siblings. The presence of such decreases in the non-psychotic siblings of schizophrenia subjects suggests that heritable factors may be involved in the development of cortical abnormalities in schizophrenia.

Keywords: Cingulated; Schizophrenia; Volume; Thickness; Cortex; Sibling; Depth mapping

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1. Introduction

Post-mortem studies of the brains of individuals with schizophrenia have provided evidence of abnormalities in the neuroanatomical architecture of the cortex, especially the cingulate gyrus (Benes et al., 1991; Benes 1991; Benes and Bird 1987; Benes et al., 2001; Chana et al., 2003; Dolan et al., 1995; Todtenkopf et al., 2005). In turn, *in vivo* neuroimaging studies comparing individuals with schizophrenia to healthy controls have shown evidence of decreased gray matter volume in the anterior cingulate gyrus (Ha et al., 2004; Job et al., 2002; Shapleske et al., 2002; Sigmundsson et al., 2001), the posterior cingulate gyrus (Hulshoff Pol et al., 2001; Sowell et al., 2000), and across the entire cingulate gyrus (Mitelman et al., 2003; Narr et al., 2005; Wang et al., 2007). These abnormalities may be relevant to the cognitive disturbances associated with schizophrenia, as the cingulate gyrus is involved in a variety of cognitive functions, including error detection (anterior cingulate gyrus) and spatial memory (posterior cingulate gyrus), which are known to be disturbed in schizophrenia (Garavan et al., 2003; Kerns et al., 2005; Mayes et al., 2004). However, the causes of such changes, more specifically whether they are due to heritable or environmental influences associated with the disorder, are unknown.

The influence of heritable factors on the pathogenesis of a neurobiological abnormality associated with schizophrenia may be examined by studying relatives of individuals with schizophrenia. Assuming that a particular abnormality is heritable in the general population and related to a heritable vulnerability to develop the disorder, one would expect it to be present in an attenuated form in the siblings of schizophrenia subjects (Cardno et al., 1999). For example, the non-psychotic siblings of individuals with schizophrenia demonstrate attenuated impairments in several elements of neurocognitive function (Cannon et al., 1994; Delawalla et al., 2006; Karlsgodt et al., 2007), and studies of brain structures among the first-degree relatives of schizophrenia subjects are also consistent with this hypothesis (Boos et al., 2007; Cannon et al., 1998; Gogtay et al., 2003; Harms et al., 2007; Staal et al., 1998).

In the present study, we examined the gray matter volume, thickness and area of the anterior and posterior cingulate cortices in schizophrenia subjects and their non-psychotic siblings. We selected the cingulate gyrus as a cortical region of interest for this study because we previously reported a decrease in cingulate gyrus volume and associated cortical thinning in schizophrenia subjects (Wang et al., 2007). Moreover, neurocognitive functions relevant to the cingulate gyrus (e.g., attention) have been observed to be impaired in the relatives of patients with schizophrenia (Cannon et al., 1994). Finally, measures of cortical structure have been found to be heritable in the general population (Lenroot et al., 2007). Therefore, given these prior observations, we hypothesized that the non-psychotic siblings of individuals with schizophrenia would demonstrate cingulate gyrus gray matter volumes and thicknesses intermediate between their affected siblings and the healthy control subjects.

2. Methods

2.1. Subjects

The subjects included in this study were drawn from a larger population of 216 subjects who volunteered for studies of brain structure and function at the Conte Center for the Neuroscience of Mental Disorders at Washington University School of Medicine in St. Louis. The study was approved by the internal review board of Washington University School of Medicine. Subjects consisted of complete pairs of individuals with schizophrenia and their non-psychotic siblings ($n=28$ pairs), and healthy control subjects and their siblings ($n=38$ pairs), matched for age, race, and parental socioeconomic status (Table 1). This cohort of subjects was highly overlapping (122 subjects in common) with the cohort used in our previous reports on the thalamus (Harms et al., 2007) and basal ganglia (Mamah et al., 2008).

