

## Paracingulate sulcus morphology in men with early-onset schizophrenia

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**Background** Cingulate dysfunction has been reported in schizophrenia. Although the paracingulate sulcus (PCS) is known to be asymmetric in healthy people, little information is available about its morphology in schizophrenia.

**Aims** To search for morphological anomalies of the PCS in men with early-onset schizophrenia.

**Method** The PCS was examined in magnetic resonance images of the brains of men with schizophrenia and 100 healthy men.

**Results** A significant asymmetry was found in the brains of healthy volunteers, whose sulci were more frequent and more marked in the left hemisphere. In contrast, the sulcus was as frequent in the right as in the left hemisphere in the patient group. Moreover, patients displayed significantly more rightward asymmetry, and overall less-asymmetrical patterns than the comparison group.

**Conclusions** Since the PCS has developed at 36 weeks of gestation, these findings suggest an impaired maturation of the cingulate region during the third trimester.

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Reversals, reductions or absence of normal cerebral asymmetries have been described in schizophrenia in several structures such as the planum temporale (Rossi *et al*, 1992; Barta *et al*, 1997), the Sylvian fissure (Crow *et al*, 1992; Falkai *et al*, 1995), both occipital and frontal lobes (Bilder *et al*, 1994), and the cerebral ventricles (Crow *et al*, 1989a). Moreover, people with early-onset schizophrenia might be more likely to exhibit reduced brain asymmetries (Crow *et al*, 1989b). Cerebral sulcal and gyral patterns and their asymmetries may provide a robust marker of the contribution of neurodevelopmental factors to the aetiology of schizophrenia. Indeed, cerebral sulci are formed during the second and third trimesters (Chi *et al*, 1977; Huang, 1991) and remain relatively stable after birth (Armstrong *et al*, 1995; Magnotta *et al*, 1999), whereas other brain measurements such as cerebral volumes can vary with ageing, life experiences, nutrition (Dalman & Cullberg, 1999), substance misuse (Pfefferbaum *et al*, 1997; Wilson *et al*, 2000) and even neuroleptic medication (Chakos *et al*, 1994). Yücel *et al* (2002a) reported a lack of leftward paracingulate sulcus asymmetry among right-handed men with schizophrenia compared with a control group. Since these findings are relevant to the study of the neurobiological aspects of schizophrenia, they need replication in independent samples. Our hypothesis was that the asymmetric patterns of the paracingulate sulcus observed in healthy individuals would be disrupted in men with early-onset schizophrenia. Such abnormalities could provide evidence of abnormal neurodevelopment of paralimbic areas in schizophrenia.

### METHOD

#### Study participants

The study included 40 right-handed male patients (mean age 27.2 years, s.d.=6.6)

fulfilling DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994), with clinical onset before age 25 years (Crow *et al*, 1989b; Corrigal & Murray, 1994). Patients were recruited from the psychiatric departments of several hospitals in the Paris area of France, and from Barcelona in Spain. Clinical ratings and review of research and medical records were performed by senior psychiatrists (M.B., I.B., M.-L.P.-M., C.R. and J.-L.M.). Clinical symptoms were assessed by means of the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) (mean score 27.5, s.d.=17.6) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982) (mean score 53, s.d.=25.6). The comparison group included 100 right-handed healthy male volunteers (mean age 28.5 years, s.d.=7.7), with no family history of psychiatric disorders. All participants were examined to exclude medical conditions, including substance misuse, and all were found to be right handed according to Annett's questionnaire (Annett, 1970).

#### Magnetic resonance imaging

Whole-brain  $T_1$ -weighted images were acquired using a 1.5 T magnetic resonance imaging (MRI) scanner. A three-dimensional inversion-recovery-prepared fast-spoiled gradient echo sequence was used with the following scanning parameters: 256 × 256 matrix, 124 or 248 contiguous slices of 1.5-mm or 0.6-mm thickness, field of view 24 cm × 24 cm, flip angle 10°, echo time 2.2 ms,  $T_1$  600 ms, repetition time 12.5 ms. Everyone who was scanned first gave written informed consent, according to the local ethics committee requirements.

#### Paracingulate sulcus rating

The paracingulate sulcus extends dorsally and parallel to the cingulate sulcus, lying in the medial walls of the frontal lobes. Measurements were made using the method of describing paracingulate sulcus patterns defined by Yücel *et al* (2001) in healthy adults. The origin of the paracingulate sulcus was defined as the point where the sulcus extends posteriorly, from a coronal plane parallel to the line through the anterior commissure, and perpendicular to the line through the anterior and posterior commissures (Yücel *et al*, 2001). The paracingulate sulcus was classified as 'prominent' if the sulcus extended at least 40 mm and exhibited no more than



**Fig. 1** Magnetic resonance images of the cingulate sulcus (black arrow) and paracingulate sulcus (white arrow):  $T_1$ -weighted sagittal views showing the distinct paracingulate sulcus patterns evaluated in this study; (a) absent, (b) present, (c) prominent.

