Surface-Based Morphometry of the Anterior Cingulate Cortex in First Episode Schizophrenia

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Abstract: The anterior cingulate cortex (ACC) appears to be critically involved in the pathophysiology of schizophrenia, but past attempts at characterizing pathological changes in the region using magnetic resonance imaging have been restricted by a limited appreciation of its functional and anatomical diversity and a reliance on relatively coarse metrics (e.g., volume) to index anatomical change. In this study, we applied a novel, surface-based protocol to T1-weighted scans acquired from 40 first episode schizophrenia patients and 40 healthy controls individually matched for age, sex, and morphology of the paracingulate sulcus, a major anatomical variation that has been shown to affect morphometric estimates in the region. The surface-based approach enabled calculation of regional grey matter volume, surface area and curvature, cortical thickness, and depth of the cingulate sulcus, with sub-millimeter precision. Relative to controls, schizophrenia patients displayed a bilateral reduction in thickness of paralimbic regions of the ACC, along with a concomitant increase in surface area of both the limbic and paralimbic ACC. No differences were identified for regional grey matter volume, surface curvature, or CS depth. These findings illustrate the advantages of moving beyond traditional volume-based approaches when investigating cortical morphometry, and indicate that the early stages of schizophrenia are associated with a specific pattern of ACC abnormalities that cannot be attributed to variations in sulcal and gyral morphology. *Hum Brain Mapp* 29:478–489, 2008. © 2007 Wiley-Liss, Inc.

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INTRODUCTION

Schizophrenia is frequently characterized as a disorder of cognitive and emotional integration [Andreasen et al., 1998; Benes, 1996]. Accordingly, the anterior cingulate cortex (ACC), a region considered to be a nexus point where cognition, emotion, and motivational drive are integrated in support of goal-directed behavior [Bush et al., 2000; Devinsky et al., 1995; Paus, 2001; Ridderinkhof et al., 2004; Vogt et al., 1992], is frequently implicated in the disorder's pathophysiology [Benes, 1993; Sanders et al., 2002; Tamminga et al., 2000; Yücel et al., 2003a,b]. Clarifying the nature of ACC abnormalities in schizophrenia is therefore

Figure 1.

Example of region-of-interest (ROI) boundaries and their relationship with local variations in cortical folding. Top row presents a case with an “absent” paracingulate sulcus (PCS) and “continuous” superior rostral sulcus (SRS) and bottom row presents a case with a “present” PCS and “separate” SRS. Left column presents a representative sagittal slice through the T1-weighted image with major sulci marked in yellow. Middle column presents the reconstructed white matter surfaces with the delineated ROIs. Sulci on the white matter surface correspond to indentations or “crevasses,” whereas gyri correspond to protrusions or “ridges.” The posterior red line represents the caudal border of the dorsal region. The anterior red line separates the rostral and dorsal regions dorsally, and rostral and subcallosal regions ventrally. The middle red line represents the posterior border of the subcallosal region. Right column presents the ROIs overlaid on reconstructions of the pial surface. As can be seen, if the PCS was “present” the paralimbic anterior cingulate cortex (ACC_P)

comprised the grey matter between the fundus of the cingulate sulcus (CS) and that of the PCS. If the PCS was “absent” the ACC_P was located on the dorsal bank of the CS. Similarly, if the SRS and CS were “separate,” the ACC_P extended from the fundus of the CS to that of the SRS. If the two sulci were “continuous,” the ACC_P was located on the rostro-ventral bank of the CS. The limbic ACC (ACC_L) always comprised the grey matter between the callosal and cingulate sulci. ROIs were delineated on the white matter surface to facilitate tracing inside sulcal walls. They were then projected onto the pial surface to check for accuracy and consistency prior to continuing. Note how the ACC_P is not visible from the pial surface in “absent” or “continuous” cases. [Figure adapted from Fornito A, Wood SJ, Whittle S, Fuller J, Adamson C, Saling MM, Velakoulis D, Pantelis C, Yücel M. Variability of the paracingulate sulcus and morphometry of the medial frontal cortex: Associations with cortical thickness, surface area, volume, and sulcal depth. *Hum Brain Mapp* 29:222–236.]

important for understanding the neurobiological basis of the disorder’s clinical manifestations, but the considerable anatomical and functional heterogeneity of the ACC [Bush et al., 2000; Devinsky et al., 1995; Mega and Cummings, 1997; Vogt et al., 1992, 1995] has made this a difficult task.

This difficulty has featured prominently in structural imaging studies, with both manual region-of-interest (ROI) and voxel-based morphometric (VBM) approaches yielding inconsistent findings regarding the precise side, subregion, and nature of the abnormalities. Authors have reported

Figure 2. (legend on page 480.)

either left-sided [Haznedar et al., 2004; Paillere-Martinot et al., 2001], right-sided [Choi et al., 2005; Zhou et al., 2005], or bilateral reductions [Goldstein et al., 1999; Mitelman et al., 2005; Suzuki et al., 2002; Takahashi et al., 2003; Yamasue et al., 2004], with others reporting no volumetric changes [Crespo-Facorro et al., 2000; Noga et al., 1995; Riffkin et al., 2005; Szeszko et al., 1999] or even grey matter increases [Kopelman et al., 2005; Marquardt et al., 2005].

