Anatomical Abnormalities of the Anterior Cingulate Cortex in Schizophrenia: Bridging the Gap Between Neuroimaging and Neuropathology

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The anterior cingulate cortex (ACC) is a functionally heterogeneous region involved in diverse cognitive and emotional processes that support goal-directed behaviour. Structural magnetic resonance imaging (MRI) and neuropathological findings over the past two decades have converged to suggest abnormalities in the region may represent a neurobiological basis for many of the clinical manifestations of schizophrenia. However, while each approach offers complimentary information that can provide clues regarding underlying pathophysiological processes, the findings from these 2 fields are seldom integrated. In this article, we review structural neuroimaging and neuropathological studies of the ACC, focusing on the unique information they provide. The available imaging data suggest grey matter reductions in the ACC precede psychosis onset in some categories of high-risk individuals, show sub-regional specificity, and may progress with illness duration. The available post-mortem findings indicate these imaging-related changes are accompanied by reductions in neuronal, synaptic, and dendritic density, as well as increased afferent input, suggesting the grey matter differences observed with MRI arise from alterations in both neuronal and non-neuronal tissue compartments. We discuss the potential mechanisms that might facilitate integration of these findings and consider strategies for future research.

Key words: psychosis/neuron/VBM/glia/limbic/prefrontal

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Neurobiological research has been critical in identifying the brain regions involved in the pathogenesis of schizophrenia, implicating several structures extending across limbic, frontal, temporal, and subcortical areas.[1–5] One brain region commonly reported to show abnormal structure and function in patients with the disorder is the anterior cingulate cortex (ACC), an area crucial for integrating cognitive and emotional processes in support of goal-directed behaviour.[6–10] The functional diversity of the ACC, which encompasses executive, social cognitive, affective, and skeleto- and visceromotor functions,[6,11–17] suggests that abnormalities in the region may partly explain the difficulties in cognitive and emotional integration that characterize the clinical manifestations of schizophrenia.[15,18]

Both neuropathological and neuroimaging findings support a role for ACC dysfunction in schizophrenia. Neuropathological research has revealed alterations in the cellular and synaptic architecture of the region,[19,20] while imaging work has identified ACC abnormalities that correlate with the disorder's characteristic symptoms and cognitive deficits,[21,22] and which ameliorate with treatment response.[23,24] However, the precise ACC sub-region affected, and the nature of the underlying changes, has varied across these reports, making it difficult to discern their pathophysiological significance. Moreover, while both neuroimaging and neuropathological approaches offer complimentary information, their findings are seldom integrated systematically, making it unclear how changes in cell density or synaptic morphology relate to volumetric differences identified with imaging.

In this article, we review magnetic resonance imaging (MRI) and neuropathological studies of the ACC in schizophrenia in an attempt to understand the pathological processes underlying the changes observed with in vivo imaging. Our discussion is organized around key questions that speak to the particular strengths of the 2 approaches. For neuroimaging research, we ask whether there is evidence of (1) regionally specific abnormalities, (2) abnormalities predating illness onset, and (3) variation in the abnormalities across different illness stages. For neuropathological work, we ask whether the evidence (1) supports the existence of volumetric changes in the ACC, (2) supports the occurrence of

cell loss in the ACC of schizophrenia patients, and (3) identifies changes in the intercellular neuropil. We then discuss the influence of psychotropic treatment on the findings, before providing a synthesis and consideration of their implications for uncovering underlying pathophysiological mechanisms. We primarily discuss structural MRI research and neuropathological studies of cell counts and cortical, axonal, dendritic, and cellular morphology, as these data are the most comparable, although we draw on other relevant literature where necessary. Rather than propose a definitive unitary pathophysiological process, we use the available data to stimulate discussion regarding which mechanisms might be most useful in integrating findings from these diverse fields. We begin with a brief overview of ACC anatomy and function.

Structure and function of the anterior cingulate cortex

Located bilaterally in the medial frontal lobes, the ACC comprises the cytoarchitectonic areas 24/24' and 32/32', with area 25, commonly called the subgenual cingulate,[25] located posterior to the subcallosal extension of area 24, ventral to the genu. Areas 24'/32' are located dorsal to the corpus callosum, while areas 24/32 occupy a pregenual position.[26] Areas 32 and 32' have been termed transition cortex because they possess cytoarchitectonic features common to areas 24/24' and adjacent frontal regions.[26] Other authors have labeled areas 32/32' as paralimbic, or paracingulate, cortex and areas 24/24' as limbic ACC due to the latter's denser connections with emotional centres.[6] The relative location and size of these regions change in accordance with variability in sulcal and gyral anatomy. In particular, the paracingulate sulcus (PCS), which is present in 30%–60% of cases and runs dorsal and parallel to the cingulate sulcus (CS),[27,28] is associated with a relative expansion of area 32, such that it extends from the depths of the CS across the crown of the paracingulate gyrus that forms between the CS and PCS, contrasting its location on the dorsal bank of the CS when a PCS is absent.[26] This variability has functional consequences[29–34] and is an important consideration when interpreting morphometric studies of the region, as discussed below. Figure 1 presents a simplified illustration of how the major cytoarchitectonic fields vary as a function of PCS variability.

Several meta-analyses of functional MRI (fMRI) and positron emission tomography (PET) studies have demonstrated that cognitive paradigms tend to elicit activation in dorsal areas 24'/32', whereas affective tasks produce increased activation in rostral areas 24/32, a distinction that parallels the greater connectivity between these rostral areas and limbic structures.[12,14,17,35] Within the rostral ACC, activation during negative emotional conditions tends localize within the subcallosal extension of area 24 and the adjacent area 25, while positive emotions

elicit activations in the pregenual portion of area 24, supporting a further functional distinction.[17] Evidence of functional dissociations between areas 24 and 32, and 24' and 32', are also being uncovered,[7,36] consistent with differences in their functional connectivity with other brain regions.[37,38] Some evidence suggests certain paralimbic areas mediate self-reflective and social cognitive processes,[14,39,40] although the precise nature of functional specialization in this region remains unclear. Broadly however, such findings suggest the ACC may be grossly partitioned into limbic (ACC_L) and paralimbic (ACC_P) regions, each containing dorsal, rostral, and subcallosal divisions (see figure 1). There is also evidence for a caudal division involved in motor control,[16] but it will not be considered further in this discussion. (For further details regarding ACC functional specialization, see [6–9,11,12,14,17,41,42].)

Structural magnetic resonance imaging research

Are changes in the ACC regionally specific?

Structural MRI studies have used 2 approaches to investigating neuroanatomical changes in patients with schizophrenia. One, the region-of-interest (ROI) method, involves manual delineation of the ACC on each scan, with morphometric parameters such as gray matter volume calculated secondarily. The second, commonly termed voxel-based morphometry (VBM), is an automated technique that involves spatial normalization of each participant's scan to a common stereotactic space, followed by voxelwise statistical comparison of group differences in gray matter measures. This has provided an attractive alternative to the ROI methodology because it affords a relatively unbiased assessment of gray matter changes across the entire brain, although errors in spatial normalization, particularly in morphologically variable regions such as the ACC, can complicate interpretation of findings.[43–45] We collectively refer to reports using one of the several variants of this technique[46–50] as whole-brain mapping (WBM) studies from hereon.

The findings of cross-sectional WBM studies investigating anatomical changes in the ACC of patients with schizophrenia are summarized in table 1, and stereotactic foci representing regions of maximal gray matter change reported in these studies are plotted in figure 2. The results suggest ACC gray matter reductions in schizophrenia are dispersed across dorsal and rostral divisions of the limbic and paralimbic regions, with few differences being noted in the subcallosal area. One-third (13/39) of WBM studies failed to identify any significant differences in ACC grey matter.