20 mm of interruptions between its origin and a coronal plane passing through the anterior commissure (Fig. 1c). If interruptions exceeded 20 mm and the length was at least 20 mm, the paracingulate sulcus was classified as ‘present’ (Fig. 1b). Finally, when no clearly horizontal sulcus parallel to the cingulate sulcus could be found or was less than 20 mm in length, it was classified as ‘absent’ (Fig. 1a). Leftward asymmetry was defined as a ‘prominent’ pattern in the left hemisphere with a ‘present’ or ‘absent’ pattern in the right hemisphere, or as ‘present’ left and ‘absent’ right patterns. Conversely, rightward asymmetry was defined as a right ‘prominent’ pattern occurring with a left ‘present’ or ‘absent’ pattern, or as a right ‘present’ pattern and a left ‘absent’ pattern. Symmetry of the paracingulate sulcus was rated when the same pattern was observed in both hemispheres. Two independent raters, masked to participant status, examined the images. Intrarater reliability was assessed by one examiner (J.-B.L.P.), who examined all cases ( $\kappa=0.92$ ). Interrater reliability was assessed by using a second rater (D.B.-F.) to evaluate 70 randomly chosen participants ( $\kappa=0.90$ ).

Intragroup asymmetry was assessed using McNemar’s test for symmetry. Hemispheric differences for paracingulate sulcus presence were assessed within each group using  $\chi^2$  tests. Afterwards, between-group differences for rightward/leftward asymmetry rates were also assessed using  $\chi^2$ . Statistical significance was set at  $P=0.05$ . Correlations between clinical scores and paracingulate sulcus patterns were searched for in the patient group, using the Spearman rank order statistic.

**RESULTS**

**Within-group comparisons**

Healthy volunteers had a significant paracingulate sulcus asymmetry (McNemar’s test  $\chi^2=31.47$ ,  $P<0.00001$ , d.f.=3). The presence of a paracingulate sulcus (‘prominent’ or ‘present’) was more frequent in the left hemisphere than in the right ( $\chi^2=30.5$ ,  $P<0.001$ ) and it was more often defined as ‘prominent’ than ‘present’ in the left hemisphere ( $\chi^2=6.7$ ,  $P=0.009$ ). In participants with schizophrenia however, no significant asymmetry was detected (McNemar’s test  $\chi^2=2.33$ ,  $P=0.51$ , d.f.=3). The frequency of a paracingulate

sulcus (‘prominent’ or ‘present’) did not differ between left and right hemispheres ( $\chi^2=0.05$ ,  $P=0.82$ ). When a ‘prominent’ paracingulate sulcus was found, it was equally frequent on both sides ( $\chi^2=1.13$ ,  $P=0.29$ ).

**Between-group comparisons**

Paracingulate sulcus patterns (Table 1) were more often leftwardly asymmetric in healthy participants than in patients ( $\chi^2=7.48$ ,  $P=0.006$ ). In contrast, patients had more rightward asymmetric patterns ( $\chi^2=4.84$ ,  $P=0.03$ ). The incidence rates of

**Table 1** Hemispheric distribution of the morphological patterns of the paracingulate sulcus in healthy men and men with schizophrenia. Values are percentages of cases presenting distinct patterns of paracingulate sulcus morphology in both left and right hemispheres

Pattern of morphology in right hemisphere	Pattern of morphology in left hemisphere			
	Prominent	Present	Absent	Total
<b>Control group (n=100)</b>				
Prominent	6	4	4	14
Present	4	3	6	13
Absent	42	7	24	73
Total	52		14	
	66		34	100
<b>Patient group (n=40)</b>				
Prominent	8	5	22	35
Present	0	5	3	8
Absent	22	5	30	57
Total	30		15	
	45		55	100

a symmetrical pattern were similar in both groups ( $\chi^2=1.12$ ,  $P=0.29$ ).

### Clinical correlates

The presence or absence of paracingulate sulcus, either in the right or left hemisphere, was not related to any clinical measure (SANS and SAPS scores). Spearman correlation tests were applied to search for relationships between asymmetry or symmetry of the paracingulate sulcus (leftward, rightward or symmetrical) and clinical measures. No significant correlation was observed.

### DISCUSSION

The main finding of this study was a lack of paracingulate sulcus asymmetry among male patients with early-onset schizophrenia; this was due to both the less-frequent leftward asymmetry and the more-frequent rightward asymmetry of paracingulate sulcus patterns than in healthy participants.