One major reason for such inconsistencies is that the methods used to date for assessing ACC morphometry have failed to adequately account for the substantial inter-individual variability in gross anatomy of the region. The ACC comprises the limbic cortex of areas 24/24' and paralimbic (also termed paracingulate) cortex of areas 32/32' (Fig. 1). The precise location and extent of these regions is greatly affected by sulcal variability in the region, particularly the incidence of the paracingulate sulcus (PCS), a tertiary structure that runs dorsal and parallel to the cingulate sulcus (CS) in 30–60% of cases [Paus et al., 1996b; Yücel et al., 2001]. PCS variability has previously been shown to affect the size of both limbic and paralimbic ACC (ACC_L and ACC_P, respectively) [Paus et al., 1996a; Vogt et al., 1995], with some estimates indicating it can produce an up to 88% increase in ACC_P volume and a 39% decrease in ACC_L volume [Fornito et al., 2006a]. When coupled with evidence that patients with schizophrenia are less likely than healthy individuals to display a PCS (particularly in the left hemisphere) [Le Provost et al., 2003; Yücel et al., 2002, 2003b], such effects indicate that neglecting consideration of this variation ignores a major determinant of variance in regional morphometric estimates and may lead to spurious group differences if patients and controls are not well matched for sulcal anatomy. The problem is exacerbated in voxel-based studies that attempt to minimize or average-out sulcal variations when normalizing images into standard space, as the registration algorithms they employ may be particularly prone to error in morphologically variable regions [Bookstein, 2001; Crum et al., 2003; Van Essen, 2005]. This makes it difficult to determine unambiguously whether the identi-

fied group differences are a consequence of variations in cortical morphology, a bona fide pathological anomaly, or both.

A second drawback limiting the conclusions that can be drawn from past work has been the relatively coarse metrics used to index anatomical differences. VBM studies typically test for differences in grey-matter density, which is an abstraction of the imaging procedures employed rather than a true physical measure and cannot be expressed in standard measurement units. While additional processing steps allow the derivation of volumetric estimates [Good et al., 2001], volume is a gross measure that reflects the product of a region's surface area and cortical thickness. Variations in each of these parameters may have distinct pathophysiological implications [Rakic, 1988], but changes in either can be obscured unless they are measured independently. Recent advances in reconstructing the inner and outer surfaces of the cortical mantle have facilitated the separate calculation of these measures [Dale et al., 1999; Fischl et al., 1999; MacDonald et al., 2000; Van Essen, 2004], in addition to other metrics, such as sulcal depth and surface curvature, that have shown promise as markers of pathological and/or atrophic change [Magnotta et al., 1999; Van Essen et al., 2006; White et al., 2003].

In this study, we used a novel surface-based protocol for parcellating the ACC into functionally relevant regions, while accounting for individual variations in sulcal anatomy [Fornito et al., 2006a]. The approach enabled calculation of multiple indices of anatomical change, including regional grey matter volume, surface area, cortical thickness, and sulcal depth and curvature with sub-millimeter precision. By focusing on a sample of patients experiencing their first episode (FE) of schizophrenia, we minimized the potential confounding influences associated with prolonged illness and treatment effects [Keshavan and Schooler, 1992]. Importantly, we individually matched patients and healthy controls for age, sex, and PCS morphology to ensure that any identified changes could not be attributed to group differences in cortical folding patterns.

Figure 2.

Illustration of how cingulate sulcus (CS) depth was calculated. **(A)** A broad region-of-interest (ROI) was delineated on the intermediate surface that included the gyral crowns abutting either side of the CS. **(B)** Concurrently, a model of the convex hull of the cortex was generated by dilating and eroding the intermediate surface to produce a surface that ran along the external contour of the cortex without dipping into the sulci [see Van Essen, 2005 for more details]. **(C)** A depth map for the entire cortex was generated by measuring the geodesic distance from each point on the intermediate surface to the cerebral hull. **(D)** The depth map was thresholded for each individual using tools in Caret 5.2 by beginning at the hull and moving deeper in incre-

ments of 0.5 mm until only sulcal surface points were included in the ROI (i.e., all cortex on the gyral surface was excluded). The depth at each point within the thresholded region was then averaged to obtain an estimate of mean CS depth. The CS was not traced in the subcallosal region as it did not always extend into the area and gyri in the region tend to be quite shallow, making it difficult to set appropriate thresholds. [Figure adapted from Fornito A, Wood SJ, Whittle S, Fuller J, Adamson C, Saling MM, Velakoulis D, Pantelis C, Yücel M. Variability of the paracingulate sulcus and morphometry of the medial frontal cortex: Associations with cortical thickness, surface area, volume, and sulcal depth. *Hum Brain Mapp* 29:222–236.].

