Gyral and Sulcal Cortical Thinning in Adolescents with First Episode Early-Onset Psychosis

Joost Janssen, Santiago Reig, Yasser Alemán, Hugo Schnack, J. M. Udias, Mara Parellada, Montserrat Graell, Dolores Moreno, Arantzazu Zabala, Evan Balaban, Manuel Desco, and Celso Arango

Background: Psychosis is associated with volumetric decreases of cortical structures. Whether these volumetric decreases imply abnormalities in cortical thickness, surface, or cortical folding is not clear. Due to differences in cytoarchitecture, cortical gyri and sulci might be differentially affected by psychosis. Therefore, we examined differences in gyral and sulcal cortical thickness, surface, folding, and volume between a minimally treated male adolescent population with early-onset first-episode psychosis (EOP) and a healthy control group, with surface-based morphometry.

Methods: Magnetic resonance imaging brain scans were obtained from 49 adolescent EOP patients and 34 healthy control subjects. Subjects were younger than 18 years (age range 12 years–18 years), and EOP patients had a duration of positive symptoms of <6 months.

Results: Early-onset first-episode psychosis was associated with local bilateral cortical thinning and volume deficits in both the gyri and sulci of the superior temporal cortex and the inferior, middle, medial, and superior prefrontal cortex. In the pars triangularis and opercularis cortex of patients, gyral cortical thickness was thinner, whereas sulcal thickness was not. Patients exhibited cortical thinning together with a decreased degree of cortical folding in the right superior frontal cortex.

Conclusions: Cortical thinning of both gyri and sulci seem to underlie most cortical volume deficits in adolescent patients with EOP. Except for the right superior frontal region, the degree of cortical folding was normal in regions showing decreased cortical thickness, suggesting that the process of cortical thinning in adolescent patients with EOP primarily takes place after the formation of cortical folds.

Key Words: Adolescence, cortical folding, cortical thickness, magnetic resonance imaging, psychosis, surface-based morphometry, volume

From the Department of Experimental Medicine and Surgery (JJ, SR, YA, MD); Adolescent Unit (JJ, SR, YA, MP, DM, AZ, CA), Department of Psychiatry, Hospital General Universitario Gregorio Marañón, CIBERSAM; Grupo de Física Nuclear (JMU), Física Atómica, Molecular y Nuclear, Universidad Complutense de Madrid; Department of Psychiatry (MG), Hospital Universitario Infantil Niño Jesús, Madrid; Psychiatry Section (AZ), Neuroscience (UPV-EHU), University of the Basque Country, Bilbao, Spain; Rudolf Magnus Institute of Neuroscience (HS), Department of Psychiatry, University Medical Center Utrecht, The Netherlands; and the Behavioral Neurosciences Program (EB), McGill University, Montreal, Canada.

Address correspondence to Joost Janssen, Ph.D., Hospital General Universitario Gregorio Marañón, Department of Experimental Medicine, Surgery and Psychiatry, Adolescent Unit, C/Dr. Esquerrão, 46, 28007 Madrid, Spain; E-mail: janssen@mce.hglm.es.

Received Mar 31, 2009; revised Jul 10, 2009; accepted Jul 19, 2009.

patients refused a magnetic resonance imaging (MRI) scan because of fear. Furthermore, 2 subjects were excluded because of insufficient image quality for neuroimaging analyses, leaving a sample of 49 patients. The inclusion criteria for patients were male gender and presence of positive psychotic symptoms before the age of 18 years (within a DSM-IV diagnosis) for <6 months at the time of assessment on enrollment in the study. Exclusion criteria were presence of a concomitant Axis I disorder, mental retardation, a pervasive developmental disorder, neurological diseases, or a history of head trauma with loss of consciousness. All patients had a thorough medical examination as part of our standard clinical guidelines protocol. Patients with substance abuse and/or dependence were generally excluded; however, those with substance use who continued to show positive symptoms after 14 days of a negative urine drug screen were retained.

