Reduced anterior cingulate gray matter volume and thickness in subjects with deficit schizophrenia

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Abstract

Background: Patients with deficit schizophrenia (D-SZ) differ from patients with the non-deficit form of schizophrenia (ND-SZ) in several aspects such as risk factors, neurobiological correlates, treatment response and clinical outcome. It has been debated if brain morphology could differentiate D-SZ from ND-SZ. Anterior cingulate gyrus (ACG) region regulates cognitive and emotional processing and past studies reported structural changes in this region in patients with SZ.

Methods: 1.5-T 3D MRI scans were obtained from 18 D-SZ patients, 30 ND-SZ patients and 82 healthy controls (HCs). We used FreeSurfer-initalized labeled cortical distance mapping (FSLCDM) to measure ACG gray matter volume, cortical thickness, and area of the gray/white interface. Furthermore, cortical thickness was compared among the 3 groups using the pooled labeled cortical distance mapping (LCDM) method.

Results: The right ACG gray matter volume was significantly reduced in D-SZ patients as compared with healthy controls ($p = 0.005$). Pooled LCDM demonstrated that the ACG cortex was bilaterally thinner in both the ND-SZ group and the D-SZ group compared with the control group. The ACG cortex of the D-SZ group was thinner than the ND-SZ group.

Conclusion: Our data suggest that qualitative, categorical differences in neuroanatomy may distinguish between deficit and non-deficit subtypes of schizophrenia.

Introduction

Since Kraepelin, the observed clinical heterogeneity of schizophrenia has been the source of considerable controversy. The deficit syndrome of schizophrenia (D-SZ) has been proposed as a clinical subtype defined by severe primary negative symptoms that endure as trait-like features even during periods of clinical stability(Carpenter et al. 1988). By definition, primary negative symptoms are not attributable to secondary causes such as depression, medication side-effects, mental retardation or social deprivation. Patients with D-SZ differ from patients with the non-deficit form of schizophrenia (ND-SZ) in terms of risk factors(Messias et al. 2004), neurobiological correlates(Lahti et al. 2001;Quarantelli et al. 2002), treatment response(Kirkpatrick et al. 2001), and long-term clinical outcome(Tek et al. 2001). Patients with D-SZ also demonstrate cognitive deficits relative to healthy adults and patients with ND-SZ (Cascella et al. 2008;Wagman et al. 1987).

In a previous neuroimaging study using magnetic resonance imaging (MRI), we investigated the differences in regional gray-matter volume between D-SZ with ND-SZ by using voxel-based morphometry (VBM) and found that patients with D-SZ showed decreased gray matter volume in brain areas including the anterior cingulate gyrus (ACG)(Cascella et al. 2010) which is part of the limbic lobe and whose main function is regulation of cognitive and emotional processing(Bush et al. 2000). This is consistent with several structural neuroimaging studies of the ACG in SZ that have showed reduced bilateral gray matter (GM) volume (Fujiwara et al. 2007;Suzuki et al. 2002;Yamasue et al.

2004).

However results have not been unanimous (Kopelman et al. 2005;Ohnuma et al. 1997). A more specific measurement of ACG pathology in SZ has been reported by Yücel et al.(2002a; 2002b) who examined the sulcal-gyral morphology of the ACG, focusing on the presence or absence of a paracingulate sulcus (PCS) and continuity of the cingulate sulcus (CS). They found that SZ patients were less likely to manifest a well-developed PCS/CS in the left hemisphere, resulting in a lack of 'normal' leftward asymmetry. Bilateral volume reduction in Brodmann area 32 was observed in 27 schizophrenia subjects with prominent negative symptoms compared with 27 control subjects (Sigmundsson et al. 2001). Also Preuss et al. (Preuss et al. 2010) reported that right hemispheric ACG volume reduction in SZ patients compared to healthy controls were most pronounced in SZ patients with more negative symptoms (Preuss et al. 2010). Similar findings have been reported recently in SZ patients in their early stages of the disease (Aston et al. 2012).