Results obtained using the ROI approach are summarized in table 2. Studies examining the entire anterior cingulate gyrus (ie, the ACC_L) have been variable, reporting right-sided,[51,52] bilateral,[53–59] or no group
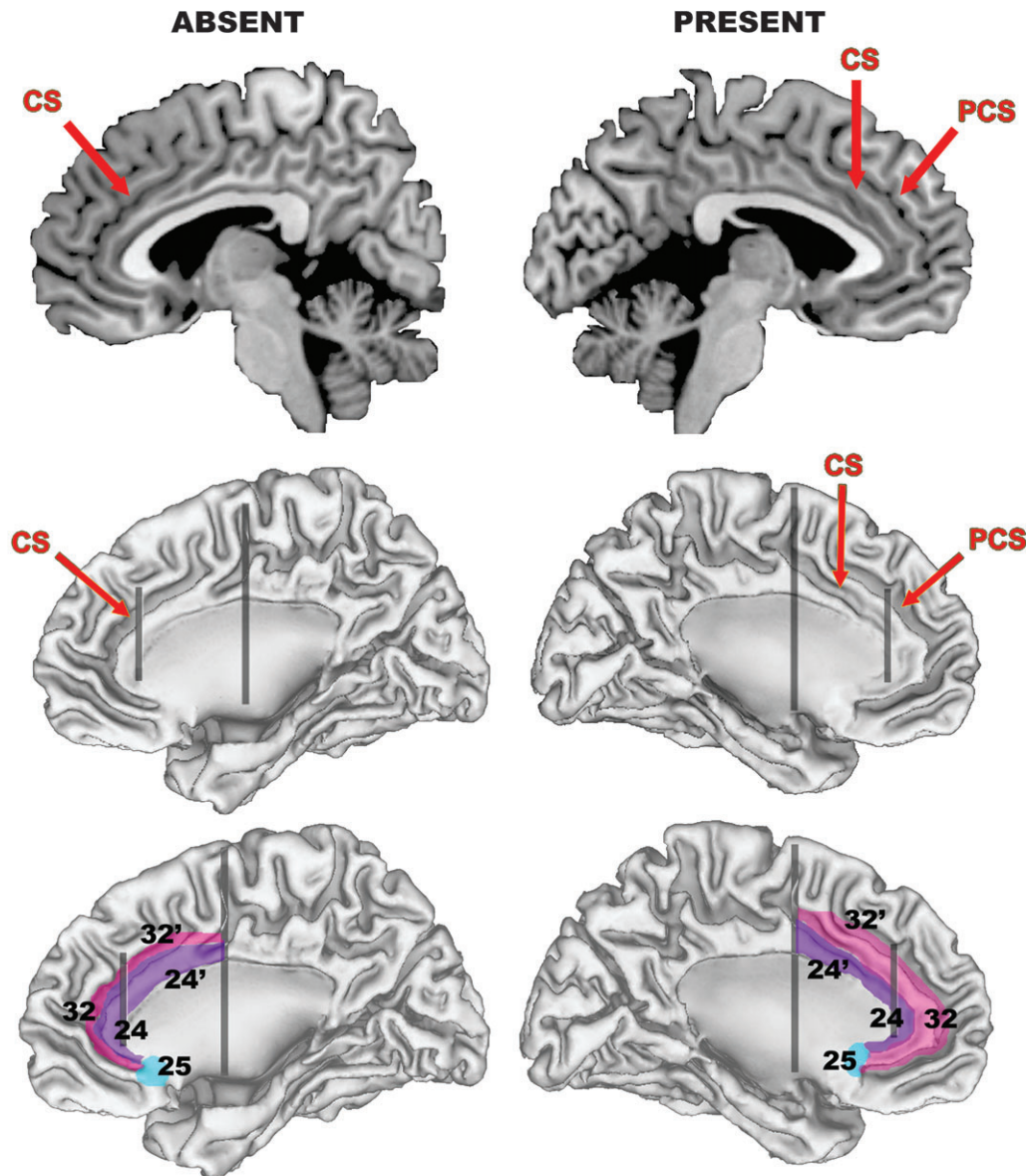
Fig. 1. Simplified Illustration of How Anterior Cingulate Cortex (ACC) Cytoarchitecture is Altered by Variations in Morphology of the Paracingulate Sulcus (PCS). Top row presents a sagittal slice through the left (right column) and right (left column) hemisphere of the N27 template,[179] which provides a good example of a "present" and "absent" PCS. Middle row illustrates the locations of the PCS and cingulate sulcus (CS) on cortical surface reconstructions generated from the N27 template using freely available software (http://brainmap.wustl.edu/caret). The surfaces run midway through the thickness of the cortical ribbon, facilitating visualization inside the sulcal walls. Bottom row illustrates how major cytoarchitectonic fields in the area are altered by PCS variability. The posterior vertical black line approximates the caudal border of what is termed the dorsal division of the ACC, and the anterior vertical black line approximates the border between areas 24/32 and 24'/32'. Note how areas 32/32' extend across the crown of the paracingulate gyrus when a PCS is present, in contrast to being buried in the depths of the CS when the PCS is absent. The purple area corresponds to what is termed the limbic ACC, the pink area to the paralimbic ACC. The borders are only intended as a rough approximation of their actual location.

differences.[21,60–62] Similarly, those focusing on the dorsal ACC$_L$ have found either left-sided[63] or right-sided[64,65] reductions or no group differences.[66–68] Studies of the rostral ACC have been more consistent, with most finding no gray matter differences,[63,65,67–69] although one found a left lateralized thickness increase that was positively correlated with years of antipsychotic treatment.[70] Relatively few (4/28) ROI studies have examined the subcallosal ACC, with no significant differences reported.[52,68,71,72]

Only 3 ROI studies have separately parcellated the ACC$_P$. The first[53] found bilateral volumetric reductions in the region to be among the largest seen across 48 ROIs in patients with established schizophrenia. The second[73] found a right-sided reduction in a first-episode (FE) sample but not patients with established schizophrenia. In the

Table 1. Details of Voxel-Based, Whole-Brain Mapping Studies in Schizophrenia

Study	Sample (No. of males)	Method (Measure)	Stereotactic Coordinates (x, y, z)[a]
Wright et al[180]	15 (15) SZ; 15 (15) CON	SPM96_T (GMC)	Nil
Sowell et al[181]	9 (3) COS; 10 (2) CON	Customized SPM96 (GMC)	Nil
Foong et al[182]	25 (19) SZ; 30 (22) CON	SPM 96_T (MTR, PD)	Nil
Hulshoff Pol et al[183]	159 (112) SZ; 158 (106) CON	MNI (GMC)	Nil
Paillere-Martinot et al[184]	20 (20) SZ; 20 (20) CON	SPM96_T (GMC)	-8 56 10; -6 39 -12
Sigmundsson et al[185]	27 (26) SZ; 27 (25) CON	BAMM (GMC)	-0.5 46 1
Wilke et al[186]	48 (27) SZ; 48 (27) CON	SPM99_T (GMC)	Nil
Ananth et al[187]	20 (10) SZ; 20 (10) CON	SPM99_T (GMV)	Nil
Job et al[188] [c]	34 (17) FE SZ; 36 (23) CON	SPM99_O (GMC)	3.96 40.87 1.64
Kubicki et al[189]	16 (14) FE SZ; 18 (16) CON	SPM99_T (GMC)	-6 2 40; 9 14 33
Shapleske et al[190]	72 (72) SZ; 32 (32) CON	BAMM (GMC)	3 -4 4[b]
Suzuki et al[191]	45 (23) SZ; 42 (22) CON	SPM96_T (GMC)	4 30 28
Bagary et al[192]	30 (19) FE SZ; 30 (18) CON	SPM99_O (MTR, GMC, GMV)	-4 40 12; -3 33 17; -1 25 22; 1 37 17; 2 38 12 (differences observed for MTR but not GMV or GMV)
Kuperberg et al[193]	33 (26) SZ; 32 (27) CON	SBM (GMT)	Left r-ACC_L/r-ACC; Right d-, r-, & s-ACC_L/ACC_P
Marcelis et al[194]	31 (15) SZ; 27 (12) CON	BAMM (GMC)	0.5 17.2 42.2
Salgado-Pineda et al[195]	13 (13) Neuroleptic-naïve FE SZ; 13 (13) CON	SPM99_T (GMC)	9 24 33; 10 32 25
Hyon Ha et al[196]	35 (21) SZ; 35 (21) CON	SPM99_T (GMC)	0 42 14; 4 50 -8[b]; 2 9 -12[b]
Kawasaki et al[86]	25 (14) SZ; 50 (28) CON	SPM99_T (GMC)	-2 57 8; -1 54 19; -1 36 26; 4 44 24; 1 54 6; 2 22 41
McIntosh et al[77]	26 (13) familial SZ; 49 (23) CON	SPM99_O (GMC)	Nil
Moorhead et al[197] [d]	25(14) SZ; 29(14) CON	SPM99_O&T (GMC & GMV)	5 9 30 (differences observed for GMV, but not GMC)
Salgado-Pineda et al[198]	14(7) SZ; 14(7) CON	SPM2_O (GMV)	-08 10 35; 10 -01 40
Antonova et al[199]	45(27) SZ; 43(25) CON	SPM99_O (GMC)	Nil
Davatzikos et al[200]	69(46) SZ; 79(41) CON	RAVENS (GMV)	Bilateral d-ACC_L/ACC_P, s-ACC_L/ACC_P
Farrow et al[89]	25(18) FE SZ; 22(13) CON	SPM99_O (GMC)	-8 39 15; -3 55 -12
Jayakumar et al[201]	18(9) FE SZ; 18(9) CON	SPM2_O (GMV)	Nil
McDonald et al[202]	25(18) SZ; 52(24) CON	SPM99_O & BAMM (GMV)	34 44 -8[b]
Narr et al[203]	72(37) FE SZ; 78(51) CON	CPM (GMT)	L r-ACC_L/ACC_P; R d-ACC_L/ACC_P
Suzuki et al[55]	4(3) Simple SZ; 20(10) CON	SPM99_T (GMC)	Nil
Whitford et al[204]	31(20) FE SZ; 30(20) CON	SPM99_O (GMV)	Nil
Necklemann et al[205]	12(n/a) SZ; 12(n/a) CON	SPM99_O (GMC)	Nil
Ohnishi et al[206]	47(24) SZ; 76(30) CON	SPM2 TBM (GMV)	9 33 20; -11 32 20; -12 -16 39
Park et al[207]	16 SZ; 16 CON	SBM (GMT)	Left r-ACC
Vidal et al[141]	12(6) COS; 12(6) CON	CPM (GMC)	Bilateral d- & r-ACC_P
Whitford et al[90]	41(26) FE SZ; 47(33) CON	SPM2_O (GMC)	-11 36 17
Chua et al[208]	26(12) med-free FE SZ; 38(18) CON	BAMM (GMC)	2.6 14 1[b]
Kašpárek et al[209]	22(22) FE SZ; 18(18) CON	SPM2_O (GMV)	2 20 64[b]
Kawasaki et al[210]	30(16) SZ; 30(16) CON	SPM2_O (GMC)	-3 33 21; 7 38 25; 6 50 11

