

# Morphology of the anterior cingulate cortex in young men at ultra-high risk of developing a psychotic illness

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**Background** The anterior cingulate cortex (ACC) is consistently implicated in the pathophysiology of schizophrenia, and our own work has identified morphological anomalies in the ACC of people with this disorder.

**Aims** To examine whether ACC morphological anomalies are present in a group at ultra-high risk of psychosis and whether such anomalies can be used to predict the subsequent development of a psychotic illness.

**Method** Magnetic resonance imaging of 75 healthy volunteers and 63 people at ultra-high risk of developing a psychotic disorder (all right-handed males) was used to examine ACC sulcal and gyral features.

**Results** Compared with the controls, significantly fewer people in the ultra-high risk group had a well-developed left paracingulate sulcus and significantly more had an interrupted left cingulate sulcus. There was no difference between those who did ( $n=21$ ) and did not ( $n=42$ ) subsequently develop a psychotic illness.

**Conclusions** Although ACC anomalies are present in young people considered to be at ultra-high risk of psychosis, they do not identify individuals who subsequently make the transition to psychosis.

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Although a number of lines of research have implicated the anterior cingulate cortex in the pathophysiology of schizophrenia (Benes, 1993), the evidence to date provides only limited information about the stage of life at which such disturbances occur. To address this, we developed a reliable method of capturing the sulcal and gyral variation in the anterior cingulate cortex (Yücel *et al.*, 2001). In the initial studies we focused on the presence or absence of the paracingulate sulcus, and found that people with schizophrenia were less likely to manifest a well-developed, 'prominent' paracingulate sulcus in the left hemisphere, resulting in a lack of the 'normal' leftward asymmetry (Yücel *et al.*, 2002a). Since cortical folding is nearly complete by birth, such anomalies are likely to have arisen early in development, supporting the notion that there is an intimate relationship between the mechanisms that determine asymmetrical brain maturation during neurodevelopment and the disease process of schizophrenia (Crow *et al.*, 1989). In this study we examined whether ACC morphological anomalies were present in those at 'ultra-high' risk of a psychotic disorder, and whether such anomalies were more frequent in those who made the transition to psychosis.

## METHOD

### Participants

Of the 150 persons meeting the inclusion criteria prior to scanning, 138 were included in the study. Nine people from the ultra-high-risk group and 3 from the control group were excluded after magnetic resonance imaging (MRI): (5, significant loss of consciousness; 4, excessive MRI artefact; 1, epilepsy; 1, cyst; 1, no follow-up data available).

Participants were recruited to the study using methods detailed in previous publications (Velakoulis *et al.*, 1999; Phillips *et al.*,

2002; Pantelis *et al.*, 2003). Briefly, healthy volunteers were recruited from ancillary hospital staff and the general population through advertisements. Attempts were made to recruit these individuals from socio-demographic backgrounds similar to those of the ultra-high-risk participants, and they were excluded if they had a personal or family history of psychotic illness. All members of the control group ( $n=75$ ) had already participated in a larger normative study of the anterior cingulate cortex (Yücel *et al.*, 2001), as well as a diagnostic comparison study (Yücel *et al.*, 2002a). The ultra-high-risk group ( $n=63$ ) was recruited from referrals to the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, Australia, between April 1995 and November 1999 (McGorry *et al.*, 2001a,b; Yung *et al.*, 2003). All participants were screened for comorbid medical and psychiatric conditions by clinical assessment, physical examination and neurological screen. Handedness was assessed using the Edinburgh Inventory (Oldfield, 1971). Exclusion criteria for all groups were: history of prior psychotic episode (treated or untreated); a history of significant head injury and/or loss of consciousness for more than 1 min; seizures; neurological disease such as epilepsy or cerebrovascular accident; impaired thyroid function; steroid use; preferred language not English; IQ < 70; or DSM-IV criteria of alcohol or substance misuse or dependence (American Psychiatric Association, 1994). Given the gender-related differences found in the normal anterior cingulate cortex (Paus *et al.*, 1996; Yücel *et al.*, 2001), the finding of ACC anomalies in male patients with established schizophrenia (Yücel *et al.*, 2002a) and the general association of gender and handedness with brain anatomy (Petty, 1999), the sample was limited to right-handed males. Written informed consent was obtained from all participants, and local research and ethics committees approved the design and aims of the study.