Thirty-four healthy control subjects were recruited from the same schools and residential areas as the patients. The inclusion criteria for control subjects were male; age similar to patients; and absence of psychiatric and/or neurological disorders or a family history of an Axis I or Axis II diagnosis, head trauma, or mental retardation.

The study was approved by the institutional review boards of both participating clinical centers. After the study was thoroughly explained to the subjects, written informed consent was obtained from both the legal representatives and the patients. All the subjects met MRI safety criteria.

Clinical Assessment

All patients met DSM-IV criteria for a first episode of psychosis, assessed with the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) (20). Control subjects were also assessed with the K-SADS-PL to rule out current and previous illness. Clinical diagnostic interviews were performed during the initial hospitalization by four experienced psychiatrists trained in this interview. Diagnostic consensus was reached in cases where presence or absence of psychiatric diagnoses was in doubt. Psychotic symptoms were assessed with the validated Spanish version of the Positive and Negative Syndrome Scale (PANSS) (21). Intraclass correlation coefficients (ICCs) (22) for the four psychiatrists who conducted the K-SADS interview with parents or legal guardians were employed during SBM analysis (see following) for the four psychiatrists who conducted the K-SADS interview with parents or legal guardians.

Stability of Diagnosis

The age at onset of psychosis was defined as the age at which the patient experienced positive psychotic symptoms for the first time (delusions or hallucinations of any kind that qualify for a DSM-IV diagnosis) (Supplement 1). This information was gathered during the K-SADS interview with parents or legal guardians present. Duration of psychosis was defined as the time between age at onset of psychosis and scan acquisition. Duration of treatment was defined as the time between initiation of antipsychotic treatment and scan acquisition.

Medication

At the time of the baseline assessment, all patients were taking antipsychotic medication. Eighty percent (n = 39) of the sample (n = 49) were receiving only one antipsychotic, and the other 20% (n = 10) were receiving two antipsychotics simultaneously. With the exception of two cases, patients were receiving a second-generation antipsychotic. Distribution of the antipsychotic treatment was as follows: 51% (n = 25) risperidone, 33% (n = 16) quetiapine, 29% (n = 14) olanzapine, 4% (n = 2) ziprasidone, and 4% (n = 2) haloperidol. The chlorpromazine equivalent dose (CPE) (24,25) was calculated from the dose of antipsychotics received (Table 1). The mean daily antipsychotic dose in chlorpromazine equivalents was 401.05 mg ± 782.62 mg.

Estimation of IQ

See Supplement 1.

MRI Acquisition

All participants were scanned on a 1.5-T Philips MRI scanner (Philips Gyroscan; Philips Medical Systems, Best, The Netherlands). Two MR sequences were applied to all the participants: a T1-weighted, 3-dimensional, gradient echo scan with 100 1.5-mm contiguous axial slices (echo time [TE], 4.6 msec; repetition time [TR], 9.3 msec; flip angle, 30°; field of view (FOV), 256 mm; and in-plane voxel size, 98 mm × .98 mm) and a T2-weighted Turbo Spin Echo scan with 3.5-mm contiguous axial slices (turbo factor, 15; TE, 120 msec; TR, 5809 msec; FOV, 256 mm; and in-plane voxel size, 98 mm × .98 mm). Both T1- and T2-weighted images were used for clinical neurodiagnostic evaluation by an independent neuroradiologist. No participants showed clinically significant brain pathology. The cortical surface reconstruction algorithms we employed during SBM analysis (see following) are computer-intensive. The cortical surface reconstructions were performed in parallel on a Linux cluster composed of 24 SUN V20z nodes, each of them with two dual core AMD Opteron