Table 1. Continued

Study	Sample (No. of males)	Method (Measure)	Stereotactic Coordinates (x, y, z)[a]
Pagsberg et al[211]	29(11) COP; 29(25) CON	SPM99$_O$ (GMV)	Nil
Yamada et al[212]	20(10) SZ; 20(10) CON	SPM2$_O$ (GMC and GMV)	5 56 -3; 2 7 -6 (differences observed for GMC but not GMV)

Note: Studies were published before September 2007 and identified using the online PubMed database using the following search terms: schiz* (or psychosis) and VBM; schiz* (or psychosis) and SPM; schiz* (or psychosis) and voxel; schiz* (or psychosis) and MRI. Listed results are for gray matter comparisons only. SZ = schizophrenia; CON = control; COP = childhood-onset psychosis COS = childhood-onset schizophrenia; FE = first episode; GMC = gray matter density; GMD = gray matter density; GMT = gray matter thickness; MTR = magnetic transfer ratio; PD = proton density; TBM = tensor-based morphometry; SBM = surface-based morphometry, as implemented in Freesurfer (surfer.nmr.mgh.harvard.edu); MNI = Montreal Neurological Institute (www.bic.mni.mcgill.ca); BAMM = Brain Activation and Morphological Mapping (www-bmu.psychiatry.cam.ac.uk/BAMM); CPM = Cortical Pattern Matching, as described by Thompson et al[47]; RAVENS refers the approach described by Davatzikos et al[48]; SPM96, SPM99, and SPM2, refer to the different versions of the Statistical Parametric Mapping software package (www.fil.ion.ucl.ac.uk/spm) used for data analysis. The subscript $_T$ refers to the traditional method, whereas the subscript $_O$ refers to the optimized approach (see [46, 213]). All foci represent areas of relative gray matter decreases in patients. ACC$_L$ = limbic anterior cingulate cortex; ACC$_P$ = paralimbic anterior cingulate cortex; the prefixes d-, r-, and s-, refer to dorsal, rostral, and subcallosal subdivisions, respectively.
[a]Coordinates for the studies by Sigmundsson et al, Job et al, Shapleske et al, Marcelis et al, Salgado-Pineda et al, [195], Hyon Ha et al, Ohnishi et al, Whitford et al, and Chua et al, are in Talairach and Tourneoux [214] space. All other coordinates are in MNI space (see [215]). Verbal descriptions of regions showing significant differences are provided for studies that did not report stereotactic coordinates (there may be some ambiguity inherent in such descriptions, given that the figures did not always present slices optimum for visualizing medial frontal regions). Studies that did not report coordinates specifying significant differences in the ACC, did not verbally state that significant differences in these regions were identified, or did not display figures demonstrating change in these areas, were considered to show no differences.
[b]These foci were not near the ACC but formed part of a large cluster of significant voxels that extended into these regions. As such, they are not plotted in figure 2.
[c]These authors ran several patient-control comparisons to examine the effects of using different templates and covariates. We only included foci for what these authors termed their "primary" comparison (reported in table 2, p. 883 of their article).
[d]These authors ran several patient-control comparisons to examine the effects of using parametric vs non-parametric statistics, and to compare traditional and optimised VBM processing streams. We only retained parametric results for the traditional and optimised approach. These authors also published a second study using the same sample to investigate methodological effects. We only report on results from the first study here.

third, we found a bilateral reduction in thickness, but not volume or surface area, of the ACC$_P$ extending across dorsal, rostral, and subcallosal subregions in FE patients,[68] with no differences being identified in limbic subregions.

In summary, most MRI studies suggest schizophrenia patients show reduced ACC gray matter, although the location of these changes has been variable. Generally, the reductions seem to extend across the dorsal and rostral ACC$_L$ and ACC$_P$, with limited subcallosal involvement. Methodological differences, such as variations in ROI parcellation schemes or image pre-processing steps implemented in WBM research, likely contribute to these inconsistencies, as do variations in sample characteristics. An additional, major and often-neglected influence on the findings is variability in the incidence and extent of the PCS. As previously mentioned, PCS variability can alter the location and extent of paralimbic ACC,[26] with MRI studies suggesting its appearance can produce up to an 88% increase in ACC$_P$ volume and 39% decrease in ACC$_L$ volume.[28,45] People with schizophrenia are less likely to show a PCS in the left hemisphere,[56,74,75] suggesting that the results of ROI or WBM studies

will be biased unless the comparison groups are well matched for sulcal morphology. Our recent study of FE patients[68] attempted to control for this variability by matching patients and controls for PCS morphology.[34,45] While our finding of reduced bilateral ACC$_P$ thickness suggests that gray matter reductions in schizophrenia are not entirely attributable to group differences in sulcal and gyral anatomy, it needs to be replicated in independent samples.

Do anatomical changes in the ACC predate illness onset?