Criteria for the identification of the ultra-high-risk cohort have previously been outlined and their rationale described (Phillips *et al.*, 1999; McGorry *et al.*, 2001a; Yung *et al.*, 2003). Briefly, individuals were categorised as being at ultra-high risk if they met operationally defined criteria for ultra-high risk of early transition to first-episode psychosis, defined as membership of at least one of three subsets. Identification of the first subset was based

on ‘state and trait’ risk factors, in which the individual has a first-degree relative with any history of a psychotic or bipolar illness, or has a schizotypal personality disorder as well as a reduction in the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) of more than 30 points from premorbid level maintained for at least 1 month. The second group was identified by the presence of ‘attenuated psychotic symptoms’, in which a sub-threshold form of at least one of the following was experienced: ideas of reference, magical thinking, perceptual disturbances, paranoid ideation, and odd thinking and speech. Further, these symptoms had to have occurred at least several times per week and for at least 1 week. The third and final group was identified on the basis of ‘brief limited intermittent psychotic symptoms’ (BLIPS) – brief, self-limited bursts of acute psychotic symptoms occurring daily but with a duration of less than 1 week (and therefore meeting DSM-IV diagnostic criteria for brief psychotic disorder). Symptoms must have resolved spontaneously. The composition of the ultra-high-risk cohort in terms of these subsets was: ‘state and trait’, 17.5% (*n*=11); attenuated psychotic symptoms, 39.7% (*n*=25); BLIPS, 12.7% (*n*=8); attenuated psychotic symptoms plus BLIPS, 9.5% (*n*=6); attenuated psychotic symptoms plus ‘state and trait’, 19% (*n*=12); BLIPS plus ‘state and trait’, 1.6% (*n*=1). In addition to these inclusion criteria, all those in the ultra-high-risk group were aged 14–30 years. The 63 members of this group were drawn from a larger cohort of people at ultra-high risk who had participated in a series of studies within the PACE clinic; they were included in the current study if they agreed to an MRI scan and if they had been followed up for at least 12 months (maximum length of follow-up was 44 months) in terms of

development or not of acute psychosis. About half (31) of the ultra-high-risk group initially agreed to participate in an intervention study prior to scanning, but treatment did not commence until after scanning was performed. Of these, 10 subsequently refused to participate and received supportive therapy alone (‘refusers’), 12 received risperidone (mean daily dosage 13 mg) and cognitive-behavioural therapy (treatment group), and 9 received supportive therapy alone (control group).

In order to identify the onset of acute levels of first-episode psychosis in the ultra-high-risk group, operationalised criteria for onset of psychosis were defined (Yung *et al*, 1998). Frank psychotic symptoms must be experienced for longer than 1 week to fulfil these criteria, which are informed by the common threshold for prescribing anti-psychotic medication. Participants in the ultra-high-risk group were monitored regularly following the baseline scan to detect whether this threshold for onset of acute psychotic symptoms had been reached, and were subsequently divided into two groups depending on outcome at the most recent follow-up interview: those with psychotic symptoms (*n*=21) and those without (*n*=42). The predominant diagnosis in the psychosis subgroup was schizophrenia (*n*=10), but there were also diagnoses of schizoaffective disorder (*n*=2), affective psychosis (*n*=6) and other psychotic disorder (*n*=3). The majority of the non-psychosis subgroup had no diagnosis at follow-up (*n*=24), and the remainder were diagnosed with major depressive disorder (*n*=4), panic disorder (*n*=2), obsessive-compulsive disorder (*n*=2), social phobia (*n*=3), dysthymia (*n*=2), adjustment disorder (*n*=1) and substance-induced mood disorder (*n*=2). Two members of the non-psychosis subgroup did not receive a formal diagnostic interview at the 12-month follow-up.