TABLE I. Sample characteristics

	Schizophrenia	Controls	<i>P</i>
No. males/females	31/9	31/9	
No. right/left/mixed handers	36/2/2	36/4/0	
Age (years)	22.29 ± 3.22	21.66 ± 3.22	0.40
NART-IQ	89.54 ± 16.61	101.58 ± 10.13	<0.01
Illness duration (years)	0.10 (0.01–1.48)		

NART-IQ, National Adult Reading Test-estimated Intelligence Quotient.

Values for age and NART-IQ represent means ± standard deviations (NART-IQ data was unavailable for three schizophrenia patients and two controls). Values for illness duration correspond to medians with minimum and maximum values in parentheses. *P* values correspond to results of Student's *t*-tests.

METHOD

Participants

The patient sample comprised 40 individuals with FE schizophrenia (where "FE" was defined as the first contact with psychiatric services for a psychotic illness) recruited from the Early Psychosis Prevention and Intervention Centre in Melbourne, Australia [see McGorry et al., 1996] as part of ongoing research being conducted by our centers. DSM-IV diagnoses of schizophrenia were confirmed over a minimum 6-month follow-up period and assigned based on medical record review and the Structured Clinical Interview for DSM-IV (SCID-IV) [First et al., 1998]. Details regarding recruitment procedures are published elsewhere [Velakoulis et al., 2006]. Twenty-four patients were receiving atypical antipsychotic treatment at the time of scanning, while 15 were taking typical agents. (Medication data was unavailable for one patient.)

Healthy controls with no personal history of mental or neurological illness and no family history of psychosis were selected from our larger database to individually match them to each patient for age, sex, and PCS morphology (see later). Exclusion criteria for all participants included history of steroid abuse, substantial head injury, impaired thyroid function, and substance abuse/dependence. Patients with comorbid psychiatric, neurological, or significant medical conditions were also excluded from the study [see Velakoulis et al., 2006]. All participants gave written, informed consent in accordance with local ethics committee guidelines. Demographic details are presented in Table I.

Magnetic Resonance Imaging

Image acquisition

Scans were acquired using a GE Signa 1.5 Tesla scanner at the Royal Melbourne Hospital, Victoria, Australia. A three-dimensional volumetric SPGR sequence generated 124 contiguous coronal slices. Imaging parameters were: time-to-echo, 3.3 ms; time-to-repetition, 14.3 ms; flip angle,

30°; matrix size, 256 × 256; field of view, 24 × 24 cm²; voxel dimensions, 0.938 × 0.938 × 1.5 mm³. magnetic resonance imaging (MRI) data were transferred from DAT tape to a Linux Debian 3.1 workstation for the bulk of image processing and coded to ensure participants' confidentiality and blinded rating. The surface reconstruction algorithms we employed (see later) are computer intensive, requiring ~24 h per individual to generate accurate surfaces. Individual reconstructions were therefore performed in parallel on a networked cluster of 12 dual-processor Apple Mac G5 computers at the National Neuroscience Facility, Melbourne, Australia [Kolbe et al., 2005].

Image preprocessing

Prior to classifying sulcal morphology, each participants' image was stripped of extracerebral tissue [Smith, 2002] and aligned to the N27 template [Holmes et al., 1998] via a six-degree rigid-body transformation [Jenkinson and Smith, 2001] using tools contained in the FSL software package (<http://www.fmrib.ox.ac.uk/fsl>). No rescaling or warping was performed, but the images were resampled to 1 mm³ voxels in the process.

Classification of Sulcal Variability

Two major morphological variations affected ROI boundaries; the incidence and extent of the PCS, and the confluence of the CS with the superior rostral sulcus (SRS). The PCS was classified according to a previously described, reliable method [Fornito et al., 2006a; Yücel et al., 2001]. Briefly, a classification of "present" was assigned if there was a clearly identifiable sulcus running dorsal and parallel to the CS that was at least 20 mm in length. An "absent" classification was assigned if no such sulcus was apparent. The SRS was classified as being "continuous" with the CS if the two were connected rostral to the genu of the corpus callosum, with all other cases being classified as "separate" [see Fornito et al., 2006a. See also Fig. 1]. All sulcal classifications were performed on the N27-aligned images, using Analyze 6.0 (Mayo Software).