All subjects gave informed consent after the risks and benefits of participation were explained. Using the Diagnostic and Statistical Manual for Mental Disorders — Fourth Edition (DSM-IV) (American Psychiatric Association 1994), all subjects were diagnosed on the basis of the consensus of a psychiatrist who conducted a semi-structured interview and a specially-trained research assistant who used the Structured Clinical Interview for the DSM-IV (First et al., 1995). The subjects with schizophrenia met DSM-IV criteria for schizophrenia, while the healthy comparison subjects had no lifetime history of DSM-IV psychotic or major mood disorders (i.e., major depressive disorder and bipolar disorder) and no first-degree relatives with a psychotic disorder. The subjects with schizophrenia were treated with antipsychotic medications, and had been clinically stable for at least two weeks prior to their participation. Subjects in any group were excluded if they met DSM-IV criteria for substance abuse or dependence within the month preceding assessment, met DSM-IV criteria for mental retardation, had a severe or unstable medical disorder, or had a head injury with neurological sequelae or loss of consciousness.

The siblings of the schizophrenia subjects were excluded if they had a lifetime history of a DSM-IV psychotic

Table 1
Demographic characteristics of subjects with schizophrenia (SCZ) and their siblings (SCZ–SIB), and control subjects (CON) and their siblings (CON–SIB)

Demographic profiles of subjects					
N	SCZ	SCZ–SIB	CON–SIB	CON	χ^2 or *F*, *p*
	28	28	38	38	
Gender (M/F)	23/5	12/16	11/27	21/17	$\chi^2(3)=19.3$, $p=0.0002$
Age: mean (std)	22.5 (3.0)	22.1 (3.4)	20.4 (3.5)	21.2 (3.5)	$F(3,128)=2.5$, $p=0.07$
Race (Caucasian/African American	18/10	18/10	30/8	30/8	$\chi^2(3)=3.5$, $p=0.3$
Handedness (R/L)	24/4	25/3	36/2	33/5	$\chi^2(3)=1.8$, $p=0.6$
Parental SES: mean (std)	3.0 (1.2)	3.0 (1.1)	3.1 (0.9)	2.9 (0.9)	$F(3,128)=0.2$, $p=0.9$

Minor differences in how the siblings reported their parental information account for the small differences in SES between the siblings of a sib-pair. Mean duration of illness for the schizophrenia subjects was 4.3 (SD 4.3) years.

disorder, but not other DSM-IV disorders. Therefore, the siblings of healthy comparison subjects were included as a comparison group to control for possible effects on brain structure arising from psychiatric disorders other than schizophrenia. The siblings of healthy comparison subjects were enrolled in an identical manner to the siblings of the schizophrenia subjects, and met the same inclusion and exclusion criteria.

2.2. Clinical and cognitive assessments

Psychopathology and cognitive function were assessed as previously described (Delawalla et al., 2006; Harms et al., 2007) so that we could examine the correlation between these measures and the neuroanatomical measures in the schizophrenia subjects and their siblings. Briefly, psychopathology was measured using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 1999), and the Chapman Psychosis Proneness Scales (Chapman et al., 1995). Cognitive function was assessed using a battery of neuropsychological tests (Delawalla et al., 2006; Harms et al., 2007). The raw scores from the individual psychopathological and neuropsychological tests were first converted to *z*-scores using the mean and standard deviation computed from the center-wide sample of 216 subjects. The *z*-scores of the items comprising each domain were then averaged to yield three domains of clinical symptoms – positive symptoms, negative symptoms, and thought disorganization – and four broad cognitive domains – working memory, episodic memory, executive function, and attention. The mean scores of these domains by subject group were nearly identical to those reported in Harms et al. (2007), as expected given the highly overlapping subject pools.

2.3. MR scanning and image analysis

All MR scans were collected on a 1.5-Tesla VISION system (Siemens Medical Systems). The MR scanning protocol included the collection of multiple (2–4) high-resolution, 3D T1-weighted MPRAGE volumes: voxel resolution: 1 mm × 1 mm × 1.25 mm, TR: 9.7 ms, TE: 4.0 ms, flip angle: 10°10°, scan time: 6.5 min per acquisition. The MPRAGE scans for each subject were aligned with the first scan and averaged to create a low-noise image volume (Buckner et al., 2004), which was then trilinearly interpolated into 0.5 mm × 0.5 mm × 0.5 mm isotropic voxels to produce smoother intensity histograms for more accurate segmentation.