The question of whether neuroanatomical changes precede illness onset has typically been examined by studying individuals at elevated risk for schizophrenia to determine whether they show changes similar to those observed in affected probands. Cross-sectional studies of unaffected relatives of patients have yielded conflicting findings. Goghari et al,[76] using an ROI approach, found a bilateral reduction in ACC thickness in patients' relatives, in addition to a right-sided decrease in volume and surface area extending across the entire cingulate gyrus, although 2 earlier WBM studies failed to find any association
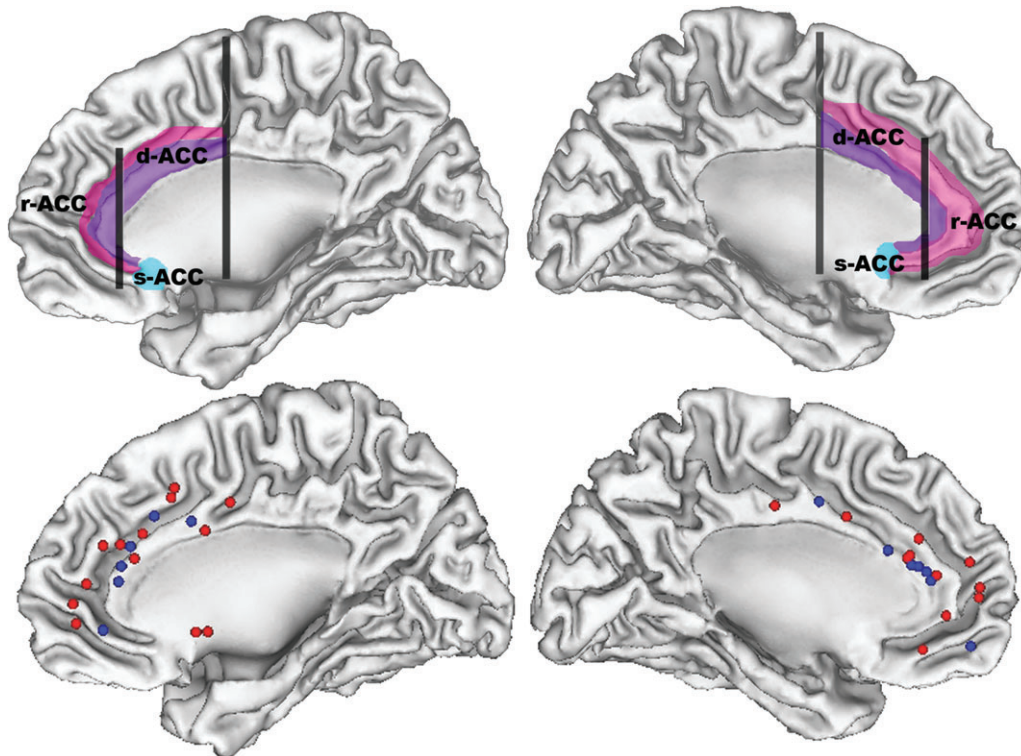
Fig. 2. Stereotactic Foci (Bottom Row) Representing Regions of Maximal Anterior Cingulate Cortex (ACC) Gray Matter Reductions Reported in Whole-Brain Mapping Studies of Schizophrenia. Blue foci correspond to differences between first-episode patients and controls, and red foci correspond to differences between patients with established schizophrenia and controls. Top row presents the same surfaces illustrating the approximate locations of the dorsal (d-ACC), rostral (r-ACC) and subcallosal (s-ACC) divisions of the anterior cingulate cortex. Limbic ACC is shown in purple and paralimbic ACC is in pink. Left hemisphere is presented on the right side.

between changes in ACC gray matter and genetic risk for schizophrenia.[77–79] This discrepancy may partly reflect differences in the sensitivity of ROI and WBM methods for assessing ACC changes, as a WBM study by Job et al[80] found reduced ACC gray matter in a sample of individuals at genetic risk for schizophrenia after restricting their analysis to this region (the differences did not emerge in a whole brain analysis). However, the unknown rate of illness transition in these samples makes it difficult to determine whether the findings reflect changes associated with imminent illness onset or a generalized at-risk status.

Studies incorporating a longitudinal component to ascertain the diagnostic outcome of their high-risk samples have yielded more consistent findings. The first such study applied WBM techniques to scans acquired in a group of individuals deemed to be at ultra-high risk (UHR) for psychosis onset[81] based on a combination of state and trait criteria associated with a 30%–40% rate of transition to frank psychosis within 1 year.[82] Comparing UHR individuals who did develop psychosis (UHR-P) with those who did not (UHR-NP) revealed reduced ACC gray matter in UHR-P individuals prior to psychosis onset, as well as longitudinal reductions in this region during the transition to psychosis that were

not apparent in the UHR-NP group. Independently, Borgwardt et al[83] found reduced ACC gray matter in their UHR-P group (defined using similar criteria) when using uncorrected thresholds to account for their limited sample size. However, in a longitudinal study of individuals at genetic high risk, Job et al[84] found no differences in ACC gray matter between those who did and those who did not subsequently become psychotic, despite there being ACC gray matter reductions in the high-risk sample as a whole at baseline.[80] Job et al[84] also found no ACC differences in a small subgroup (*n* = 8) who eventually developed schizophrenia. The discrepancy in these findings suggests that prepsychotic ACC abnormalities may vary depending on whether individuals are at elevated risk for genetic or nongenetic reasons because a positive family history was not necessary for inclusion in the UHR samples.

We have recently examined ACC morphometry in the largest cohort of high-risk people making the transition to psychosis to date (Fornito, Yung, Wood, Phillips, Nelson, Cotton, Velakoulis, McGorry, Pantelis & Yücel, in revision), using the same approach implemented in our previous work[68,85] to account for the confounding effects of PCS variability. Relative to healthy controls, UHR-P (*n* = 35) individuals displayed bilateral thinning of the

Table 2. Details of Region-of-Interest Magnetic Resonance Imaging Studies Examining the Anterior Cingulate Cortex in Schizophrenia

Study	Sample Size (no. of males)	ROI (Measures)[a]	Major Findings
Noga et al[66]	14(n/a) SZ; 14(n/a) CON	d-ACC$_L$ [b] (V)	No group differences.
Hirayasu et al[71]	17(14) FE SZ; 20(18) CON	s-ACC$_L$ (V)	No group differences.
Szeszko et al[216]	19(10) FE SZ; 26(16) CON	ACG (V)	No group differences.
Goldstein et al[53]	29(17) SZ; 26(12) CON	ACG; PaG[c] (V)	SZ < CON in ACG & PaG bilaterally.
Crespo-Facorro et al[67]	26(26) med-naïve FE SZ; 34(34) CON	d-ACC$_L$; r-ACC$_L$ (V & A)[d]	No group differences.
Convit et al[60]	9(9) SZ; 9(9) CON	ACG (V)	No group differences.
Yücel et al[74]	55(55) SZ; 75(75) CON	PCS incidence	SZ less likely to possess a PCS in the left hemisphere.
Takahashi et al[e][64]	40(20) SZ; 40(20) CON	d-ACC$_L$ (V)	Female SZ < Female CON in right d-ACC$_L$. R>L asymmetry observed in Female CON was not seen in Female SZ.
Le Provost et al[75]	40(40) SZ; 100(100) CON	PCS incidence	SZ less likely to possess a PCS in the left hemisphere, and were more likely to display a right-lateralized PCS asymmetry.
Takahashi et al[f][69]	58(31) SZ; 61(30) CON	r-ACC$_L$ (V)	No group differences. SZ did not show the Male>Female difference seen in CON.
Haznedar et al[63]	27(20) SZg; 32(25) CON	d-ACC$_L$; r-ACC$_L$[h] (V)	SZ < CON left d-ACC$_L$.
Yamasue et al[54]	27(20) SZ; 27(20) CON	ACG (V)	SZ < CON ACG bilaterally.
Choi et al[65]	22(15) SZ; 22(15) CON	d-ACC$_L$; r-ACC$_L$[d] (V)	SZ < CON right d-ACC$_L$.
Coryell et al[72]	10(6) SZ; 10(6) CON	s-ACC$_L$[i] (V, A, T)	No group differences.
Marquardt et al[217]	13(7) COS; 18(10) CON	ACG (PaG included if PCS present) (V)	SZ > CON right ACG.SZ did not show Left>Right asymmetry in present in CON.
Mitelman et al[52]	37(27) SZ; 37(23) CON	Areas 24 (dorsal & rostral combined) & 25[j] (V)	SZ < CON area 24 bilaterally.
Kopelman et al[70]	30(30) SZ; 30(30) CON	r-ACC$_L$ (V, A, T)	SZ > CON left r-ACC$_L$ volume & thickness; Left r-ACC$_L$ thickness positively correlated with years of antipsychotic treatment.
Riffkin et al[61]	18(18) SZ; 18(18) CON	ACG (V)	No group differences.
Suzuki et al[55]	22(9) SZ; 44(18) CON	ACG (V)	SZ < CON bilaterally.
Zhou et al[51]	59(31) SZ; 58(30) CON	ACG (V)	SZ < CON right ACC.
Lopez-Garcia et al[73]	21(13) SZ; 22(16) FE SZ; 24(12) CON	Area 32 (V)[k]	SZ = CON; FE SZ < CON right area 32.
Szendi et al[62]	13(13) SZ; 13(13) CON	ACG (V)	No group differences.
Fujiwara et al[56]	26(13) SZ 20(10) CON	ACG (V)	SZ < CON bilaterally.
Szeszko et al[57]	20(17) Cannabis using SZ; 31(25) Non-cannabis using SZ; 56(36) CON	ACG (V)	Cannabis using SZ showed reduced volume bilaterally compared to CON and non-cannabis using SZ.
Fornito et al[68]	40 (31) FE SZ; 40 (31) CON[l]	d-, r-, & s-ACC$_L$ & -ACC$_P$ (V, A, T)	SZ < CON in d-, r-. & s-ACC$_P$ bilaterally in thickness, but not volume or area.
Mitelman et al[52]	51(40) good outcome SZ; 53(43) poor outcome SZ; 41(28) CON	Areas 24(dorsal & rostral combined), 25, & 32[j] (V)	Both good & poor outcome SZ < CON right area 32.No differences between good & poor outcome SZ.