Following our previous work [Fornito et al., 2008], we classified patients into one of four categories that described the incidence of the PCS in both hemispheres for each individual. These categories were: "present" in the left and "absent" in the right (*n* = 14), "present" in both hemispheres (*n* = 13), "absent" in both hemispheres (*n* = 8), or "absent" in the left and "present" in the right (*n* = 5). Controls were then selected from a larger database and individually matched to each patient on the basis of this PCS classification, sex, and age. Since PCS and SRS classifications tend to be related [Fornito et al., 2008], this procedure also resulted in good matching for SRS morphology. 31/40 and 27/40 schizophrenia patients and 29/40 and 24/40 of their controls had a "separate" left and right SRS, respectively. [While there can still be considerable variation in the rostro-caudal extent of the PCS within partici-

pants classified as “present,” our previous work has shown that such variations did not have a major influence on the measures examined in this study. See Fornito et al., 2008.

Cortical Surface Reconstruction

The white (i.e., grey/white matter boundary) and pial (grey/cerebrospinal fluid boundary) cortical surfaces were tessellated with a triangular mesh comprising ~150,000 vertices per hemisphere, using methods described in detail by Dale et al. [1999] and Fischl et al. [1999], and as implemented in the Freesurfer software package (<http://surfer.nmr.mgh.harvard.edu>). These surface representations enabled calculation of regional grey matter volume, surface area, and mean cortical thickness for each of six ACC subregions per hemisphere (see later), using methods developed by Fischl and Dale [2000]. All surfaces were reconstructed using the raw, unaligned images in native space to minimize the influence of unnecessary interpolation or resampling on our measures.

ROI Delineation

We adapted our volumetric method for parcellating the ACC [Fornito et al., 2006a] for use with cortical surface reconstructions using procedures detailed in Fornito et al. [2008]. Briefly, the method divides the ACC_L and ACC_P into rostral, dorsal, and subcallosal divisions designed to approximate previously identified functional subdivisions within the area [Amodio and Frith, 2006; Bush et al., 2000; Devinsky et al., 1995; Phan et al., 2002]. Boundaries distinguishing between the ACC_L from the ACC_P varied in accordance with PCS and SRS variability, and were based on postmortem work documenting how cytoarchitectonic areas in the region shift in accordance with sulcal variability [Vogt et al., 1995]. Examples are presented in Figure 1 and a more detailed description of these boundaries (and their justifications) can be found elsewhere [Fornito et al., 2006a, 2008]. We have recently shown that intra- and inter-rater reliabilities for this surface-based protocol are satisfactory (all >0.8, with most >0.9) [Fornito et al., 2008].

We note that while our earlier papers referred to ACC_P regions as paracingulate cortex and ACC_L regions as ACC, we have renamed these regions as ACC_P and ACC_L to emphasize that the paralimbic region is still part of the cingulate cortex, as initially proposed by Brodmann [1909]. We do not wish to suggest however, that our ACC_L and ACC_P ROIs are perfect representations of the histologically defined limbic and paralimbic subdivisions of the ACC. Rather, they should be interpreted as approximations of these cytoarchitectonic areas (indeed, this is a limitation common to most ROI MRI studies).

Sulcal Depth

CS depth was calculated using Caret 5.2 (<http://brain-map.wustl.edu/vanessen.html>). The freesurfer-generated

white and pial surfaces were imported into Caret and averaged to produce an intermediate surface that ran parallel to, and half-way in between, the white and pial surfaces. This intermediate surface facilitated tracing on the gyral crowns bordering each sulcus (which appear as quite thin on the white matter surface), while still opening the sulci up enough to allow appropriate boundary delineation (which is not possible on the pial surface). The steps involved in calculating CS depth (and the reliability of the method) are illustrated in Figure 2 and have been detailed elsewhere [Fornito et al., 2008; Van Essen, 2005 for a more general description]. Briefly, inclusive borders were traced along the gyral crowns abutting either side of the CS. Multiple dilation and erosion operations were applied to the intermediate surface to obtain a model of the cerebral hull. The geodesic distance from the hull to each point on the intermediate surface was measured (in mm) to produce a depth map of the entire surface. Beginning at the hull (i.e., 0 mm) and progressing deeper in increments of 0.5 mm, a threshold was set on the depth map of each individual to create a mask that comprised only buried cortex (i.e., cortex on gyral crowns was excluded). This mask was used to threshold the CS ROI so that only buried (i.e., sulcal) cortex was retained. In this regard, our depth measure is similar in principle to that of Rettmann et al. [2006].

The curvature of the CS fundus was calculated using the thresholded CS ROI. The crown of the anterior cingulate gyrus was then delineated by applying the inverse of the thresholded depth map (this time including only surface points on the exposed cortical surface) to an ROI created by merging the rostral and dorsal ACC_L regions (subcallosal regions were excluded because the CS did not always extend into the area). The mean curvature was calculated at each point using methods described by Fischl et al. [1999] and Van Essen and Drury [1997] and averaged across all surface points in the region. The resulting values were unsigned, with higher values indicated a more steeply peaked curvature and values approaching zero indicating more flattened curvature. Previous work has shown that atrophy associated with ageing tends to increase curvature in gyral crowns and decrease curvature in sulcal fundi, suggesting this pattern may reflect atrophic changes [Magnotta et al., 1999]. Curvature and depth estimates for the paracingulate gyrus and PCS were not calculated since these structures were not apparent in all individuals.