The anatomic boundaries of the cingulate gyrus, and its division into anterior (ACC) and posterior (PCC) sections, were defined as previously reported (Ratnanather et al., 2004; Wang et al., 2007). The paracingulate gyrus between the cingulate sulcus and any paracingulate sulcus was not included as part of the ACC. However, variability in the presence of the paracingulate sulcus influences measures of ACC morphometry (Fornito et al., 2008a) (Fornito et al., 2008a,b). Therefore, the prominence of the paracingulate sulcus was coded using a 3 tiered rating system (0 for absent, 1 for present, 2 for prominent), according to the guidelines in Yucel et al. (2001), and was used as a covariate in the analyses of the ACC measures.

We used Labeled Cortical Mantle Distance Map (LCMDM) to derive estimates of cingulate gyrus volume and thickness (Miller et al., 2003; Miller et al., 2000; Priebe et al., 2006; Ratnanather et al., 2004; Wang et al., 2007). First, a region of interest (ROI) containing the cingulate gyrus and its surrounding voxels was first defined in the preprocessed image volume (Fig. 1A), and the alternating kernel method (AKM) (Ratnanather et al., 2004) was used to segment the ROI into gray matter (GM), white matter (WM) and cerebral-spinal fluid

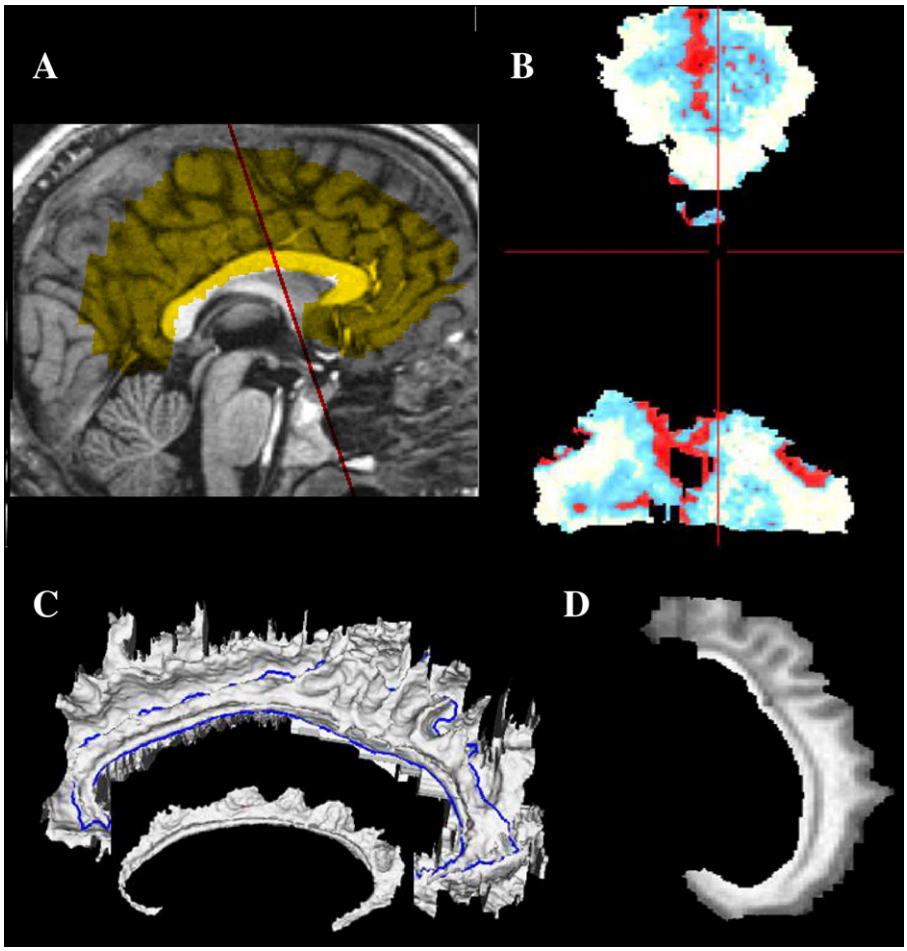

Fig. 1. Outline of cingulate gyrus procedure. A. Panel depicts the rough region of interest (yellow) surrounding the cingulate gyrus in a sagittal view. The red line shows the division between ACC and PCC. B. The alternating kernel method was used to segment gray matter (blue), white matter (white), and cerebral-spinal fluid (red) in a local region of interest, in coronal view. As the cingulate gyrus follows a "C" shape (in sagittal view), a coronal section sometimes contains a top and bottom region, as depicted here. Here the top region corresponds to a section through the dorsal portion of the PCC, and the bottom region corresponds to the isthmus of the PCC. C. A path following the sulcal boundaries of the cingulate was traced along the surface corresponding to the cingulate gyrus ROI, from which the cingulate subsurface was extracted. The top part of the panel shows the ROI-surface with the sulcal boundary path drawn in blue, and the bottom part of the panel shows the extracted cingulate subsurface, which was the portion of the ROI-surface surrounded by the blue path, in sagittal view. D. The cingulate region of interest was created by projecting voxels into the subsurface, shown in a sideways sagittal view. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(CSF) (Fig. 1B). A topologically correct isosurface was then generated at the GM/WM interface (Han et al., 2001; Han et al., 2002). We then used dynamic programming to delineate the boundary of the anterior and posterior cingulate gyrus subsurfaces (Khaneja et al., 1998) (Fig. 1C,D). All of these neuroanatomical algorithms were implemented by one of the authors (DC), who was blind to diagnosis and subject information. Finally, LCMDM was used to compute the gray matter volume and thickness, while area of the GM/WM interface was calculated from the delineated isosurfaces of the ACC and PCC as detailed in Wang et al. (2007).

