Paracingulate sulcus morphology in men with early-onset schizophrenia


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). Yucel 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; Corrigan & 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.=23.6). 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 T1-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, T1 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 Yucel 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
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>
<thead>
<tr>
<th>Pattern of morphology in right hemisphere</th>
<th>Pattern of morphology in left hemisphere</th>
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<tbody>
<tr>
<td>Prominent</td>
<td>Present</td>
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<tr>
<td>Control group (n=100)</td>
<td></td>
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<tr>
<td>Prominent</td>
<td>6</td>
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<td>Present</td>
<td>4</td>
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<tr>
<td>Absent</td>
<td>42</td>
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<tr>
<td>Total</td>
<td>52</td>
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<td>66</td>
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<td>Patient group (n=40)</td>
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<tr>
<td>Prominent</td>
<td>8</td>
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<td>Present</td>
<td>0</td>
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<td>Absent</td>
<td>22</td>
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<tr>
<td>Total</td>
<td>30</td>
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<td>45</td>
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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 corre-
lation tests were applied to search for
relationships between asymmetry or sym-
metry 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 schizo-
phrenia; 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 pre-
vious studies have reported more-frequent
brain anomalies in early-onset cases (Crow,
1989b) and an interaction between
diagnosis and gender on frontal lobe mea-
surements in patients with schizophrenia
(Highley et al, 1998). Moreover, previous
investigations conducted in normal indivi-
duals have found gender differences in
paracingulate sulcus patterns, as well as in
intrusulcal paracingulate sulcus grey matter
volumes (Paus et al, 1996a; Yucel et al,
2001). Therefore, it is possible that differ-
ent findings would be observed in older or
female patients. Thus, it should be stated
that our results pertain to a homogeneously
categorized group of patients (right-handed, male,
with early-onset disease) and may not be
generalizable to other types of patients 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; Yucel et
al, 2001). Furthermore, our results replicate
those reported by Yucel 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, suggest-
ing an involvement of the cingulate and
paracingulate region in the pathophysiol-
y of schizophrenic disorders (Albanese et
al, 1995; Wright et al, 1999; Paillère-
Martinot et al, 2001; Sigmundsson et
al, 2001). Further evidence implicate these
limbic or paralimbic regions in schizo-
phrenia 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 (Yucel et al,
2002b).

**Folding and connectivity**
Functional neuroimaging studies indicate
that schizophrenia is characterized by an al-
teration 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
intrinsically intrinsically connective con-
ectivity (Welker, 1990). A proposed mechanism derived from the ten-
sion-based morpogenesis theory explains
cortical folding as depending on differences
in mechanical tension along axons, den-
rites 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
(Brodman’s areas 32) and adjacent regions
(Brodman’s areas 6, 8 and 9). In contrast,
the reduction in paracingulate sulcus fold-
ing, 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 sulcogyrical 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 asym-
metries could denote indexes of brain
dysmaturational (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 (Pearson et al, 1996; Crow,
1999) might result from genetic factors that
would enhance the vulnerability to schizo-
phrenia. 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 gyriﬁ-
cation 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 peculi-
arities in this paralimbic region during the
third trimester do not preclude more wide-
spread and earlier anomalies in folding
symmetry, which remain to be investigated
(Vogeley et al, 2000, 2001). Consequently,
sulcogyrical measurements can be used to ex-
ploratively 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.

JEAN-BERNARD LE PROVOST, MD, DAVID BARTRES-FAZ, PHD, MARIE-LAURE PAILLÈRE-MARTINOT, MD, PhD, ERIC ARTIGES, MD, PhD, SABINA PAPPATA, MD, PhD, INSERM–CEA, Frédéric Joliot Hospital Department, Orsay; CHRISTOPHE RECASENS, MD, Albert Chenevier Hospital, Créteil, France; MERCEDES PÉREZ-GOMEZ, MD, Department of Psychiatry and Psychobiology, University of Barcelona; MIQUEL BERNARDO, MD, PhD, DIMMA BAEZA, MD, Hospital Clinic i Provincial de Barcelona, Spain; FRANCK BAYLE, MD, Sainte-Anne Hospital, Paris; JEAN-LUC MARTINOT, MD, PhD, INSERM–CEA, Frédéric Joliot Hospital Department, Orsay, France

Correspondence: Jean-Luc Martinot, ERM 0205 Imagerie Cérébrale en Psychiatrie, INSERM–CEA, Service Hospitalier Frédéric Joliot, 4 Place du General Leclerc, 91410 ORSAY Cedex, France. Tel: 1698 67719; fax: 1698 67816; e-mail: martinot@shfj.cea.fr.


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