Intracranial Volume

Intracranial volume (ICV) was calculated for each individual to control for any group differences in brain size using a previously described method [Eritaia et al., 2000]. Inter- and intra-rater reliabilities for this method were 0.99.

Statistical Analyses

All analyses were performed using SPSS 12.0 for Windows. Regional grey matter volumes, cortical thickness,

and surface area were analyzed with mixed within- and between-subjects ANOVA, with hemisphere (left or right), region (dorsal, rostral, and subcallosal), and cortex (ACC_L or ACC_P) as within-subjects factors, and diagnosis and sex as between-subjects factors. CS depth was analyzed in a similar fashion except hemisphere was the only repeated-measure. The within-subjects factors for the analyses of curvature were hemisphere and location (sulcal fundus or gyrus crown). Main effects and interactions were evaluated using Greenhouse–Geisser corrected degrees of freedom (sphericity assumptions were invariably violated) with $\alpha = 0.05$. Significant effects were further investigated with post hoc pairwise contrasts evaluated against a Bonferroni-adjusted α to correct for multiple comparisons. Effect sizes, expressed as Cohen's d [Cohen, 1992, 1994], are also reported for these pairwise contrasts (negative values indicate a decrease in the patient group). Only effects involving diagnosis are reported, as these were the primary focus of the current study.

We corrected for grey matter volume, surface area, and CS depth estimates for ICV using equations described in Free et al. [1995] to adjust for group differences in head size, while avoiding violation of ANCOVA homogeneity of regression assumptions. ICV was not a significant covariate in the analysis of cortical thickness [$F(1, 75) = 0.908$, $P = 0.344$] or surface curvature [$F(1, 75) = 0.556$, $P = 0.458$], so we report the results of models without any covariates for these measures. Moreover, while there was a significant difference between schizophrenia patients and controls on NART-IQ [Nelson and Willison, 1991; see Table I], this was not a significant covariate for any of the analyses and was not used in the final models.

RESULTS

Volume, Surface Area, and Cortical Thickness

Means for each group on each measure are presented in Table II. There was no significant effect of diagnosis [$F(1, 76) = 2.459$, $P = 0.121$], sex [$F(1, 76) = 0.846$, $P = 0.361$] or diagnosis $\times$ sex interaction [$F(1, 76) = 0.521$, $P = 0.472$] for grey matter volume, nor did diagnosis interact with any of the within-subjects factors. For surface area, there was a significant main effect of diagnosis [$F(1, 76) = 6.173$, $P = 0.015$], indicating that schizophrenia patients had larger surface area in the entire ACC region bilaterally when compared with controls ($d = 0.56$). There was no diagnosis $\times$ sex interaction [$F(1, 76) = 0.964$, $P = 0.329$], or interaction between diagnosis and any of the within-subjects factors.

For cortical thickness, the analysis revealed a significant main effect of diagnosis [$F(1, 76) = 5.697$, $P = 0.019$], and a significant diagnosis $\times$ cortex interaction [$F(1, 76) = 4.192$, $P = 0.044$]. Post hoc contrasts indicated that schizophrenia patients displayed thinner cortex in the ACC_P bilaterally ($d = -0.734$, $P = 0.002$, corrected), collapsing across dorsal, rostral, and subcallosal regions (Fig. 3), with no significant differences in ACC_L thickness ($d = -0.224$, $P = 0.319$,

TABLE II. Mean volume, surface area, and cortical thickness for each group in each region-of-interest