Table 2. Continued

Study	Sample Size (no. of males)	ROI (Measures)[a]	Major Findings
Wang et al[58]	53(32) SZ; 68(35) CON	ACG (V, A, T)	SZ < CON volume bilaterally; trend for a thickness reduction; no differences in surface area.
Qiu et al[m] [59]	49 SZ; 64 CON	ACG (T)	SZ < CON bilaterally.

Note: Studies were published before September 2007 and identified using the online PubMed database using the following search terms: schiz* (or psychosis) and cing*; schiz* (or psychosis) and paracing*; schizo* (or psychosis) and MRI. Listed results are for gray matter comparisons only. One study, conducted by Yamasue, et al[218], was also not listed because the authors used a region-of-interest (ROI) derived from a voxel used to localize spectroscopic measurements, rather than an anatomically-driven protocol. SZ = schizophrenia; CON = control; FE = first episode; COS = childhood-onset schizophrenia; ACC_L=limbic anterior cingulate cortex; ACC_P=paralimbic anterior cingulate cortex; the prefixes d-, r-, and s-, refer to dorsal, rostral, and subcallosal subdivisions, respectively; ACG = anterior cingulate gyrus; PaG = paracingulate gyrus; PCS = paracingulate sulcus; V = gray matter volume; A = surface area; T = cortical thickness.
[a]Where we were confident the ROIs described by the authors were similar to the ACC subregions we illustrated in figure 1, we have used our terminology. In cases where we were uncertain, we retained the ROI nomenclature assigned by the authors.
[b]Estimated by taking the coronal slice in which the septum pellucidum was visible, and tracing 6 mm either side.
[c]Used the whole-brain parcellation method described in Caviness[219]. Although the ACC_P was parcellated separately, PCS variability was not explicitly considered.
[d]Border between rostral and dorsal ACC taken from the method of Crespo-Facorro et al[220]. Part of the sub-ACC is included in r-ACC with this method. Choi et al[65] included the ACC_P as part of their ROI if a PCS was apparent.
[e]Takahashi et al[88] used a similar methodology to Takahashi et al[64] in an extended sample that also looked at patients with schizotypal personality disorder. The results were unchanged in the schizophrenia group, so only the latter is listed.
[f]Takahashi et al[221] used a similar method in a sample extended from the Takahashi et al. study listed above. Again, the results were unchanged, so only the 2003 study is listed.
[g]7 patients were neuroleptic-naïve, 20 had been medication free for ~ 3 weeks prior to scanning.
[h]Dorsal & rostral ACC delineated using proportions of Brodmann Areas 24 & 25 taken from the atlas of Talairach & Tourneoux[214].
[i]A region posterior to the s-ACC, approximating Brodmann area 25, was also parcellated separately.
[j]Regions were delineated by geometrically dividing consecutive coronal slices into distinct portions and comparing them with a post-mortem cytoarchitectonic map divided in a similar fashion. See Mitelman et al[52] for more details. Samples partially overlap across all these studies.
[k]Parcellated by registering the a template onto each individual's image.
[l]Controls were matched to patients for morphology of the PCS.
[m]This sample partially overlaps with that studied by Wang et al, but the authors applied a different method for comparing group thickness differences.

rostral ACC_P, whereas UHR-NP (*n* = 35) individuals showed increased thickness bilaterally in the dorsal ACC_L. Subdiagnostic analyses suggested that these pre-onset changes were specific to UHR-P individuals that went on to develop a schizophrenia-spectrum psychosis, with none being noted in those who developed affective or other psychoses.

Together, these findings suggest that ACC gray matter reductions precede psychosis onset and that these pre-onset changes may be specific to schizophrenia-spectrum disorders. However, they may be more prevalent in individuals at clinical, rather than genetic, high risk. Studies of people with schizotypal personality disorder have generally failed to find any ACC differences,[63,86–88] further underscoring the need to examine how different risk factors relate to pre-onset neuroanatomical changes in schizophrenia.

Do the changes vary across illness stages?

The most straightforward method for examining whether ACC changes vary across illness stages is to compare results identified in FE and established patient samples. In this context, the most notable finding in ROI work is that none of the FE studies published to data have found significant group differences in ACC_L gray matter.[21,67,68,73] In contrast, both of the studies that parcellated the ACC_P separately reported gray matter reductions in their FE samples,[68,73] suggesting that the earliest changes in schizophrenia occur in paralimbic regions. Consistent with this view, a recent longitudinal study of childhood-onset schizophrenia found the earliest gray matter reductions extended across the dorsal and rostral ACC_P and spread to encompass the ACC_L over a 5-year period. Such findings are also consistent with evidence of gray matter reductions in the rostral ACC_P prior to schizophrenia onset[81] longitudinal changes in the rostral and dorsal ACC_P during the transition to psychosis,[81] and more diffuse reductions extending across the rostral, dorsal, and subcallosal ACC_P in FE patients,[68,73] with further reductions possibly occurring after the first episode.[89]

However, not all imaging findings support a paralimbic to limbic progression of abnormalities in schizophrenia. As indicated in figure 2, comparing the peaks of gray

Table 3. Details of Studies Examining Anterior Cingulate Volume and/or Cortical Thickness in Schizophrenia

Metric	Study	Sample[a]	Region[b]	Measures[c]	Findings
Volume	Highley et al[97]	24 SZ; 28 CON	Bilateral ACG	Stereology of gray and white mater volume	No group differences
	Ongur et al[99] (2001)	11 SZ; 11 CON	s-24[d]	Stereology of gray matter volume	No group differences
	Stark et al[96] (2004)	12 SZ; 14 CON	Bilateral 24/24' & 32/32'[e]	Stereology of gray matter volume	No group differences
	Kreczmanski et al[98]	13(13) SZ; 13(13) CON	Bilateral 24'	Stereology of grey matter volume	SZ < CON bilaterally
Thickness	Benes et al[101]	11 SZ; 12 CON	r-24[f]	Laminar thickness	No group differences
	Bouras et al[100]	44 SZ; 55 CON	Left d-24a-b; & s-24a	Laminar thickness	SZ<CON in LII, V, VI of s-24; total thickness decreased in 24'
	Kreczmanski et al[98]	13(13) SZ; 13(13) CON	Left and right 24'	Total cortical thickness	SZ < CON bilaterally

Note: Studies were published before September 2007 and identified using the online PubMed database using the following search terms: schiz* (or psychosis) and cing*; schiz* (or psychosis) and paracing*; schizo* (or psychosis) and MRI. SZ = schizophrenia patients; CON = control; L = cortical layer; ACG = anterior cingulate gyrus; d-, r-, and s- refer to dorsal, rostral, and subcallosal subregions, respectively, of the anterior cingulate cortex.
[a]The number of males in each sample is not presented as few studies reported the gender composition of their samples.
[b]Where we were confident the ROIs described by the authors were similar to the anterior cingulate cortex subregions we illustrated in figure 1, we have used our terminology. In cases where we were uncertain, we retained the ROI nomenclature assigned by the authors.
[c]All stereological studies used the Cavalieri principle to calculate volume.
[d]Specimens were obtained randomly from left and right hemispheres.
[e]These authors studied the entire regions, as defined using cytoarchitectonic criteria, but did not differentiate between areas 24 and 24' or areas 32 and 32'.
[f]The hemisphere from which samples were taken was not specified.