In another previous study, individuals with SZ showed smaller ACG gray matter volume and thickness, but not surface area, than healthy controls using labeled cortical distance mapping (LCDM) (Wang et al. 2007) . Thinning of the left ACG correlated with a longer duration of illness and a greater severity of psychotic symptoms (Wang et al. 2007).

LCDM is a powerful tool in quantifying such morphometric differences and characterizes the morphometry of the laminar cortical mantle of cortical structures. Specifically, LCDM data are distances of labeled gray matter (GM) voxels with respect to the gray/white matter cortical surface and thus are local measures characterizing the

morphometry of the cortical mantle (Ceyhan et al. 2011). LCDMs have been used to quantify cortical thickness in the cingulate in subjects with Alzheimer's (Miller et al. 2003) and schizophrenia (Wang et al. 2007), in the ventral medial prefrontal cortex in subjects with major depressive disorder (Ceyhan et al. 2011), and in the planum temporale in subjects with schizophrenia (Qiu et al. 2008).

It is therefore opportune to apply the new methodology of LCDM to confirm and expand on previously reported ACG structural abnormality in the D-SZ subgroup adding thickness and surface area to the analysis. Specifically we employ a recently developed automated LCDM pipeline by integrating data from FreeSurfer (Fischl 2012) with LCDM to examine the gray matter volume, thickness and surface area of the ACG in D-SZ and ND-SZ patients.

Methods and materials

Participants

Forty-eight adults (35 males, 13 females) with schizophrenia, diagnosed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders－Fourth Edition (DSM-IV)(American Psychiatric Association 1994) participated in the study. Of these, 18 were recruited for a study of apathy in schizophrenia and traumatic brain injury and constitute the D-SZ group (the Apathy study), 30 were recruited for a study of structural neuroimaging and cognition in psychosis and represent the ND-SZ group (the Psychosis

study). All the patients in both studies were recruited from outpatient clinics, inpatient services, and psychiatric day hospitals affiliated with the Johns Hopkins University and Hospital. Patients were excluded if they had any untreated major medical condition like diabetes or high blood pressure or had had traumatic brain injury with loss of consciousness for more than 1 hour or had a diagnosis of substance abuse for the previous 6 months or dependence for the previous 12 months. The HC group consisted of 82 healthy adult participants in a study of normal aging, brain imaging, and cognition (the ABC study). Participants in the ABC study were recruited from the Baltimore metropolitan region primarily via random digit dialing, although a few were recruited via telephone calls to randomly selected listings from the Baltimore metropolitan area residential telephone directory. ABC study participants who reported any history of dementia, stroke, transient ischemic attack, traumatic brain injury with >1 loss of consciousness, Parkinson's disease, multiple sclerosis, severe heart disease, complicated diabetes, bipolar disorder, schizophrenia, current major depression, current alcohol/drug abuse or dependence were excluded from the present analysis.

Although all the study subjects were from our previous published research (Cascella et al. 2010) we were unable to process some images (one D-SZ patients, one ND-SZ patients, 8 HCs) with Freesurfer and LCDM due to the quality of the raw images.

All three studies (Psychosis, Apathy, and ABC) were approved by the Johns Hopkins Medicine Institutional Review Board and all participants provided written informed consent.

Procedure

Diagnostic and clinical assessments of patients recruited for the Psychosis study included the Diagnostic Interview for Genetic Studies (DIGS)(Nurnberger et al. 1994), Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS)(Andreasen and Olsen 1982), and the Scale to Assess Unawareness of Mental Disorders－Abridged (SUMD-A)(Amador et al. 1994), all of which were administered by a study psychiatrist or psychologist. Patients recruited for the Apathy study underwent a Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (First et al. 1997) rather than the DIGS, but they also received SANS, SAPS, and SUMD. Prior to making a diagnosis, the study clinician also reviewed any available medical and psychiatric records. The designation of deficit syndrome schizophrenia was based on the Schedule for the Deficit Syndrome (SDS), a semi-structured interview with known reliability (Kirkpatrick et al. 1989) by a study psychiatrists (N.G.C.) trained for reliability at the Maryland Psychiatric Research Center (kappa=.79). Collateral information was obtained whenever possible.