	Dorsal ACC_L		Dorsal ACC_P		Rostral ACC_L		Rostral ACC_P		Subcallosal ACC_L		Subcallosal ACC_P	
	L	R	L	R	L	R	L	R	L	R	L	R
Schizophrenia												
Volume (mm^3)	1903.66 $\pm$ 572.78	2348.74 $\pm$ 616.01	1585.30 $\pm$ 671.91	1290.93 $\pm$ 580.11	1596.69 $\pm$ 999.62	2101.52 $\pm$ 827.61	2537.62 $\pm$ 880.20	2275.11 $\pm$ 713.16	287.21 $\pm$ 182.22	337.91 $\pm$ 142.44	282.07 $\pm$ 163.70	181.65 $\pm$ 109.28
Area (mm^2)	684.45 $\pm$ 190.04	827.44 $\pm$ 191.79	570.78 $\pm$ 241.65	462.73 $\pm$ 202.40	498.75 $\pm$ 314.78	679.58 $\pm$ 272.55	906.69 $\pm$ 310.49	833.47 $\pm$ 252.39	109.17 $\pm$ 56.54	114.73 $\pm$ 49.42	94.23 $\pm$ 55.57	62.04 $\pm$ 38.33
Thickness (mm)	2.75 $\pm$ 0.27	2.78 $\pm$ 0.22	2.72 $\pm$ 0.23	2.74 $\pm$ 0.23	3.12 $\pm$ 0.30	3.06 $\pm$ 0.28	2.73 $\pm$ 0.24	2.69 $\pm$ 0.23	2.46 $\pm$ 0.45	2.94 $\pm$ 0.38	3.02 $\pm$ 0.53	3.04 $\pm$ 0.53
Controls												
Volume (mm^3)	1869.99 $\pm$ 527.94	2268.79 $\pm$ 544.54	1479.10 $\pm$ 774.44	1253.60 $\pm$ 511.65	1403.13 $\pm$ 981.37	1925.71 $\pm$ 840.22	2467.29 $\pm$ 912.61	2293.84 $\pm$ 832.30	258.20 $\pm$ 190.68	289.84 $\pm$ 171.21	282.27 $\pm$ 177.60	242.77 $\pm$ 179.24
Area (mm^2)	667.91 $\pm$ 155.38	798.19 $\pm$ 179.20	512.05 $\pm$ 256.32	438.27 $\pm$ 166.57	433.51 $\pm$ 300.16	604.12 $\pm$ 262.24	823.58 $\pm$ 290.46	793.32 $\pm$ 275.15	95.32 $\pm$ 60.88	95.48 $\pm$ 55.27	94.05 $\pm$ 61.01	77.46 $\pm$ 59.62
Thickness (mm)	2.74 $\pm$ 0.29	2.80 $\pm$ 0.23	2.82 $\pm$ 0.52	2.81 $\pm$ 0.26	3.20 $\pm$ 0.47	3.11 $\pm$ 0.35	2.90 $\pm$ 0.19	2.86 $\pm$ 0.24	2.59 $\pm$ 0.27	2.98 $\pm$ 0.22	3.04 $\pm$ 0.55	3.19 $\pm$ 0.51

L, left; R, right; ACC_L , limbic anterior cingulate cortex; ACC_P , paralimbic anterior cingulate cortex. Values correspond to means $\pm$ standard deviations. Volume and area values are corrected for intracranial volume as detailed in the "Method."

Figure 3.

Mean thickness for limbic and paralimbic anterior cingulate cortices (ACC_L and ACC_P, respectively) in patients with schizophrenia and matched controls. Error bars represent standard deviations. ** $P < 0.01$, corrected.

corrected). There was no diagnosis $\times$ sex interaction [$F(1, 76) = 1.001$, $P = 0.322$], or interaction between diagnosis and any of the within-subjects factors. The difference in ACC_P thickness remained significant after excluding five patients with a NART-IQ below 70 ($d = -0.74$, $P = 0.003$, corrected), and trended towards significance at the corrected level when females were excluded ($d = -0.48$, $P = 0.068$, corrected).

Sulcal Depth and Surface Curvature

There was no main effect of diagnosis [$F(1, 76) = 0.004$, $P = 0.949$], diagnosis $\times$ sex interaction [$F(1, 76) = 0.077$, $P = 0.781$], or diagnosis $\times$ hemisphere interaction [$F(1, 76) = 0.051$, $P = 0.822$] for CS depth. There was no significant main effect of diagnosis on surface curvature [$F(1, 76) = 0.157$, $P = 0.693$], nor was there a significant diagnosis $\times$ sex interaction [$F(1, 76) = 0.278$, $P = 0.600$] or interaction between diagnosis and any of the within-subjects factors.

Medication Effects

To investigate whether medication class had an influence on the findings, patients taking typical antipsychotics were matched to those taking atypicals for PCS morphology using the procedures described earlier, with any patients who could not be matched being excluded from the analysis. This resulted in 12 patients taking typicals being matched to 12 taking atypicals. The analysis revealed no significant main effect of antipsychotic class on either thickness or surface area [$F(1, 22) = 0.773$, $P = 0.389$ and $F(1, 22) = 0.016$, $P = 0.901$, respectively], nor did medication class interact with any of the within-subjects factors in either analysis.

DISCUSSION

In this study, we implemented a novel surface-based approach to derive a detailed characterization of anatomical

abnormalities of the ACC in a sample of FE schizophrenia patients. Our findings indicate that changes in early phases of the illness are similar for both male and female patients, and are characterized by a bilateral thinning of the paralimbic ACC and a generalized expansion in surface area of both limbic and paralimbic cortices. Importantly, this is the first study to explicitly match patients and controls for sulcal variability, a procedure that ensured the identified differences are unlikely to be an artifact of group biases in cortical folding patterns.