**Socio-demographic and related measures**

Information on age and height was gathered at intake from participants in all groups (Table 1). All those in the ultra-high-risk group were assessed at baseline and over the follow-up period with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). A Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First *et al*, 1997) was used to assess all members of the ultra-high-risk group at the 12-month follow-up point.

**Scanning protocol**

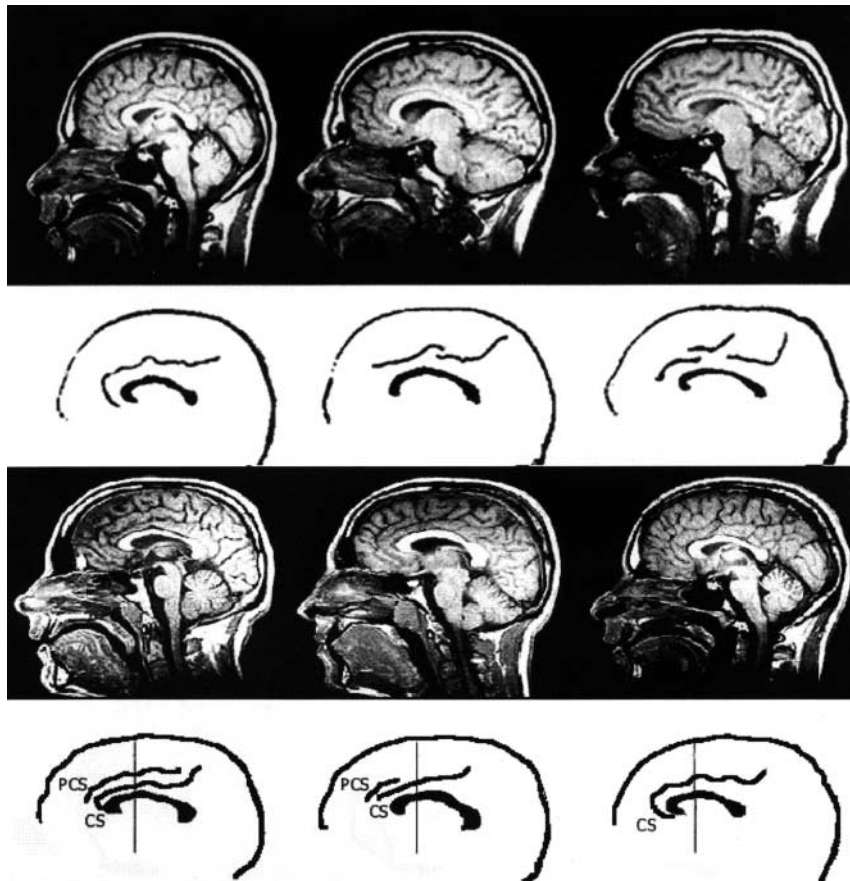
Participants were scanned using identical 1.5 T scanners at the Cabrini Hospital, the Royal Melbourne Hospital or the Royal Children’s Hospital, Melbourne. The sequences obtained from the latter two hospitals were identical. A three-dimensional volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous, 1.5-mm coronal slices. Imaging parameters for the Cabrini Hospital sequences (those for the Royal Melbourne and Royal Children’s Hospitals are given in parentheses) were: echo time (TE) 9 ms (3.3 ms); repetition time (TR) 36 ms (14.3 ms); flip angle 35° (30°); matrix size 256 × 192 (256 × 256); field of view 20 cm × 15 cm (24 cm × 24 cm) voxel dimensions 0.781 mm × 0.781 mm × 1.5 mm (0.938 mm × 0.938 mm × 1.5 mm). Head movement was minimised by foam padding and by straps secured across the forehead and chin. Each scanner was calibrated fortnightly using the same proprietary phantom to ensure stability and accuracy of measurements. In a direct comparison of whole-brain volumes obtained from these machines we have previously shown that