Each HC group participant also underwent diagnostic and clinical assessments by a study psychiatrist or psychologist. These included the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al. 1996), review of medical history, physical and neurological examinations, laboratory blood studies, anatomic brain magnetic resonance imaging (MRI), and cognitive testing.

Neuropsychological assessment of all study participants included a battery of tests designed to cover a broad range of cognitive abilities. Testing required about 2 hours and

yielded 18 individual measures. Results of the cognitive assessment have been reported elsewhere (Cascella et al. 2008). However, premorbid IQ was assessed using the Hopkins Adult Reading Test (HART) (Schretlen et al. 2009) and is reported.

MRI data acquisition

Brain imaging was acquired on the same single 1.5T GE Sigma scanner (General Electric, Milwaukee, WI) to assure continuity of scan parameters. Participants were scanned from 2000 to 2004. Images were acquired with a 3D volumetric radiofrequency spoiled gradient echo (SPGR) series with the following scan parameters: repetition time = 35 ms, echo time = 5 ms, flip angle = 45, matrix size = 256 × 256, field of view = 240 mm. This sequence produced 124 contiguous, T1-weighted images (slice thickness = 1.5 mm).There was no major upgrade of the scanner during the period of brain imaging acquisition.

FreeSurfer-initialized labeled cortical distance mapping (FSLCDM)

The FSLCDM pipeline provides measures for cortical thickness, volume, and surface area of multiple cortical regions in the brain. The pipeline has two steps: first FreeSurfer (FS) generates the gray/white cortical surface and parcellates the brain into regions of interest (ROIs) and then labeled cortical distance mapping (LCDM) segments the cortical ROI and computes the distance of each gray matter voxel from the FS surface.

FreeSurfer (FS) initiates the FSLCDM Pipeline by generating the GM/WM surface and parcellating the brain MRI image into ROIs. FS reconstructs the cortical surface

defined by the white/gray matter boundary in 3-D MRI volume (Dale et al. 1999; Fischl and Dale 2000). Region labels are assigned to each point on the cortical surface based on a probabilistic estimate from a manually labeled training set (Fischl et al. 2004; Desikan et al. 2006). Geometric information from the cortex as well as neuroanatomical convention is used to assign labels. In this study, the anterior cingulate spans from the rostral extent of the cingulate sulcus to the mammillary bodies and from the medial aspect of the cortex to the superior frontal gryus.

Once the cortical surface and labels are determined, this information is fed into the LCDM Pipeline to calculate the thickness, surface area, and volume of the ROI. The FS developed region labels are used to extract the ROI from the original skull-stripped MRI. The ROI is then segmented into white matter, gray matter, and cerebrospinal fluid using a mixture model averaging method (Lee et al. 2008; Wentz 2012).

The procedure for generating LCDMs previously developed for the cingulate (Miller et al. 2003; Miller et al. 2000;(Ratnanather et al. 2004) is then applied. To get a distance map for the gray matter, the distance between each GM voxel and the closest GM/WM surface vertex is calculated at a 1x1x1 mm resolution. Voxels in the range of -2 to 8mm were included in the data analysis. This data gives information on the probability distribution function of the gray matter distance from the GM/WM surface. A cumulative distribution function (CDF) is then calculated and the cortical thickness is determined by the distance where the CDF reaches 95 percent. Due to outlier voxels at distances greater than 6mm, the area under the CDF up to this 95 % point is used as the volume for the region. The

surface area was calculated from the triangulated surface.

Statistical analysis

Demographic variables (e.g., age, gender, race) and clinical characteristics (i.e., medications and SANS/SAPS scores) were compared among groups via one-way analysis of variance (ANOVA), two-sample t test and chi square test.

We compared cortical thickness, volume and surface area of ACG across the diagnostic groups by analysis of covariance (ANCOVA) with diagnosis (i.e., D-SZ, ND-DZ or HC) as the between-subject factor, and age, gender and intracranial volume (ICV) as covariates. To prevent possible type 1 errors, we used Bonferroni correction for post hoc pairwise comparison. The associations of the ACG measures and clinical variables (i.e., SAPS/SANS scores, medications, estimated IQ, and the duration of illness) were examined by calculating partial correlation coefficients controlling for age, gender and ICV.