matter differences identified in WBM studies of FE and chronic patients does not reveal clear, regionally specific changes associated with illness stage. Furthermore, not all longitudinal studies have reported evidence for a progression of ACC abnormalities. Job et al[84] failed to find any evidence of longitudinal changes in ACC gray matter in genetic high-risk individuals who either developed schizophrenia or subthreshold psychotic symptoms, although power may have been limited due to restricted sample sizes. In a larger sample, Whitford et al[90] found no evidence of excess ACC gray matter reduction in the first 2–3 years following schizophrenia onset, nor were excess reductions found in a separate 5-year follow-up study of patients with established schizophrenia.[91]

In summary, while there is some cross-sectional and longitudinal evidence to suggest that the earliest ACC changes in schizophrenia appear in the rostral ACC$_P$ prior to psychosis onset, extend across the ACC$_P$ during the transition to a FE psychosis, and spread to engulf limbic areas with continued illness, not all data support this view. Medication is likely to complicate interpretation of these findings, following evidence that exposure to atypical antipsychotics is associated with increased ACC gray matter over time whereas treatment with typical agents is associated with decreased ACC gray matter.[92] Further longitudinal work that accounts for these medication effects will therefore be necessary to better characterize the trajectory of ACC changes across the course of schizophrenia.

Neuropathology of the ACC in schizophrenia and bipolar disorder

Are volume changes apparent in postmortem samples?

The preceding discussion indicates that most imaging studies in schizophrenia have found evidence for reduced ACC gray matter. However, anatomical changes detected using MRI may result from a variety of nonpathological physiological and developmental processes,[93–95] highlighting the need to validate such findings with postmortem techniques. This task is complicated by the relative paucity of postmortem work published in this area and the considerable variability in the ACC subregions sampled (see table 3).

Two postmortem studies, both examining the volume of the entire anterior cingulate gyrus, found no significant volumetric differences,[96,97] while one focusing on dorsal area 24' reported reduced volume in both the left and right hemispheres of schizophrenia patients.[98] In a separate

report, no group differences were found in the subcallosal portion of area 24,[99] consistent with the aforementioned MRI findings suggesting few changes in this region. However, some of these studies collapsed data from samples taken from both hemispheres,[96,99] adding noise to the group comparisons. Moreover, only one study attempted to control for differences in overall brain size.[97] The sole postmortem investigation of paralimbic ACC found no significant differences.[96]

Three studies have investigated ACC laminar thickness in patients with schizophrenia. Two studies examining dorsal area 24' both found reductions in total cortical thickness (collapsed across all layers), with one reporting a bilateral reduction[98] and the other examining left hemisphere samples only.[100] Bouras et al[100] also reported reduced thickness in specific layers of subcallosal area 24, while the only study of rostral area 24 found no significant differences in laminar thickness.[101] Together, these findings suggest that schizophrenia is associated with volumetric and thickness reductions, at least in the dorsal and subcallosal ACC. These results are broadly consistent with the gray matter reductions reported in imaging research, although more postmortem studies are required before firm conclusions can be drawn.

Is there evidence of cell loss?

Cortical gray matter reductions are often interpreted as reflecting neuronal loss, although providing unambiguous evidence for neuronal loss is a nontrivial task as a definitive answer requires precise counting of each neuron within a defined region, a goal that poses several technical challenges (see [102,103] for detailed discussion). Only 2 studies have estimated absolute cell counts in the ACC of schizophrenia patients (see table 4). The first, by Ongur et al,[99] found no differences in overall neuronal number in subcallosal area 24, consistent with their finding of no changes in the gray matter volume of this region. The second, by Stark et al,[96] examined multiple sections through the limbic (24/24') and paralimbic (32/32') ACC and also found no differences.

Most cell-counting studies have examined cell density rather than absolute cell number. Cell density is a more practical measure because it can be obtained from a restricted tissue sample rather than the entire extent of a region. It therefore estimates the relative cellular abundance per unit volume, rather than providing an absolute cell count. The reported findings have been somewhat contradictory, with decreases,[101,104,105] increases,[106] and no changes[99,100,107,108] being found in patients relative to controls (see table 4). Part of this inconsistency is likely related to differences in the precise ACC subregion sampled. For example, most studies of dorsal area 24' have reported no changes in neuronal density,[99,100,107] with one reporting increased density in patients.[106] Only 2 studies have examined the subcallosal ACC region

separately,[99,100] with neither reporting group differences in overall neuron density. However, they did find a decrease in the density of large-diameter neurons and an increase in small-diameter neurons in both subcallosal and dorsal regions, suggesting a selective shrinkage of large (presumably pyramidal) neurons. (Reports by others of changes in neuron size have been variable; see table 4.) Findings in the rostral ACC have been more consistent, although all the work in this area has been conducted by one group (table 4). A recent meta-analysis of their findings[19] suggests that, while the density of both pyramidal and nonpyramidal neurons is reduced in schizophrenia patients, the reduction is greater for pyramidal neurons. In contrast, patients with bipolar disorder showed larger reductions in nonpyramidal neuron density. Independent replication of these results will be critical in establishing their generalizability.

In summary, the only 2 studies reporting absolute cell counts do not support neuronal loss in the ACC of schizophrenia patients, while the much larger literature examining cell density suggests that there are indeed reductions in the number of neurons per unit volume in some subregions. However, for a reduction in neuronal density to reflect neuronal loss, the degree of neuronal loss would either have to be accompanied by no change in cortical volume, or the reduction in neuron number would need to exceed the magnitude of any volumetric reduction since findings of reduced neuron density may also arise if neuron number remains unchanged but volume is increased (see [109] for similar arguments). Given the aforementioned MRI and neuropathological evidence for gray matter reductions in some ACC subregions, any reductions in neuron density would need to exceed the magnitude of the volumetric decrement to be interpreted as neuronal loss. Differences in cell-counting methodologies and subregions sampled across studies make it difficult to obtain a robust estimate of the magnitude of the density or volumetric reductions observed, and the 4 studies that have measured neuron density and gray matter thickness or volume concurrently have yielded inconsistent results: Benes et al[101] found that minimal change in rostral ACC thickness was accompanied by a 40% reduction in pyramidal and 16% reduction in nonpyramidal neurons; Bouras et al[100] reported larger reductions in thickness than neuron density in dorsal and subcallosal subregions; Ongur et al[99] reported comparable reductions in density and volume in the subcallosal ACC; and Stark et al[96] found no differences in either neuron density or volume in areas 24 and 32. Such results suggest that neuronal loss may be more pronounced in the rostral ACC, consistent with other reports of quite large (~50%) reductions in some neuronal subtypes in this area.[110] However, differences in cell-counting techniques might contribute to inconsistencies across studies, given the ongoing debate regarding the accuracy and validity of 2- vs 3-dimensional methods (see [103] and related

Table 4. Details of cell-counting and synaptic morphology studies of the anterior cingulate cortex in schizophrenia.