Volume, Surface Area, and Cortical Thickness

No differences in grey matter volume were identified. This is likely explained by the fact that patients showed a simultaneous decrease in thickness and increase in surface area; that is, the different direction of these changes are likely to have cancelled each other out when combined in the summary volumetric measure. This highlights the advantages associated with moving beyond grey matter volume when examining cortical abnormalities in clinical populations, since our analysis would have yielded a conclusion of no anatomical differences had more subtle changes in surface area and thickness not been measured. To date, only two other ROI studies have explicitly measured ACC surface area in schizophrenia. One examined a region similar to our subcallosal ACC_L ROI in patients with established illness [Coryell et al., 2005], while the other examined regions similar to our dorsal and rostral ACC_L ROIs in a FE sample [Crespo-Facorro et al., 2000], with neither reporting any significant differences. In contrast, the decrease in cortical thickness of the ACC_P shown by our schizophrenia patients is consistent with the results of previous whole-brain studies [Kuperberg et al., 2003; Narr et al., 2005; Suzuki et al., 2002; Vidal et al., 2006] and the limited number of ROI studies that have separately parcellated the paralimbic region separately [Goldstein et al., 1999, 2002] reporting evidence for reduced grey matter in the region. Unfortunately, direct comparison between these past studies and our findings is complicated by methodological differences (e.g., ROI vs. VBM approaches and different ROI parcellation protocols) and past failures to match for sulcal anatomy.

The combined decrease in cortical thickness and increase in surface area provides some clues regarding the underlying pathophysiology causing the change. Similar changes are also seen during normal adolescent (and early adult) brain maturation, to the extent that continued brain growth is accompanied by a reduction in cortical grey matter, the changes being particularly protracted in frontal regions [Giedd, 2004; Sowell et al., 2001, 2004]. In this regard, decreased thickness coupled with increased surface area may reflect an exaggeration of normal neurodevelopmental processes. This view is consistent with our recent longitudinal work demonstrating that the rate of anatomical change across the lateral surface of the cortex shortly after the onset of schizophrenia is similar in nature, but

exaggerated in magnitude, to that shown by age-matched controls, with the greatest changes occurring in frontal regions [Sun et al., 2003]. The specificity of the thickness reduction to paralimbic, but not limbic, areas in the current sample (which contrasts the surface area expansion of both) may reflect a regionally specific pathology that spreads from the ACC_P to the ACC_L with illness progression. In support of this view, the relationship between cortical thickness reductions and brain growth can show a high degree of regional specificity in normal development [Sowell et al., 2004] and a recent longitudinal voxel-based study of childhood-onset schizophrenia by Vidal et al. [2006] found that the earliest reductions in grey matter density occurred in the ACC_P and medial superior frontal gyrus, with ACC_L reductions subsequently emerging over a four-year follow-up period (notably, the changes were observed across dorsal, rostral and subcallosal subdivisions, consistent with our findings). Kuperberg et al. [2003] have reported thickness reductions in both the limbic and paralimbic ACC of patients with established schizophrenia, but with more prominent differences occurring in the latter. By way of speculation, the gradual progression of anatomical abnormalities from paralimbic to limbic regions may represent a pathophysiological basis for the increasing prominence of negative symptoms in the clinical presentation of patients with prolonged illness, consistent with reports of ACC_L involvement in motivational function [Paus, 2001; Ridderinkhof et al., 2004] and evidence that lesions in the area can lead to apathy and/or akinetic mutism [Devinsky et al., 1995; Mega and Cummings, 1997]. The earlier involvement of paralimbic regions may be associated with the deficits in executive function and social cognition known to occur from the outset of the illness and even prior to psychosis onset [Cannon et al., 1997; Cornblatt and Erlenmeyer-Kimling, 1985; Cornblatt et al., 1989; Marjoram et al., 2006; Wood et al., 2003], consistent with evidence that the ACC_P is critically involved in these functions [Amodio and Frith, 2006; Cohen et al., 2000], and functional imaging studies demonstrating abnormal ACC_P activation in schizophrenia patients performing such tasks [Harrison et al., in press; Kerns et al., 2005; Lee et al., 2006]. Further work examining the functional correlates of these neuroanatomical changes will be an important goal of future research.

Notably, the cortical grey matter reduction seen in MRI studies of normal adolescent development is thought to reflect partial volume effects caused by ongoing myelination of fibers penetrating the cortical mantle, rather than overt neuronal loss [Paus et al., 2001; Sowell et al., 2001]. Postmortem studies have found increased axonal input into the limbic ACC of patients with schizophrenia [Benes et al., 1987, 1992], suggesting that myelination of these excess fibers in early illness stages may contribute to a thinning of the cortical ribbon. In this regard, our findings need not necessarily imply a loss in the cortical neuropil [although this should not be ruled out, given reports of reduced ACC cell density in schizophrenia; e.g., Todtenkopf

et al. 2005], but may also reflect ongoing myelination of excess afferent input into the ACC. While our results indicate that this effect should be most pronounced in the paralimbic ACC (at least in early stages), no postmortem studies to date have investigated the density of afferent input into this region in schizophrenia patients.