Pooled LCDM

To explore the differences between the control, ND-SZ, and D-SZ groups, LCDM distance data is pooled together within each group. The LCDM distances are combined across subjects resulting in three distributions which emphasizes the common group morphometric traits and lessens the effect of individual variation. The pooled LCDMs for each group are statistically compared to each other under the null hypothesis that they come from the same distribution. Pooling LCDMs is a technique that has been validated (Ceyhan et al. 2011). Three nonparametric statistical tests were performed. The nonparametric tests employed

are Kruskal-Wallis test (KW) for multi-group comparisons, Mann-Whitney-U test (MWU) for pairwise comparisons, and Kolmogorov-Smirnov (K-S) test for CDF comparisons. Although, there is an overlap in what these methods are testing, they provide different, but potentially useful information. In particular, K-W and MWU tests are based on the ranking of the distances, and they indicate significant differences in the ranks and hence in the distributions of the distances between the groups. Furthermore, MWU test also provides a direction in the sense that which group tends to be smaller and which tends to be larger compared to another. On the other hand, K-S test directly tests the distributions between the groups, however, by construction it also may provide stochastic ordering of the distances, which may not be obtained from K-W and MWU tests without careful and detailed investigation of the CDF plots. If KW test for multi-group comparison gave significant results, a greater than and less than test were performed in order to determine the direction of significance. The Kolmogorov-Smirnov test (KS-test) was performed to compare the shape of the pooled LCDM distributions. In this test the empirical CDFs of the pooled distances are compared for two groups. The distance where the CDFs differs the most in the horizontal direction is calculated and the statistical significance of this parameter is determined. Significance in the 'less than' test implies that the first sample is actually stochastically greater than the second meaning that if one chooses a voxel at random in the cingulate from each of the groups, it is more likely to be closer to the gray-white boundary in the first group rather than the second group. MWU test was performed to assess if one dataset tended to have larger values than the other. The null

hypothesis being that the distributions are equal. Briefly, this test involves combining all the data from the two groups and assigning each data point a rank. These ranks are then added up for the two groups and using these sums the distributions are compared. We performed a final parametric test, Welch's t-test which evaluates the null hypothesis that the means of the distance data for two groups are equal.

Compared to nonparametric tests, parametric tests assume normality (i.e., Gaussianity) of the distances, which is severely violated by LCDM distances hence preference is given to nonparametric tests above described. However, our Monte Carlo validation study (Ceyhan et al., 2011) revealed that this assumption violation has mild influence on the results of LCDM distances (as we are using it for comparative purposes, not for a test as “mean of a group equals a certain value”, in that case, this violation would render the results invalid). Hence, we choose to employ parametric tests as well. Furthermore, parametric tests provide different information compared to nonparametric ones. In particular, parametric tests (ANOVA and t-tests, the counterparts of K-W and MWU tests) provide a comparison in location (i.e., means) of the LCDM distances, and are more sensitive to the magnitude of the distances, rather than their distributions. Hence we extract related but different information from the LCDM distances using both parametric and nonparametric tests.

The statistical significance level was set as $p < 0.05$ (two-tailed).

Results

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the study samples. Patients with D-SZ were significantly younger than ND-SZ patients and HCs (p=0.035).The male/female ratio did not differ between the two patient subgroups, but there were fewer female patients than female HCs (p=0.01). D-SZ patients completed fewer years of schooling than HCs (11.8 vs. 14 years) ($p < 0.001$) but not fewer years of schooling than the ND-SZ patients (12.2 years), and had lower estimates of premorbid IQ (p=0.001). Also the patients with D-SZ and ND-SZ did not differ significantly in mean age at illness onset or number of psychiatric hospital admissions. Those with ND-SZ were ill longer than those with D-SZ at the time of study ($p = 0.038$). As expected, D-SZ patients were rated as showing more severe negative symptoms (SANS) than ND-SZ patients ($p < 0.001$). However, D-SZ patients showed less severe positive symptoms (SAPS) than the ND-SZ (p=0.027). Finally, more ND-SZ than D-SZ patients were being treated with antidepressant medications (p=0.038).