**Table 1** Characteristics of the participants at baseline assessment

	Control ( <i>n</i> =75)		UHR-P ( <i>n</i> =21)		UHR-NP ( <i>n</i> =42)		Significance tests
	mean	(s.d.)	mean	(s.d.)	mean	(s.d.)	
Age (years)	29.1	(11.4)	18.4	(3.7)	19.9	(3.8)	<i>F</i> (2,135)=20.87, <i>P</i> <0.001; control > both UHR groups
Height (cm) <sup>1</sup>	179.9	(7.2)	176.7	(7.7)	175.5	(8.1)	<i>F</i> (2,131)=4.78, <i>P</i> =0.01; control > both UHR groups
BPRS score			17.3	(6.2)	20.3	(9.9)	<i>F</i> (1,61)=1.59, <i>P</i> =0.212
SANS score <sup>1</sup>			18.46	(3.7)	20.1	(3.8)	<i>F</i> (1,59)=2.71, <i>P</i> =0.105

BPRS, Brief Psychiatric Rating Scale; SANS, Scale for Assessment of Negative Symptoms; UHR-P, ultra-high-risk group with psychosis; UHR-NP, ultra-high-risk group without psychosis.

1. Data missing for some participants.



**Fig. 1** Magnetic resonance images and corresponding line drawings of three right hemispheres illustrating the variations in cingulate sulcus continuity (CS) (upper panel) and paracingulate morphology (PCS) (lower panel). Upper panel: the hemisphere on the left shows a single and continuous cingulate sulcus, whereas those in the middle and on the right show an interrupted cingulate sulcus. Lower panel: the hemisphere on the left shows a 'prominent' paracingulate sulcus, whereas those in the middle and on the right show a 'present' and 'absent' paracingulate sulcus, respectively (adapted from Yücel *et al.*, 2001, with permission).

there is no significant group by scanner interaction (Velakoulis *et al.*, 1999). In any case, our measures of gross morphological features (i.e. the presence or absence of major sulci) are unlikely to be influenced by minor variations between scanners. Imaging data were coded to ensure participant confidentiality and masked rating. Image analysis was performed using MEDx version 3.0 (Sensor Systems, Stirling, VA, USA).

### Classification of anterior cingulate morphology

#### *Paracingulate morphology and cingulate continuity*

A protocol was generated to classify aspects of anterior cingulate cortex sulcal and gyral patterns including the presence and absence of the paracingulate sulcus (Yücel *et al.*,

2001), as well as the continuity of the cingulate sulcus. The cingulate sulcus was considered to be continuous unless there was a clear interruption (defined as a gap of more than 10 mm) in its course, present for at least three adjacent slices (Fig. 1). The paracingulate sulcus was defined as the sulcus located dorsal to the cingulate sulcus with a course clearly parallel to the cingulate sulcus. Based on the presence or absence of the paracingulate sulcus and its anteroposterior length, three categories of morphology were derived: prominent paracingulate sulcus, present paracingulate sulcus and absent paracingulate sulcus.

Raters were instructed to obtain a mid-sagittal section, align the anterior–posterior commissural (AC–PC) line horizontally and move three or four slices laterally from the midline in order to classify the anterior cingulate cortex morphologically. Assessing

the cortex over several sagittal slices in this way is important to avoid classifying superficial dimples and to eliminate the effects of sampling error from both the right and left sides of the medial frontal walls and from the fluid-filled space between them. Both intrarater and interrater reliability for the classification of paracingulate sulcus morphology had been previously established using 24 randomly chosen cases (48 hemispheres) (Yücel *et al.*, 2001): weighted  $\kappa$  values were 0.96 and 0.90, respectively. Intrarater and interrater reliability for the classification of cingulate sulcus continuity was established using 16 randomly chosen cases (32 hemispheres), with  $\kappa$  values of 0.95 and 0.92, respectively. In all cases, both raters were, at all times, blind to participant details.