Study	Sample[a]	Region[b]	Measures	Major findings
Benes et al[104]	9 SZ; 10 CON	ACC	2D neuron & glial density & size; neuron/glia ratio.	SZ<CON neuron density in L5; no changes in neuron size, glial density, or neuron/glia ratio.
Benes et al[111]	10 SZ; 10 CON	24	Inter-cellular & inter-aggregate distance of neurons & glia.	SZ>CON inter-neuronal & inter-neuronal aggregate distance; SZ<CON diameter of neuronal aggregates. No changes in glial arrangement.
Benes et al[119]	7 SZ; 7 CON	ACC	NFP-200-IR vertical & horizontal axon number.	SZ>CON number of vertical axons in L2 & 3; no changes in horizontal axonal number.
Benes et al[105]	18 SZ; 12 CON	24	2D PN & small neuron density.	SZ<CON small neuron density in L2-6; no changes in PN density.
Aganova et al[115]	5 SZ; 7 CON	24	EM of synaptic density[c].	SZ>CON axospinous & dendritic synapse density; SZ<CON axodendritic synapse density.
Benes et al[120]	17 SZ; 15 CON	24	IHC - Density of glutamate-IR axonal fibers	SZ>CON density of small & large caliber vertical fibers.
Benes et al[121]	10 SZ; 15 CON	BA 24	IHC - Density of TH-IR varicose fibers	SZ >CON density of TH-IR fibers in L5 & L6 of NPL; SZ<CON density of fibers in apposition with small neurons relative to those in apposition with large neurons in L2; no differences in density of fibers in apposition with small or large neurons.
Ongur et al[99]	11 SZ; 11 CON[d]	s-24	3D neuron & glial number, density & size.	SZ>CON number of large neurons & SZ<CON number of small neurons; no changes in overall neuronal or glial number or density.
Benes et al[101]	11 SZ; 12 CON	r-24	2D PN, NP, & glial density; NP & PN size.	SZ<CON PN density in L5; no changes in glial density or neuron size. (Abercrombie correction yielded generally similar findings.)
Bouras et al[100]	44 SZ; 55 CON	Left d-24a-b & s-24a	3D neuron density & size; axonal & dendritic morphology	SZ<CON reduced maximal neuron diameter in L5 of d24 & L6 of s24; SZ had less large & more small diameter neurons in both ROIs; no changes in neuron density; no differences in axonal/dendritic morphology in sub-group of 3 patients and 3 controls.
Cotter et al[107]	15 SZ; 15 CON	d-24b	3D neuron & glial density & size.	SZ<CON glial density in L6 (did not survive correction for multiple comparisons); no changes in neuron density or size.
Broadbelt et al[20]	11 SZ; 11 CON	r-32	Number of primary & secondary basilar dendrites	SZ<CON number of primary & secondary basilar dendrites in L3 & 5.
Jones et al[108]	7 SZ; 7 CON	r-32	PN density.	No differences in PN density in L3 or L5.
Chana et al[106]	15 SZ; 15 CON	d-24c	2D neuron & glial density, size & spatial clustering.	SZ>CON neuron density in L5 & 6; SZ>CON glial size in L1, 3, & 5; SZ<CON neuron size in L3 & 5; no changes in glial density, or neuronal or glial clustering.

Table 4. Continued

Study	Sample[a]	Region[b]	Measures	Major findings
Stark et al[96]	12 SZ; 14 CON	Bilateral 24/24' & 32/32',[e]	3D neuronal & glial number & density.	SZ<CON glial number in area 24; no changes in glial density or neuronal number or density; no changes in neuronal or glial number or density in area 32.
Steiner et al[222]	16 SZ; 16 CON	r-ACC	IHC & 2D counting of HLA-DR-IR microglial density.	No differences in HLA-DR-IR glial density.

Note: Studies were published before September 2007 and identified using the online PubMed database using the following search terms: schiz* (or psychosis) and cing*; schiz* (or psychosis) and paracing*; schizo* (or psychosis) and MRI. SZ = Schizophrenia patients; CON = control; ACC = anterior cingulate cortex; d-, r-, and s- refer to dorsal, rostral, and subcallosal subregions, respectively, of the ACC; 2D = 2-dimensional; 3D = 3-dimensional; L = cortical layer; PN = pyramidal neurons; NP = non-pyramidal neurons; NPL = neuropil; EM = electron micrograph; IHC = immunohistochemistry; IR = immunoreactive; NFP-200 = neurofilament protein 200-immunoreactive; TH = tyrosine hydroxylase; HLA = human leukocyte antigen.
[a]The number of males in each sample is not presented as few studies reported the gender composition of their samples.
[b]Where we were confident the regions-of-interest described by the authors were similar to the ACC subregions we illustrated in figure 1, we have used our terminology. In cases where we were uncertain, we retained the ROI nomenclature assigned by the authors.
[c]These authors also examined synaptic morphology, but reported no statistical results.
[d]The authors reported results from 2 separate samples. Only results from the larger sample are reported here (results were generally consistent across samples).
[e]These authors studied the entire regions, as defined using cytoarchitectonic criteria. Unless otherwise specified, all other studies restricted their analyses to specific sections.

commentaries). In this context, it is noteworthy that studies employing 3-dimensional methods have been less likely to find significant differences in cell density (see table 4). The lack of studies examining the same subregion using these different approaches complicates comparison of findings reported by different research groups. However, one early report by Benes and Bird[111] suggested that interneuronal distance is increased in the ACC of schizophrenia patients, supporting the notion that any reductions in cortical volume are not accompanied by an increase in packing density, which would be expected if cell number were unchanged. Findings of either no change [106,107,101,104 99] or a reduction in ACC glial density [96] in schizophrenia patients suggest that, if neuronal loss does occur in this disorder, it is not accompanied by the gliotic reactions associated with traditional neurodegenerative processes.[1,112]

Is there evidence of changes in the inter-cellular neuropil?

Accumulating evidence implicates synaptic pathology in schizophrenia [113,114]. The first study of ACC synaptic morphology in the disorder was conducted by Aganova and colleagues [115], who found decreased density of axospinous and axodendritic synapses in a small (n = 5) sample. A later study investigating a larger sample (n = 11) found reduced dendritic density in layers III and V of rostral area 32 [20] consistent with reports of decreased expression of synaptic proteins in the ACC of schizophrenia patients [108,116–118].

In rostral area 24, Benes et al. [119] reported an increase in the number of vertical afferents entering layers II and III in schizophrenia patients. These afferents were later confirmed to be glutamatergic in nature [120]. In separate work, they found reduced density of fibers immunoreactive for tyrosine hydroxylase in the inter-neuronal neuropil, combined with a relative increase in the density of such fibers in apposition with small compared to large neurons [121]. Collectively, these findings suggest that the ACC of schizophrenia patients possesses excess glutamatergic input, aberrant wiring of glutamatergic and dopaminergic circuits, and reduced synaptic and dendritic density.

Are the changes secondary to antipsychotic treatment?

As previously mentioned, some MRI studies have found that medication can affect ACC gray matter measures, although the precise nature of such influences remains contentious. Only 2 studies of ACC gray matter in antipsychotic-naive patients have been conducted: an ROI study that found no differences between patients and controls[67] and a WBM report finding that, relative to drug-free patients with psychosis (both schizophreniform and affective patients), those treated with typicals showed reduced ACC gray matter while those treated with atypicals showed no differences.[122] We have found no differences in ACC gray matter between FE schizophrenia patients taking typical or atypical antipsychotics, after

accounting for the confounding influence of PCS variability.[68] While our study did not include unmedicated patients, findings of pre-onset changes in UHR individuals suggest that medication effects are insufficient to account for all the ACC gray matter reductions associated with schizophrenia.[80,81] The duration of antipsychotic treatment may still play an important role however, given the aforementioned evidence suggesting that cumulative exposure to typical and atypical agents may have a differential effect on ACC gray matter over time,[70,92] although several authors have failed to find any correlations between ACC gray matter measures and antipsychotic exposure.[52,53,88]

In postmortem work, restrictions on tissue availability make it difficult to comprehensively rule out treatment influences on the findings. Some authors have tested for medication effects by dividing their sample into patients taking or not taking medications prior to death,[101] or examining statistical associations between indices of antipsychotic exposure and the measures of interest[104,107](the latter is also commonly used to rule out an influence of other confounds associated with tissue handling and processing or demographic characteristics). However, given that the initial sample is often small, the power of such secondary analyses is limited. Most of the patients studied by Bouras et al[100] lived prior to the introduction of neuroleptics, suggesting that not all neuropathological changes are attributable to medication effects, although these authors only found differences in ACC laminar thickness and neuron size, not density. Research in nonhuman primates suggests that, in some brain regions, antipsychotic exposure produces increased cortical volume and glial density with no change in neuronal number, findings that contrast with human data.[123] Further characterization of the cellular changes induced by psychotropic medications will be necessary to facilitate interpretation of neuropathological research.

Bridging the gap: implications for pathophysiology

To summarize, the available MRI data suggest that gray matter reductions in some ACC subregions, particularly dorsal and rostral areas, are a robust finding and are present prior to psychosis onset in some categories of high-risk individuals. There is some evidence to suggest that the earliest changes appear in the rostral ACC$_P$, extend across the entire paralimbic region during the transition to psychosis, and spread to engulf limbic regions with ongoing illness, but more longitudinal data are required to confirm this. The postmortem findings indicate that these changes are accompanied by a reduction in neuronal, synaptic, and dendritic density, as well as increased afferentation, in some subregions. Given these data, how might the neuropathological and neuroimaging findings be integrated in a manner that provides clues regarding underlying pathophysiological mechanisms?