Mean whole-brain cortical gray matter thickness and total cerebral brain volume were calculated using FreeSurfer (Dale et al., 1999; Desikan et al., 2006; Fischl et al., 2004; Fischl et al., 1999; Segonne et al., 2007). Total cerebral volume included cortical and subcortical gray matter plus white matter and was specifically defined as the volume (L+R) enclosed interior to the FreeSurfer pial surfaces (i.e., interface of gray matter with cerebrospinal fluid) minus the volume of the lateral ventricles (L+R) from the FreeSurfer volumetric segmentation. These measures were used as covariates in the analyses.

2.4. Statistical analysis

Group comparisons of gray matter volume were performed using a mixed-model with group, hemisphere, and group * hemisphere as fixed effect predictors. Because volume can be roughly considered as the product of thickness and area, we also performed group comparisons of these measures. The mixed-model estimated the covariance (correlation) in the residuals due to both the sibling and across hemisphere relationships. Gender was included as a covariate in all analyses since our groups differed in their gender distribution. Scores for the prominence of the paracingulate sulcus were also included as a covariate in the analyses of the ACC. The cingulate volume and area measures were analyzed both without and with total cerebral volume as an additional covariate, while cingulate thickness was analyzed without and with mean overall cortical thickness (from FreeSurfer) as an additional covariate. The significance of the predictor variables was assessed using Type III sums-of-squares. All statistical analyses were performed in SAS 9.1 (SAS Institute Inc., Cary, NC).

Correlations between neuroanatomical measures and the clinical and cognitive domain scores were computed on an exploratory basis, using Spearman's rho and without correction for multiple comparisons. The correlation analysis was confined to the cingulate measures that demonstrated a main effect of group status, and was conducted using the combined group of schizophrenia subjects and their siblings while controlling for group status. For any correlated measures with $p<0.01$, we also computed the correlations within the schizophrenia subjects and their siblings separately.

3. Results

3.1. Anterior cingulate cortex

The volume, thickness, and surface area of the ACC showed main effects of hemisphere (all $p<0.002$), but no main effect of group ($p>0.4$), and no group-by-hemisphere interaction ($p>0.2$). Based on the estimated marginal means for the hemisphere effect, volume and area were respectively 11% and 9% larger in the right than left ACC, while thickness was 9% smaller in the right than left ACC. The effect of group status on ACC volume, thickness, and area remained non-significant ($p>0.2$) when (1) total cerebral volume was added as a covariate to the analysis of volume and area and (2) mean cortical thickness was added as a covariate to the analysis of anterior cingulate thickness.