#### *Paracingulate asymmetry index*

An asymmetry index was assigned to each individual based on the combination of left and right paracingulate sulcus morphology, as described by Yücel *et al.* (2001). For example, the paracingulate sulcus in the 'prominent' classification is more explicit (i.e. greater anteroposterior extent of the sulcus) than that in the 'present' pattern, which in turn is more explicit than that in the 'absent' pattern. Thus an asymmetry index was assigned to each individual in terms of a leftward (left > right), symmetric (left = right), or rightward (left < right) bias, indicating whether an individual has a symmetrically or asymmetrically folded paracingulate sulcus and in which direction. The asymmetry index is important because it provides an alternative to the 'unpaired' comparison that examines patterns of ACC morphology across the population. That is, the individual's one cerebral hemisphere acts as a control for the other. Also, the use of the asymmetry index as a single dependent variable derived from the values for each hemisphere avoids the difficulty of analysing repeated-measures variables (i.e. left *v.* right) within this categorical analysis framework.

#### **Statistical analyses**

All data were analysed using the Statistical Package for the Social Sciences, version 10.0 for Windows. Demographic data were compared using one-way analyses of variance for psychopathology scores, age and height. McNemar's test for symmetry was used to test whether the number of cases of paracingulate sulcus asymmetry in

**Table 2** Anterior cingulate morphological classifications: cingulate sulcus continuity

	Control (n=75)		UHR (n=63)		Analysis (d.f.=1)
	Cont. (%)	Int. (%)	Cont. (%)	Int. (%)	
Left hemisphere <sup>1</sup>	87	13	65	35	$\chi^2=7.79; P<0.005$
Right hemisphere	87	13	73	27	$\chi^2=3.23; P=0.07$

Cont., continuous; Int., interrupted; UHR, ultra-high risk.  
 1. Data are proportions (%) of anterior cingulate cortex classifications.

one direction was counterbalanced by an equal number of cases with an asymmetry in the other direction. A significant value indicates an asymmetric pattern in the sample – a greater explicitness of cortical folding in one direction. More complex models including interaction effects could not be examined within this analytic framework. Therefore, the effect of diagnostic group on paracingulate sulcus morphology was further examined using chi-squared analyses in which the morphology on the left or right (with three ordered categories) or asymmetry index (with three ordered categories; see above) was the dependent variable. The effect of diagnostic group on cingulate sulcus continuity was also examined using a 2 × 2  $\chi^2$  analysis with continuity correction in which the continuity on the left or right (with two categories: one segment or more than one segment) were the dependent variables. In all analyses, age was used as an independent variable.

**RESULTS**

**Demographic characteristics**

Demographic details are presented in Table 1. Participants in the healthy control group were significantly older and taller than those in either ultra-high-risk group. There was no significant difference between the two ultra-high-risk groups with respect to global psychopathological state according to the BPRS or negative symptoms according to the SANS.

**Anterior cingulate cortex morphology**

Although the cingulate sulcus was present in all hemispheres studied, the presence or absence of the paracingulate sulcus was extremely variable within and between hemispheres. Across hemispheres, 74% of the control group and 61% of the ultra-high-risk group showed evidence of a paracingulate sulcus either ‘present’ or ‘prominent’.

*Cingulate sulcus continuity*

The proportions of participants with a continuous or interrupted cingulate sulcus can be seen in Table 2. There was a significant difference between the two groups for continuity in the left hemisphere: the ultra-high-risk group was more likely than the control group to have an interrupted cingulate sulcus on the left hemisphere. There was no significant main effect of age on cingulate sulcus continuity.

*Paracingulate morphology*

The paracingulate sulcus classifications across each hemisphere of each diagnostic group can be seen in Table 3. There was a significant difference between the groups for paracingulate sulcus morphology in the left hemisphere: the ultra-high-risk group was less likely than the control group to have a prominent paracingulate sulcus on the left hemisphere. There was no significant main effect of age on morphology.