ACG measures, analysis of covariance

Figure 1 shows each subject's LCDM of ACG. The volume, thickness and surface area measures of the left and right ACG are summarized in Table 2. ANCOVA revealed a significant main effect of diagnosis for the volume of the right ACG ($F=5.87$, $p=0.004$). Post hoc comparison showed that the right ACG volume was significantly smaller in D-SZ than that of controls (Bonferroni correction, p=0.005). ANCOVAs did not show significant effects of diagnosis for other ACG measures namely cortical thickness and surface area. There was no significant correlation between the ACG measures and age, sex, age of onset of

illness, estimated IQ, duration of illness, SANS/SAPS subscales, and medications after controlling for age, gender and ICV.

ACG measures, pooled LCDM

As shown in Table 3, all three tests on the pooled LCDM data revealed that the anterior cingulate was bilaterally thinner in both the ND-SZ group and the D-SZ group compared with the control group. The anterior cingulate in the D-SZ group was thinner than in the ND-SZ group.

Discussion

The results of this study show that the bilateral thinning of the anterior cingulate in patients group of both deficit and non-deficit schizophrenia compared with the control group, and moreover the anterior cingulate of the deficit schizophrenia group was thinner than that of the non-deficit schizophrenia group. Also we found that a reduction in the gray matter volume of the right ACG in individuals with prominent and enduring negative symptoms of schizophrenia.

In this study, we used a recently developed computational anatomy tool (i.e., Labeled Cortical Depth Mapping) to analyze the structural features of the cingulate gyrus. This method depends on the accuracy of both tissue classification and surface generation. The contrast between gray and white matter changes regionally with age due to physical changes in the tissue properties (Salat et al. 2009).This attribute makes a regional segmentation approach more desirable since it calculates threshold values only within the

region of interest. The results of the study using such method confirm our previous finding regarding the involvement of ACG in deficit SZ using VBM analysis.

Since participants in this study had been treated with antipsychotic medications, it is unknown whether our correlational findings reflect relationships between neuroanatomical structure and the original severity of such symptoms or the degree to which antipsychotic medications affected them. Nonetheless previous research with first episode SZ subjects showed that antipsychotic medication did not correlate with any ACG volume or volume change during the follow-up period of the study (Koo et al. 2008). Furthermore in that same study an exploratory analysis of ACG volume with clinical variables found that worsening negative symptoms over the follow-up period were associated with decreased cingulate gray matter volumes, particularly in the right affective cingulate subregion volumes in patients with first episode schizophrenia supported further by the good- vs poor-response group comparisons.

Abnormal lateralization of anterior cingulate volume has been previously reported with more decrease in women with schizophrenia on the right (Takahashi et al. 2002).On the other hand, Szeszko et.al.(Szeszko et al. 2000) reported that reduced ACG volume correlates with executive dysfunction in men with first-episode schizophrenia.

Our results showed that abnormalities in the right ACG distinguish between SZ patients with and without the deficit syndrome. It is tantalizing to hypothesize that these might represent markers of D-SZ, and perhaps identify first-break patients who go on to develop this subtype of the disease.

Several limitations of the present study should be noted. The D-SZ sample appears to be different from the ND-SZ and HCs samples in that the D-SZ subjects are predominantly male, younger, less well educated than HC subjects, and have lower premorbid IQ compared to the other two samples. While these differences represent a potential confound of group differences in neural anatomy, deficit pathology is more typical of male patients(Carpenter et al. 1988;Frederikse et al. 2000). In addition, we attempted to control for this potential confound by including sex as a covariate in ANCOVA models. An alternative approach is to exclude female patients to match the groups. However, we decided against this strategy because it would have reduced statistical power to demonstrate group differences, and because it would have biased gender representation in our sample. Similarly, because the two patient groups differed in age (and hence duration of illness), age was also entered as a covariate in ANCOVA models. More importantly, the reduced gray matter volume shown in D-SZ patients cannot be explained by age because they were younger than the patients with ND-SZ. Thus, if more advanced age (and longer duration of illness) were responsible, then the ND-SZ group should have shown reduced gray matter volume compared to the D-SZ, which they did not.