3.2. Posterior cingulate cortex

There was a significant effect of group status on PCC volume ($F(3,56)=3.6$, $p=0.02$). Post-hoc pair-wise group comparisons indicated that both the subjects with schizophrenia and their siblings had significantly smaller PCC volumes than the healthy control subjects (11%, $t_{88}=-2.9$, $p=0.005$, and 9%, $t_{73}=-2.4$, $p=0.02$, respectively; Table 2). Subjects with schizophrenia and their siblings had similar PCC volumes ($t_{30}=-0.5$, $p=0.6$), as did the healthy control subjects and their siblings ($t_{37}=0.25$, $p=0.8$). There was a trend toward a main effect of group on the thickness of the PCC ($F(3,57)=2.4$, $p=0.08$), with the siblings of the schizophrenia subjects having the smallest thickness (6% smaller than the controls and siblings of controls, $t_{72}=-2.3$, $p=0.02$ for both comparisons). However, schizophrenia subjects and controls did not differ significantly in PCC thickness ($p=0.26$). There was also a trend for an effect of group on PCC area ($F(3,58)=2.1$, $p=0.11$). The schizophrenia subjects had an 8% smaller area than controls ($t_{90}=-2.5$, $p=0.01$), although the area in the siblings of the schizophrenia subjects was not statistically different from either the control subjects ($p=0.33$) or their siblings ($p=0.70$). There was a main effect of hemisphere on PCC thickness (4% greater in left hemisphere) and area (6% larger in left hemisphere, $p<0.0001$ for both), but not on volume ($p=0.6$). None of the three measures showed a hemisphere-by-group interaction ($p>0.3$).

When we included total cerebral volume as a covariate, the effect of group on PCC volume became non-significant ($p=0.40$). The effect of group on PCC area and thickness remained non-significant upon inclusion of total cerebral volume and mean cortical thickness as covariates, respectively ($p=0.15$, $p=0.26$).

3.3. Covariates

There were no group differences in the prominence of the paracingulate sulcus in either hemisphere (left: $\chi^2=6.4$ $df=6$, $p=0.4$; right: $\chi^2=4.7$, $df=6$, $p=0.6$). Across the 132 total subjects, the percentage of subjects with a paracingulate sulcus rated as absent, present, and prominent was 54%, 17%, and 29%, respectively, for the left hemisphere, and 73%, 8%, and 18%, respectively, for the right hemisphere. The prominence of the paracingulate sulcus had a strong effect on volume, thickness, and area of the ACC ($p<0.0001$ for all three measures), with each step-wise increase in its prominence predicting a decrease in each of the three measures.

Table 2
Least square means (standard errors) in each hemisphere and segment of the cingulate gyrus, from a mixed-model with group, hemisphere, and group*hemisphere as fixed effect predictors, controlling for gender in the posterior cingulate (PCC), and gender and prominence of the paracingulate sulcus in the anterior cingulate (ACC)

Adjusted morphometric measures in anterior and posterior cingulate cortex												
	Volume (cm^3)				Surface area (cm^2)				Thickness (mm)			
	ACC		PCC		ACC		PCC		ACC		PCC	
	L	R	L	R	L	R	L	R	L	R	L	R
SCZ	3.75 (0.21)	4.18 (0.20)	8.08 (0.26)	7.87 (0.27)	11.52 (0.47)	12.47 (0.48)	27.37 (0.81)	25.05 (0.77)	3.37 (0.08)	3.05 (0.08)	3.09 (0.06)	2.97 (0.06)
SCZ–SIB	3.51 (0.20)	4.18 (0.19)	8.07 (0.25)	8.20 (0.26)	11.17 (0.52)	13.21 (0.52)	27.97 (0.89)	27.27 (0.84)	3.27 (0.07)	3.01 (0.07)	2.98 (0.06)	2.87 (0.06)
CON–SIB	3.77 (0.19)	4.26 (0.21)	8.95 (0.23)	8.74 (0.24)	11.78 (0.50)	12.59 (0.50)	28.96 (0.62)	27.01 (0.65)	3.43 (0.08)	3.18 (0.08)	3.19 (0.06)	3.05 (0.05)
CON	3.98 (0.19)	4.07 (0.19)	8.90 (0.24)	8.91 (0.26)	12.14 (0.47)	12.36 (0.44)	29.22 (0.69)	27.98 (0.72)	3.41 (0.06)	3.09 (0.06)	3.19 (0.06)	3.05 (0.05)

There was a significant effect of group status on PCC volume ($F(3,56)=3.6$, $p=0.02$).