**Paracingulate asymmetry**

The McNemar test for symmetry was used to test whether the number of cases of paracingulate sulcus asymmetry in one direction was counterbalanced by an equal number of cases with an asymmetry in the other direction, separately for each group. Results showed a significant asymmetry in the control group ( $\chi^2(3)=21.16; P<0.001$ ) but not in the ultra-high-risk group ( $\chi^2(3)=2.73; P<0.43$ ), indicating a biased distribution of paracingulate sulcus morphology in controls but not in those at ultra-high risk. Asymmetry of the paracingulate sulcus was further examined using the asymmetry index measure, which enables the use of  $\chi^2$  analyses to make direct group comparisons. The proportions of leftward, symmetric and rightward asymmetries were 51% (n=38), 31% (n=23) and 19% (n=14) respectively for healthy controls, and 37% (n=23), 37% (n=23) and 27% (n=17) respectively in the ultra-high-risk group. A direct comparison of the two groups on asymmetry showed no significant difference ( $\chi^2(2)= 2.97; P<0.23$ ). Finally, there was no significant main effect of age on paracingulate sulcus asymmetry.

**Psychosis v. non-psychosis ultra-high-risk groups**

There was no significant difference between the psychosis and non-psychosis subgroups of the ultra-high-risk group for either the left or right hemisphere on measures of cingulate sulcus continuity, paracingulate sulcus morphology or paracingulate sulcus asymmetry, including the McNemar test (all P values greater than 0.1).

**Effects of treatment**

Thirty-one people in the ultra-high-risk group were receiving some form of therapy after baseline (12 risperidone and 19 supportive therapy), which might have affected their transition to psychosis (McGorry *et al*, 2002). However, reanalysis of the data

**Table 3** Anterior cingulate morphological classifications: paracingulate morphology

	Control (n=75)			Ultra-high risk (n=63)			Analysis (d.f.=2)
	Prominent (%)	Present (%)	Absent (%)	Prominent (%)	Present (%)	Absent (%)	
Left hemisphere <sup>1</sup>	64	20	16	37	30	33	$\chi^2=10.91; P<0.004$
Right hemisphere	28	36	36	29	27	44	$\chi^2=1.49; P=0.47$

1. Data are proportions (%) of anterior cingulate cortex classifications.

excluding those receiving risperidone treatment ( $n=10$  in the psychosis subgroup and  $n=2$  in the non-psychosis subgroup) did not alter the results. In any case, this issue has no bearing on the findings of anterior cingulate cortex anomalies in the ultra-high-risk group as a whole.

## DISCUSSION

### Summary of findings

This is the first study to examine the surface morphology of the anterior cingulate cortex in a large sample of males at ultra-high risk of developing a psychotic illness. The major findings of this study were:

- compared with healthy controls, those at ultra-high risk were more likely to have interruptions in the course of the cingulate sulcus and less likely to have a well-developed paracingulate sulcus in the left hemisphere;
- the pattern of paracingulate folding showed a leftward bias in the healthy controls which was not observed in the ultra-high-risk group (although a direct comparison did not reveal a significant difference);
- there was no difference in any of the anterior cingulate cortex morphological measures between those at ultra-high risk who subsequently developed a psychosis and those who did not.

Overall, these findings are consistent with previous research on cingulate sulcus continuity both in healthy individuals (Paus *et al*, 1996) and in people with schizophrenia (Leonard *et al*, 1999; further information available from the author upon request), and also with work on paracingulate sulcus morphology in the disease state (Yücel *et al*, 2002a). These findings are not attributable to the differences in age between the two participating groups, since there was no relationship between age and anterior cingulate cortex morphological patterns. In addition, the fact that we studied gross sulcal and gyral patterning means that our results are unaffected by the participants' use of medication, alcohol or other drugs. This study provides evidence of a lateralised disturbance of brain morphology in men identified as being at ultra-high risk of developing a psychotic illness, in line with the notion of Crow that disturbances of cerebral asymmetry are intimately associated with the disease process of psychosis (Crow *et al*, 1989). However, our findings indicate that although anterior

cingulate cortex anomalies are present prior to illness onset, they do not identify individuals who will subsequently develop psychosis. This suggests that such anomalies are non-specific in their association with psychopathological problems in young people (i.e. sub-threshold psychosis, affective and anxiety features), in contrast to volumetric measures (Pantelis *et al*, 2003).