To the best of our knowledge, this is the first study to directly compare deficit and non-deficit subtypes of SZ using LCDM. We found that patients with D-SZ showed bilateral thinning of anterior cingulate and decreased GMV in right anterior cingulate gyrus. In conclusion, despite limitations this study shows that qualitative, categorical differences in neuroanatomy may distinguish the deficit and non-deficit subtypes of schizophrenia.

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Figure 1

The labeled cortical distance mapping (LCDM) of each subject. This shows the probability distribution of cortical distance (the distance between gray matter and GM/WM surface) of anterior cingulate gyrus of each subject.

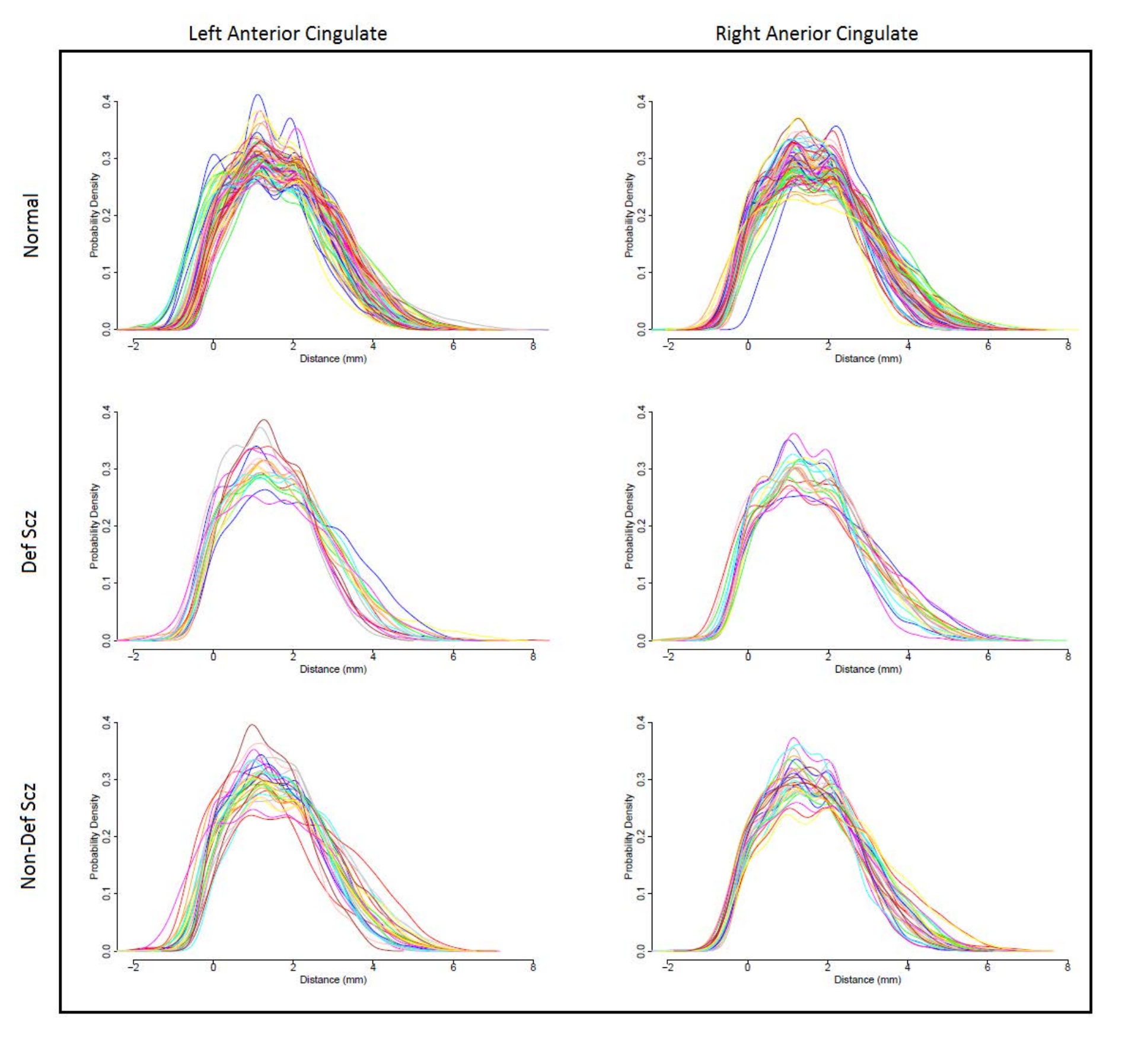
Left Anterior Cingulate
Right Anerior Cingulate
Normal
Def Scz
Non-Def Scz
Probability Density
Distance (mm)
0.0
0.1
0.2
0.3
0.4
−2
0
2
4
6
8