Mixed-model analysis with group and gender as fixed effects indicated an effect of group on both total cerebral volume and mean cortical thickness ($F(3,50)=4.9$, $p=0.004$; $F(3,51)=4.7$, $p=0.006$, respectively). Post-hoc pair-wise comparisons showed that the schizophrenia subjects had smaller total brain volumes than their siblings (schizophrenia subjects: least square mean cerebral volume=934 cm^3, SE=19.1; their siblings: 967 cm^3, SE=14.4; $t_{31}=-2.0$, $p=0.06$), who in turn had smaller brain volumes than the control subjects (1008 cm^3, SE=14.0; $t_{62}=-2.1$, $p=0.04$). However, the cerebral volumes of the control subjects and their siblings (1033 cm^3, SE=15.6) were not different ($t_{39}=-1.5$, $p=0.14$). Mean cortical thickness of the schizophrenia subjects was thinner than the controls (schizophrenia subjects: 2.42 mm, SE=0.015; controls: 2.47 mm, SE=0.015; $t_{66}=-2.4$, $p=0.02$). Mean cortical thickness of the siblings of the schizophrenia subjects (2.43 mm, SE=0.015) trended toward a reduction compared to controls ($t_{63}=-1.7$, $p=0.10$) and was significantly reduced compared to control siblings (2.50 mm, SE=0.014; $t_{62}=-3.1$, $p=0.003$).

Since there was a trend for a small age difference between groups (Table 1), we also conducted supplementary analyses using age as an additional covariate in the mixed-models that tested for group differences in volume, thickness, and surface area of the ACC and PCC. (Total cerebral volume or mean cortical thickness were not included as covariates in these models). The effect of age itself was significant on the thickness of both the ACC and PCC ($F(1,122)=6.6$, $p=0.01$, and $F(1,123)$, $p=0.01$, respectively). However, the significance of the main effect of group was unaffected by the inclusion of age as a covariate ($p=0.04$, 0.15, and 0.09 for the effect of group on volume, thickness, and area of the PCC, respectively, upon inclusion of age as a covariate).

3.4. Correlations of clinical and cognitive variables with PCC volume

Based on the premise that the schizophrenia subjects and their siblings shared a common neurobiological basis for reduction in the gray matter volume of the PCC, we computed partial correlations between PCC volume (right and left separately) and the clinical and cognitive domain scores within this combined group of subjects, controlling for group status. The only significant correlation was an inverse correlation between left PCC volume and negative symptoms (Spearman's $r=-0.36$, $p=0.007$), such that a larger left PCC volume was associated with fewer negative symptoms. An analysis of each group separately showed that this relationship was driven by the sibling group more than the group of

schizophrenia subjects (siblings: $r=-0.43$, $p=0.02$; schizophrenia subjects: $r=-0.28$, $p=0.15$), though both correlations were in the same direction.

4. Discussion

The results of this study demonstrate the presence of reduced gray matter volumes of the posterior segment of the cingulate gyrus in schizophrenia subjects and their non-psychotic siblings relative to healthy control subjects and their siblings. The PCC volumes of the non-psychotic siblings did not differ from their affected siblings. In addition, smaller PCC volumes were correlated with the intensity of negative symptoms in the combined group of schizophrenia subjects and their non-psychotic siblings. While this relationship was not hypothesized, it does suggest that the difference in PCC volume observed in association with schizophrenia may have clinical consequences. Interestingly, we have previously observed an increase in negative symptoms in the non-psychotic siblings of schizophrenia subjects as compared to healthy controls and their siblings (Delawalla, et al., 2006).

Our analysis of area and cortical thickness suggested that the observed gray matter volume reductions in the posterior cingulate most likely arose from some combination of decreases in both area and thickness. Previous studies of the cingulate gyrus in schizophrenia subjects have attributed gray matter volume decreases to cortical thinning (Bouras et al., 2001; Chana et al., 2003; Ongur et al., 2003). Reduced neuronal cell size has been suggested as an explanation for observed cortical thinning in the anterior cingulate gyrus (Cotter et al., 2001), although reduced glial density (Benes et al., 2001; Todtenkopf et al., 2005) and reductions in the density of pyramidal and nonpyramidal cells (Olney and Farber 1995) are also plausible explanations. Unfortunately, the methods available for *in vivo* neuroimaging studies cannot yet discern among these various cellular correlates of gray matter volume reduction.