One important question is whether these changes are specific to the ACC. Volumetric reductions are commonly found in MRI studies of different brain regions in schizophrenia, although their neuropathological concomitants are not always the same. For example, reductions in dendritic density have been observed in both cingulate and prefrontal cortices,[20,124] but the repeated reports of reduced cell density in some ACC subregions contrast with findings in the prefrontal cortex, where either no differences[125–127] or density increases[128,129] are more commonly found. Similarly, the increased density of ACC glutamatergic afferents identified by Benes et al[119] was not observed in prefrontal area 10, although a similar increase is apparent in the entorhinal cortex of schizophrenia patients,[130] implying similar pathologies may characterize functionally related networks.[131] Such findings indicate that attributing differences in MRI measures of gray matter to a unitary process may be inaccurate and that a greater appreciation of the regional specificity of pathological processes in schizophrenia is required.[132] Indeed, the findings reviewed in this article indicate that there is considerable heterogeneity even across ACC subregions.

When considering the histopathological correlates of gray matter reductions observed with MRI, an often overlooked fact that some authors[95,133,134] have drawn attention to is that the cortical neuropil, as represented in T1-weighted imaging (the most commonly used protocol in volumetric studies), reflects the contribution of signals emanating from various neuronal and nonneuronal tissue compartments, including glial cell bodies, dendrites and spines, blood vessels, intracortical fibers, and extracellular components. Consequently, differences in cortical gray matter may result from variations in nonneuronal tissue. Indeed, the fraction of cortical volume occupied by axons has been estimated at approximately 29%,[135] suggesting that up to one-third of the signal in T1-imaged cortex originates from white matter.[134] Based on these findings, Paus[134] and Sowell et al[133] have argued that reports of longitudinal reductions in cortical gray matter during the course of normal adolescent development [94,136–138] may actually reflect ongoing myelination of axonal fibers penetrating the cortical mantle, rather than (or in addition to) the synaptic pruning that is thought to occur throughout adolescence in some brain regions.[139,140] In this context, findings that schizophrenia patients show increased ACC afferentation[119,120] suggest that myelination of these excess connections throughout adolescence and early adulthood may contribute to the grey matter reductions observed on MRI. This may also be related to findings of progressive gray matter reductions during transition to psychosis[81] and in the first few years following illness onset[89,141] because cingulate fibers continue to myelinate well into adulthood.[142,143] However, an excess of afferent input has not yet been demonstrated in all ACC subregions, so it is unclear

whether this process can explain all the gray matter reductions observed in the area.

An additional limitation associated with positing myelination of excess afferents as the sole cause of the gray matter reductions observed in the ACC is that it cannot account for reports of reduced synaptic and cell density in the region. Excessive synaptic pruning during adolescence is commonly proposed as a key pathophysiological mechanism in schizophrenia,[144] and might partially account for the observed pre-onset grey matter reductions in the ACC and possible progression of these changes with continued illness, but it cannot explain the reductions in cell density. As previously discussed, the most straightforward interpretation of such findings is that they reflect cell loss. To some extent, the magnitude of cell density relative to volume reductions indirectly supports this conclusion, raising questions regarding the underlying mechanisms involved. Apoptosis is commonly invoked as a candidate mechanism because it is associated with cell death in the absence of gliosis, although arguments supporting its role have been based largely on speculative grounds. Indeed, the available postmortem data suggest that there is a downregulation, rather than increase, of apoptotic activity in schizophrenia. Benes et al[145] have found decreased DNA fragmentation, a marker of oxidative stress, in rostral ACC neurons, while studies of hippocampal slices by this group revealed a downregulation of several proapoptotic genes, which contrasted with the general increases seen in patients with bipolar disorder.[146] In temporal cortex, Jarskog et al[147] found no evidence for elevations in the proapoptotic protein caspase 3. They also found reduced expression of the antiapoptotic protein Bcl-2 and an increase in the Bax/Bcl-2 ratio, which they interpreted as reflecting a vulnerability to apoptosis.[147,148] Jarskog and coworkers[114,149,150] have argued that these findings may reflect a compensatory downregulation following increased apoptotic activity occurring around the time of the illness. However, experimental data are lacking, and evidence supporting the occurrence of apoptotic cell death, as defined by ultrastructural criteria, throughout the mature brain appears limited.[151,152] It is also possible that alterations in the expression of apoptotic proteins arise through their involvement in other functions.[153]

An alternative mechanism that can cause cell death in the mature brain without lasting gliosis arises from hypofunction of the *N*-methyl-D-aspartate receptor (NMDAR), a pathology receiving increasing support as a basis for schizophrenia.[154–156] According to one theory, impaired excitation of NMDARs on GABAergic interneurons results in a net reduction of inhibitory tone and consequent increase in glutamatergic and cholinergic transmission at non-NMDA glutamate and muscarinic receptor sites.[157] Evidence for its role in schizophrenia pathophysiology is based on findings

that NMDAR antagonism with agents such as phencyclidine and ketamine produces psychotic symptoms and schizophrenia-like cognitive deficits in healthy individuals[158–161] and exacerbates psychotic symptomatology in schizophrenia patients.[156,162,163] In rodents, NMDAR antagonism can cause marked neuronal injury and/or death with only transient gliosis,[164,165] and the peak period of neuronal sensitivity to such toxic effects occurs between puberty and adulthood[166]—the period of highest risk for schizophrenia onset.[167] This apparent delay in vulnerability parallels human clinical data indicating that children are relatively immune to the psychotogenic effects of phencyclidine.[168,169]

While much of the rodent work indicates retrosplenial areas are the most sensitive to the toxic effects of NMDAR hypofunction,[165] neuroimaging studies suggest that the ACC may be particularly vulnerable in humans. PET work has shown that ketamine administration causes marked blood flow and metabolism increases in the ACC that correlate with measures of psychotic symptoms in both healthy controls and schizophrenia patients.[170–173] One recent study found that while both patients and controls showed increased ACC blood flow following ketamine infusion, the magnitude of the increase was much larger in the patient group,[172] suggesting the ACC shows heightened sensitivity to the effects of NMDAR hypofunction in people with schizophrenia. That these blood flow increases are related to excess glutamatergic transmission is suggested by in vivo spectroscopy studies demonstrating elevated levels of glutamine, a metabolic precursor to glutamate, in the ACC of medication-naïve FE schizophrenia patients[174,175], and in healthy volunteers following ketamine administration[176]. Post-mortem data showing large (>50%) decreases in the density of ACC GABAergic neurons bearing NMDAR subunits are also consistent with deficient stimulation of this receptor on GABAergic cells in the region[110]. Such abnormalities are likely to be potentiated in adolescence and early adulthood by the ongoing myelination of excess glutamatergic afferents to the region[142,143]. NMDAR hypofunction can also contribute to grey matter volume reductions by affecting synaptic density[177], although apoptotic processes may also play a role[114]. Indeed, it is likely that expression of apoptotic proteins is altered in response to toxic events associated with NMDAR hypofunction[178], so an important avenue of future research will be to better understand interactions between these processes. It must be remembered however, that the evidence for neuronal loss in the ACC remains indirect, based primarily on studies of cell density rather than absolute number. The fact that only two studies, both in relatively small samples, have reported absolute cell counts concurrently with cortical volume means that further work is required to unambiguously interpret reports of reduced neuron density as evidence of cell loss.

Conclusions

The considerable methodological variability across studies makes it difficult to draw firm conclusions regarding the precise nature of ACC pathology in schizophrenia. In this regard, the gap between neuroimaging and neuropathology still needs to bridged. Nonetheless, the evidence reviewed in this article suggests abnormalities in the region are a common finding and suggests strategies for future research that will facilitate more accurate characterization of relevant pathophysiological mechanisms. For neuroimaging researchers, these involve more longitudinal work tracking neuroanatomical changes from the high-risk to chronic illness stages that considers the influence anatomical variability has on the resulting measures. For neuropathologists, comparison of absolute cell counts in cytoarchitectonically defined regions with concurrent measures of cortical volume and thickness will be necessary to characterize the cellular basis of MRI-based morphometric changes. Continued integration of findings from these 2 fields will help identify neurobiological endophenotypes that can guide molecular work aimed at treatment development.

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