Table 1

Demographic and clinical characteristics of healthy controls (HC) and patients with non-deficit (ND-SZ) or deficit (D-SZ) schiz

characteristic	Group				
	HC (n=82)	ND-SZ (n=30)	D-SZ (n=18)	Statistics	P value
Age at scan (M±SD)	43.7(12.7)[d]	44.3(10.5)[d]	35.9(11.8)[e]	F=3.451	0.04
Sex, male/female	40/42	20/10	15/3	χ^2 = 8.507	0.01
Handed, right/left	68/13	28/1	17/0	χ^2 = 5.001	0.29
Race, white/black	57/24	17/13	5/11	χ^2 = 21.856	0
Education years (M±SD)	14(2.6)[d]	12.2(2.8)[e]	11.8(2.2)[e]	F=8.3	<0.001
Estimated IQ (M±SD)	103.8(10.0)[d]	101.3(10.7)[d]	93.6(8.1)[e]	F=7.461	0
Age at onset (M±SD)	NA	24.7(8.9)	21.9(6.1)	t=1.12	0.27
Duration of ilness (M±SD)	NA	19.8(11.7)	12.4(9.2)	t=2.14	0.04
Times hospitalized (M±SD) [a]	NA	5.5(4.5)	5.3(10.3)	t=0.09	0.93
SAPS sum (M±SD)[b]	NA	6.15(3.7)	3.61(3.5)	t=2.28	0.03
SANS sum (M±SD)[b]	NA	6.14(3.8)	16.8(2.9)	t=-1020	<0.001
On typical APM (%)[c]	NA	31	33	χ^2 = 0.27	0.87
On atypical APM (%)[c]	NA	69	78	χ^2 = 1.378	0.5
On antidepressant (%)[c]	NA	31	6	χ^2 = 4.305	0.04
On anticonvulsant (%)[c]	NA	17	6	χ^2 = 1.362	0.24

[a]Number of psychiatric hospitalizations.

[b]Schedules of Positive and Negative Symptoms.

[c]Percent of patients receiving treatment with antipsychotic (APM),antidepressant, and anticonvulsant medication.

[d,e]Different superscripts denote statistically significant differences (p<0.05) between groups using ANOVA and Bonferroni post hoc comparisons.

Table2

Comparisons of ACG cortical thickness, volume and surface area among healthy controls, non deficit SZ and deficit SZ

Measures	Healthy controls (N=82)		Non deficit SZ (N=30)		Deficit SZ (N=18)		Analysis of covariance[a]					
							Diagnosis		Side		Diagnosis × Side	
	Mean	SD	Mean	SD	Mean	SD	F	p	F	p	F	p
Left volume (mm3)	4112	805	4001	661	4125	799	4.19*	0.017	0.17	0.681	2.21	0.114
Right volume (mm3)	4177	866	3929	780	3807	1048						
Left thickness (mm)	3.74	0.35	3.72	0.40	3.70	0.43	0.42	0.658	0.57	0.451	0.29	0.752
Right thickness (mm)	3.88	0.37	3.83	0.38	3.89	0.38						
Left surface area (mm2)	1148	241	1126	162	1209	265	1.16	0.318	0.48	0.492	1.26	0.286
Right surface area (mm2)	1119	247	1071	237	1087	326						