### Patient characteristics

The characteristics of our patient sample (all men, with disease onset before 25 years of age) may have influenced the findings. These patients were chosen because previous studies have reported more-frequent brain anomalies in early-onset cases (Crow *et al*, 1989b) and an interaction between diagnosis and gender on frontal lobe measurements in patients with schizophrenia (Highley *et al*, 1998). Moreover, previous investigations conducted in normal individuals have found gender differences in paracingulate sulcus patterns, as well as in intrasulcal paracingulate sulcus grey matter volumes (Paus *et al*, 1996a; Yücel *et al*, 2001). Therefore, it is possible that different findings would be observed in older or female patients. Thus, it should be stated that our results pertain to a homogeneous category of patients (right-handed, male, with early-onset disease) and may not be generalisable to other types of patient with schizophrenia.

### Consistent replication

The finding of an asymmetric pattern of the paracingulate sulcus in healthy individuals is consistent with previous anatomical MRI reports (Paus *et al*, 1996a,b; Yücel *et al*, 2001). Furthermore, our results replicate those reported by Yücel *et al* (2002a) and

extend to an independent sample of early-onset cases, indicating that the reduction of leftward paracingulate sulcus asymmetry might be a robust finding. They are also complementary to reports of grey matter volume reductions in the cingulate, suggesting an involvement of the cingulate and paracingulate region in the pathophysiology of schizophrenic disorders (Albanese *et al*, 1995; Wright *et al*, 1999; Paillère-Martinot *et al*, 2001; Sigmundsson *et al*, 2001). Further evidence implicating these limbic or paralimbic regions in schizophrenia comes from functional findings demonstrating abnormal brain activity in these regions in response to cognitive demands (e.g. Carter *et al*, 1997; Artiges *et al*, 2000) and from a report showing that brain activity patterns during a cognitive task depend on the underlying morphology of the paracingulate sulcus (Yücel *et al*, 2002b).

### Folding and connectivity

Functional neuroimaging studies indicate that schizophrenia is characterised by an alteration of brain connectivity (e.g. Fletcher *et al*, 1999; Spence *et al*, 2000). Notably, it has been suggested that gyral-shape studies might be an interesting alternative method of searching for disturbances of brain connectivity in the disorder (Highley *et al*, 2001). Indeed, brain gyrification indexes in humans would reflect the density of intrinsic connectivity (Welker, 1990). A proposed mechanism derived from the tension-based morphogenesis theory explains cortical folding as depending on differences in mechanical tension along axons, dendrites or glial processes connecting different brain regions (van Essen, 1997). Thus, the presence of a prominent paracingulate sulcus could indicate a marked local connectivity within the paralimbic cortex (Brodmann's area 32) and adjacent regions (Brodmann's areas 6, 8 and 9). In contrast, the reduction in paracingulate sulcus folding, more frequently observed in the left hemisphere in our patients, could be the consequence of weaker local connectivity in these areas. According to this model, people with sulcogyral anomalies would be more likely to exhibit dysfunctional cingulate or paracingulate connectivity.

### Folding during the third trimester

It has been historically proposed that losses, absences or reversals of hemispheric asymmetries could denote indexes of brain

dysmaturation (Crichton-Browne, 1879) in mental disturbances (Southard, 1915). A corpus of theories postulate that the absence of right shift (Annett, 1999) or the loss of the physiological asymmetry in the ontogenetically recent heteromodal cortices (Pearlson *et al*, 1996; Crow, 1999) might result from genetic factors that would enhance the vulnerability to schizophrenia. An anomaly in the paracingulate sulcus pattern in patients supports these theories. Indeed, the paracingulate sulcus develops by 36 weeks of gestation, when major cerebral asymmetry has already been established. Thus, as a tertiary sulcus, it depends on the pattern of regional gyrification previously established by primary and secondary sulci (Armstrong *et al*, 1995). Consequently, evidence of altered paracingulate development in people with schizophrenia may reflect abnormalities in the course of neurodevelopment occurring, at the earliest, during week 32 of gestation, when secondary sulci are forming – i.e. during the third trimester. Folding peculiarities in this paralimbic region during the third trimester do not preclude more widespread and earlier anomalies in folding symmetry, which remain to be investigated (Vogelely *et al*, 2000, 2001). Consequently, sulcogyral measurements can be used to explore hypotheses (e.g. Crow *et al*, 1989a; Bilder *et al*, 1994) that disturbances in brain development during the second and third trimesters are related to vulnerability to schizophrenic disorders.

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## CLINICAL IMPLICATIONS

■ Abnormal maturation of the paralimbic area may occur during the third trimester of gestation.

■ The study provides further evidence of abnormal development of the cerebral hemispheres in schizophrenia.

■ Reduced cerebral asymmetry could be a vulnerability factor for schizophrenia.

## LIMITATIONS

■ The investigation was restricted to male patients with early-onset disease.

■ Continuous measures of the sulcus length were not available, and there was no interrater assessment of schizophrenia symptom rating scales.

■ The findings cannot address the issue of anatomic specificity of the paracingulate sulcus since the characteristics of other sulci were not assessed.

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