Decreased ACC and PCC volumes have been previously reported in subjects with schizophrenia as compared to healthy controls (Ha et al., 2004; Hulshoff Pol et al., 2001; Job et al., 2002; Shapleske et al., 2002; Sigmundsson et al., 2001; Sowell et al., 2000). The absence of ACC effects in this study may be related to the relatively young age of the schizophrenia subjects, as most of the cited studies employed subjects with at least 10 years of illness. Consistent with this hypothesis, Fornito et al (2008b) found no difference in gray matter volume of "limbic" ACC in first-episode schizophrenia patients relative to controls. That we detected a decrease in ACC volume in a previous study of more chronic schizophrenia subjects suggests that deficits in ACC volume may eventually manifest as the disease progresses (Farrow et al., 2005; Vidal et al., 2006).

In the PCC, we found that the effect of group on PCC volume became non-significant after inclusion of total cerebral volume as a covariate. This indicates that the PCC volume reduction in these schizophrenia subjects and their siblings was proportionate to changes in overall cerebral volume. Notably, in our previous study of a more chronic cohort of schizophrenia subjects (mean illness duration of 12 years) (Wang et al., 2007), we found that the deficit in PCC volume between schizophrenia subjects and controls was significant even after accounting for total brain volume. This suggests that deficits in PCC volume may increase as the disease progresses, and to a greater degree than any further changes in total brain volume. Taken together, it can be suggested that the disease process of schizophrenia may have progressive effects on both the ACC and PCC over the course of the illness.

We hypothesized that the non-psychotic siblings would have intermediate changes because they share approximately half of their genes. Thus, the reduction in PCC volume in schizophrenia subjects and their non-psychotic siblings is consistent with the hypothesis that abnormalities of brain structure occur in schizophrenia because of heritable influences. However, we cannot exclude the possible effect of common environmental factors. Several studies have correlated adverse social factors with the development of psychotic disorders (Cantor-Graae 2007; Harrison et al., 2001; Wicks et al., 2005). Unfortunately, it is difficult to collect reliable information on the presence and severity of adverse environmental events that may contribute to the pathogenesis of disease (Cantor-Graae 2007).

The effects of antipsychotic drug treatment must be considered when examining neuroanatomical changes in patients with schizophrenia. Antipsychotic drugs have been shown to effect gray matter volume in patients with schizophrenia (Lieberman et al., 2005). Exposure to typical neuroleptics has been associated with increased ACC volume, while exposure to atypical neuroleptics was correlated to decreased ACC volume (Kopelman et al., 2005; McCormick et al. 2005). However, antipsychotic drug effects would not be involved in findings of neuroanatomical abnormalities in the untreated siblings of the schizophrenia subjects. Thus, our finding of reduced PCC volume in the siblings of schizophrenia subjects strongly suggests that the reduction of PCC volume in their affected siblings cannot be solely explained as a consequence of antipsychotic drug treatment.

The list of genes implicated in the pathogenesis of schizophrenia is steadily growing (Arnold et al.

2005), and many of the identified genes are known to play a role in neurodevelopment. For example, *Neuregulin 1* has been shown to moderate migration of neuronal precursors, aid in glial development and survival, and act as a neurotrophic factor (Anton et al., 1997; Rio et al., 1997). The *disrupted in schizophrenia 1* (*DISK1*) gene has also been hypothesized to play a role in neuronal migration, axonal guidance and outgrowth (Bellon, 2007; Miyoshi et al., 2003). However, the influence of such genes would be expected to exert more general effects on cortical architecture. Notably, the PCC changes observed in the siblings of the schizophrenia subjects were proportionate to overall changes in cerebral volume. Therefore, it is possible that our findings are related to genes that influence general aspects of cortical development. Alternately, genes with general effects on cortical development could have greater or lesser effects on particular cortical regions because of a relationship between the timing of their expression and the timing of maturation of particular cortical regions, become active during the period of maturation of a particular brain region. Further studies of neuroanatomical irregularities in patients with schizophrenia and their family members in conjunction with studies of genetic polymorphisms known to alter the risk of developing schizophrenia are needed to shed light on the role of genetic influences on cortical development in the pathogenesis of schizophrenia.

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Contributors

John G. Csernansky and Lei Wang designed the study and wrote the protocol. Daniel R. Calabrese and Michael P. Harms managed the literature searches and analyses, and undertook the statistical analysis, and Daniel R. Calabrese wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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