The paracingulate sulcus is a tertiary sulcus and is therefore less likely to be under the control of genetic factors, as suggested by recent twin studies of sulci and gyri (Bartley *et al*, 1997; Lohmann *et al*, 1999). Further, given that the patterns of sulci and gyri are essentially fixed early in life, anomalies of the paracingulate sulcus might be markers of subtle neurodevelopmental deviance caused by environmental or epigenetic factors and associated with an increased risk of psychopathological disorders. For example, it is known that the anterior cingulate cortex develops in close proximity to areas that are often affected by complications during the prenatal period such as haemorrhage and infarction (Pape *et al*, 1979; Slagle *et al*, 1989). Although such severe intra-uterine injuries are unlikely to be a common aetiopathological mechanism for either psychopathological disorder or psychosis, they have been associated with significant delays in development of the cingulate region, including increased interruptions in cingulate sulcus continuity (Slagle *et al*, 1989). Therefore, more subtle delays and/or alterations in the neurodevelopment of this region might be sufficient to cause the reduced prominence of the paracingulate sulcus and the increased interruption of the cingulate sulcus found in this study.

### Functional consequences of anterior cingulate cortex anomalies

Although morphological anomalies of the anterior cingulate cortex are more common in young people with psychopathological symptoms than in healthy individuals, they are not more common in those who later demonstrate a psychotic disorder. This implies that they are risk factors for mental state changes rather than for any specific diagnosis. How this occurs is still unclear, since the consequences of morphological changes in the anterior cingulate cortex have yet to be elucidated. In a functional imaging study, we found that this left-sided anomaly in the paracingulate sulcus of

patients with schizophrenia was reflected in a failure to activate the left paracingulate during Stroop task performance (Yücel *et al*, 2002b). In addition, both our own and other studies have shown that verbal fluency performance is better in healthy individuals with a 'normal' leftward asymmetry of the paracingulate sulcus (further information available from the author upon request). Taken together, these findings suggest that morphological changes in this region can have significant effects on behaviour.

Given that altered morphological asymmetry in the anterior cingulate cortex is not predictive of psychosis, it is possible that there is a multi-level (i.e. macro and micro) disturbance of anterior cingulate cortex integrity in patients who do make this transition. This could be related to the reported and heritable reductions in perfusion (Blackwood *et al*, 1999) and *N*-acetyl aspartate:choline ratios (Keshavan *et al*, 1997) in the anterior cingulate cortex of asymptomatic but 'high-risk' relatives of patients with schizophrenia, and/or to the effects of environmental influences (such as drug use or stress) on the functional integrity of this region.

There is also evidence to suggest that the anterior cingulate cortex refines its connectivity and functional circuitry throughout life (e.g. its glucose metabolism increases with age; Van Bogaert *et al*, 1998), implying that ongoing developmental factors might also be relevant. It has been recently demonstrated that Stroop-task-related activity of the anterior cingulate cortex increases linearly from age 7 years to 22 years (Adleman *et al*, 2002), and that this is specific to the left anterior cingulate cortex – the region identified as showing reduced folding in both schizophrenia (Yücel *et al*, 2002a) and ultra-high-risk states, and which is also hypoactive in people with schizophrenia during performance of the same task (Yücel *et al*, 2002b). Together, these findings lead us to speculate that the age-related improvements in anterior cingulate cortex connectivity and functional circuitry are also disrupted in people affected by schizophrenia, and perhaps to a lesser extent in those at ultra-high risk of psychotic disorder.

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CLINICAL IMPLICATIONS

- Although anomalies of the anterior cingulate cortex are present prior to the onset of psychotic illness, they do not help identify high-risk individuals who will make the transition to psychosis.
- Morphological anomalies of this brain region may be a non-specific marker of a subtle neurodevelopmental disturbance associated with an increased risk of psychopathological disorder.
- Disturbed limbic and paralimbic development and maturation may have functional implications and be relevant to a range of disturbed behaviours.

LIMITATIONS

- The focus of this study was restricted to a single region of the brain and to right-handed males only.
- Some of the group at ultra-high risk were receiving therapy after the baseline assessment, which might have affected their transition to psychosis.
- Participants were classified as being at ultra-high risk for psychosis and not for schizophrenia, limiting the comparability of the findings to previous work in schizophrenia.

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