Sulcal Depth and Surface Curvature

We found no evidence for group differences in the depth of the CS. sulcal and gyral patterns are primarily formed by birth and remain relatively stable thereafter [Armstrong et al., 1995]. As such, studying cortical folding patterns can provide a window into aberrations of early neurodevelopment, although sulcal depth may also be affected by ageing, probably due to atrophy [Rettmann et al., 2006]. In this regard, changes in depth without a corresponding change in thickness might implicate anomalous formation of the CS early in gestation. The fact that we found the reverse—a reduction in thickness with no change in CS depth—provides preliminary evidence against this possibility. When taken together with evidence for reduced incidence of the PCS in schizophrenia [Le Provost et al., 2003; Yücel et al., 2002], this suggests that the pathological process(es) causing anomalies in cortical folding of the ACC region in schizophrenia may occur later in gestation, during the formation of secondary and tertiary sulci (approximately second or third trimester), rather than earlier when the primary medial wall sulci are being formed [Chi et al., 1977]. Further work examining the functional correlates of abnormal cortical folding patterns and changes in ACC grey matter will be an important avenue of future research, given both have been associated with cognitive deficits in the disorder [Fornito et al., 2006b; Szaszko et al., 2000].

We also failed to find any differences in the curvature of the CS fundus or cingulate gyral crown. The only other study to examine surface curvature in schizophrenia was conducted by White et al. [2003] in a sample of childhood- and adolescent-onset patients. They found that, across the entire cortex, patients showed more steeply peaked gyri and more flattened curvature *in sulcal regions, but only showed a trend for a significant difference in average sulcal curvature when the frontal lobe was examined separately*. When considered with our findings, these data suggest that surface curvature measures may provide more sensitive measures of global, rather than regionally-specific, changes in schizophrenia [although see Rettmann et al., 2006 for an example of regionally-specific curvature measures applied to the study of normal aging].

Limitations

In this study, we defined “first episode” as first contact with psychiatric services for a psychotic episode, and we did not control for the effects of prodromal symptoms,

duration of untreated psychosis, or prepsychotic affective episodes. The influence of such effects is difficult to characterize unless assessed prospectively, although one recent study has found no effects of duration of untreated psychosis on ACC grey matter [Lappin et al., 2006], suggesting any such influences on our ROI measures are minimal.

We found little evidence for an effect of antipsychotic class on either cortical thickness or surface area in a reduced sample (that could be matched for PCS morphology), but it remains unclear whether similar changes would have been observed in a medication-naïve sample. Crespo-Facorro et al. [2000] found no evidence for differences between patients and controls in surface area or volume of the ACC_L in their neuroleptic-naïve sample, although the influence of PCS variability on their findings is unclear. Using VBM, Dazzan et al. [2005] have reported that patients with psychosis (incorporating both schizophrenia and affective psychosis) taking typical antipsychotics had less ACC grey matter when compared with antipsychotic-naïve patients, whereas those taking atypicals showed no significant changes in the region. In contrast, recent ROI work has suggested that ACC volume is positively correlated with exposure to typical antipsychotics and negatively correlated with exposure to atypicals [Kopelman et al., 2005; McCormick et al., 2005]. However, McCormick et al. [2005] also failed to find a difference in the rate of volumetric change between patients taking typicals or atypicals in the first 2–3 years following psychosis onset, suggesting that the effects of antipsychotic exposure on ACC morphometry are minimized in the first few years of illness. While further longitudinal work is necessary to more comprehensively characterize the neuroanatomical effects of such treatment, evidence that ACC abnormalities are apparent prior to psychosis onset [Goghari et al., 2007; Pantelis et al., 2003] suggests they are unlikely to be solely a secondary consequence of antipsychotic exposure.

One consequence of our matching procedure was that control participants were selected from a larger database of images so that they could be individually matched to patients for age, sex, and PCS morphology. While this may have introduced some sampling bias in the control group, preliminary analyses indicated no significant differences between controls selected and not selected for study inclusion with respect to NART IQ (although those selected were significantly younger, due to the narrow age range of the FE patients). We note however, that biases introduced by this procedure would only serve to reduce differences between patients and controls, since controls were selected by virtue of possessing a cerebral morphology similar to that of the patients.

CONCLUSIONS

Our findings indicate that anatomical abnormalities of the ACC are apparent from the earliest stages of schizo-

phrenia, and that they cannot be solely attributed to group differences in sulcal and gyral anatomy. Using multiple measures of regional morphometry allowed us to identify a pattern of change consistent with an exacerbation of normal neurodevelopmental processes that should be further investigated in longitudinal research. This work highlights the importance of considering the influence that interindividual sulcal variability may have in neuroanatomical studies of clinical groups, and illustrates the advantages of moving beyond traditional, volume-based approaches when investigating cortical morphometry.

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