*Post hoc comparison showed that the right ACC volume was significantly smaller in deficit SZ than that of controls (Bonferroni correction, p=0.005)

[a] Age,sex,and intracranial volume were entered as covariates

Table 3a.
Comparison of the left ACC thickness via pooled LCDM

Tests	Contrast	p	Implication
Mann-Whitney-U Test	HC vs. ND-SZ	<0.0001	HC > ND-SZ
Mann-Whitney-U Test	HC vs. D-SZ	<0.0001	HC > D-SZ
Mann-Whitney-U Test	ND-SZ vs. D-SZ	<0.0001	ND-SZ > D-SZ
Kolmogorov-Smirnov test	HC vs. ND-SZ	<0.0001	HC > ND-SZ
Kolmogorov-Smirnov test	HC vs. D-SZ	<0.0001	HC > D-SZ
Kolmogorov-Smirnov test	ND-SZ vs. D-SZ	<0.0001	ND-SZ > D-SZ
Welch's t-test	HC vs. ND-SZ	<0.0001	HC > ND-SZ
Welch's t-test	HC vs. D-SZ	<0.0001	HC > D-SZ
Welch's t-test	ND-SZ vs. D-SZ	<0.0001	ND-SZ > D-SZ

Table 3b.
Comparison of the right ACC thickness via pooled LCDM

Tests	Contrast	p	Implication
Mann-Whitney-U Test	HC vs. ND-SZ	<0.0001	HC > ND-SZ
Mann-Whitney-U Test	HC vs. D-SZ	<0.0001	HC > D-SZ
Mann-Whitney-U Test	ND-SZ vs. D-SZ	<0.0001	ND-SZ > D-SZ
Kolmogorov-Smirnov test	HC vs. ND-SZ	<0.0001	HC > ND-SZ
Kolmogorov-Smirnov test	HC vs. D-SZ	<0.0001	HC > D-SZ
Kolmogorov-Smirnov test	ND-SZ vs. D-SZ	<0.0001	ND-SZ > D-SZ
Welch's t-test	HC vs. ND-SZ	<0.0001	HC > ND-SZ
Welch's t-test	HC vs. D-SZ	<0.0001	HC > D-SZ
Welch's t-test	ND-SZ vs. D-SZ	<0.0001	ND-SZ > D-SZ

D-SZ, deficit schizophrenia; HC, healthy control; ND-SZ, non-deficit schizophrenia.

Supplemental table 1. Partial correlation coefficients of ACG measures and clinical variables among schizophrenia patients controlling for age, sex and intracranial volume.

	Clinical measures													
	Duration of ilness		Age at onset		Estimated IQ		SAPS sum		SANS sum		On typical APM		On atypical APM	
ACG Measures	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value
Left volume	-0.03	0.88	0.03	0.88	0.28	0.06	-0.21	0.19	0.07	0.65	-0.21	0.18	0.01	0.95
Right volume	-0.02	0.88	0.02	0.88	0.27	0.08	0.05	0.73	-0.18	0.25	-0.11	0.48	0.08	0.60
Left thickness	-0.18	0.27	0.18	0.27	0.07	0.66	0.14	0.39	-0.06	0.70	-0.20	0.20	0.02	0.89
Right thickness	-0.01	0.96	0.01	0.96	0.17	0.27	0.15	0.38	-0.03	0.84	0.02	0.89	-0.11	0.50
Left surface area	-0.03	0.84	0.03	0.34	0.09	0.57	-0.25	0.11	0.16	0.31	-0.02	0.90	-0.06	0.72
Right surface area	0.04	0.82	-0.04	0.82	0.14	0.35	-0.08	0.62	-0.04	0.82	-0.12	0.46	-0.03	0.83

ACG, anterior cingulate gyrus; APM, antipsychotic medication; SANS and SAPS; Scales for the Assessment of Positive and Negative Symptoms.