Table 1. Demographic and Clinical Variables of the 49 Male Patients with First-Episode EOP and the 34 Male Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>EOP n = 49</th>
<th>Control Subjects n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Range)</td>
<td>15.8 (1.5)</td>
<td>15.1 (1.7)</td>
</tr>
<tr>
<td>Handedness (r/l/ambidexter)</td>
<td>42/4/0</td>
<td>26/4/1</td>
</tr>
<tr>
<td>IQ (Range)</td>
<td>89 (17) (70–134)</td>
<td>98 (16) (73–129)</td>
</tr>
<tr>
<td>Level of Education (Yrs)</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Parental Socioeconomic Status</td>
<td>2.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Age at Onset of Psychosis (Yrs)</td>
<td>15.4 (1.5)</td>
<td>(10–17)</td>
</tr>
<tr>
<td>Duration of Psychosis (Weeks)</td>
<td>12.0 (9.0)</td>
<td>(0–24)</td>
</tr>
<tr>
<td>Duration of Treatment (Weeks)</td>
<td>2.3 (2.0)</td>
<td>(0–11)</td>
</tr>
<tr>
<td>CPE</td>
<td>401.05 (782.62)</td>
<td></td>
</tr>
</tbody>
</table>

PANSS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptoms</td>
<td>25.6 (5.4)</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>22.7 (7.0)</td>
</tr>
<tr>
<td>General psychopathology</td>
<td>48.7 (9.6)</td>
</tr>
</tbody>
</table>

Values are mean (SD) for continuous variables.

EOP, early-onset psychosis; CPE, chlorpromazine equivalents; PANSS, Positive and Negative Syndrome Scale.

*Missing data for six subjects.

The IQ was estimated by the cubes and vocabulary tests that are part of the Wechsler Adult Intelligence Scale-III/Wechsler Intelligence Scale for Children-Revised.

Parental socioeconomic status was measured with the Hollingshead-Redlich scale.

*Age at onset of psychosis was defined as the age at which positive symptoms appeared for the first time.

*Missing data for one subject.

Duration of psychosis was defined as the time between first appearance of positive symptoms and scan acquisition.

*Duration of treatment was defined as the time between start of antipsychotic treatment and scan acquisition.

www.sobp.org/journal
270 operating at 2.0 GHz. Each node had 8 Gbp of RAM, making a total of 192 Gbp of RAM and 96 computing cores.

**Image Analysis**

SBM. Volume-based neuroimaging studies assessing the cortex usually express the results in units of cortical volume, which cannot be separated into thickness and surface. Voxel-based morphometry suffers the same limitation and results in probabilities of cortical gray matter volume, which might be hard to interpret. Surface-based morphometry resolves this limitation, measuring cortical gray matter volume in millimeters cubed and its constituent parameters, cortical thickness in millimeters and surface area in millimeters squared.

**Gyral and Sulcal Cortical Thickness, Surface, Volume.** For each subject, cortical thickness was estimated as the distance in millimeters between the white matter (gray/white boundary) and gray matter (gray/cerebrospinal fluid boundary) cortical surface (26). The white and gray cortical surfaces were reconstructed from the raw unaligned images in native space, with the methods described by Fischl and Dale (26) and Dale et al. (27), as implemented in the FreeSurfer software package (version 4.0.5, http://surfer.nmr.mgh.harvard.edu). The reconstruction process was supervised and corrected when necessary by an operator blind to the subject’s diagnosis. The reconstruction procedure was repeated until accurate white and gray surfaces were obtained. For each subject, the total intracranial volume was also estimated as described by Buckner et al. (28). The reconstructed surfaces enabled calculation of cortical thickness, surface area, and regional gray matter volume at every vertex (i.e., surface point) with methods developed by Fischl and Dale (26). For each subject, the cortical surface was separated into gyri and sulci by thresholding the cortical surface curvature values (Figure 1). The curvature threshold was fixed at 0, the surface point of inflexion between gyri and sulci. This is the point where the cortical surface passed from convex to concave or vice versa. Effectively, sulci contain both sulcal wall and fundus.

Normalizing and Automatic Labeling of Gyri and Sulci. Before statistical analysis, all cortical surfaces were normalized from native space into Montreal Neurological Institute (MNI) space (29). In addition, for accurate localization of the results, a left and right hemispheric study-specific average gray matter surface template was created. To obtain this template, the normalized cortical surfaces of all control subjects and patients were automatically labeled into 32 regions with a Bayesian segmentation procedure designed to replicate the neuroanatomical labeling described by Desikan et al. (30).

Thereafter, the gray matter surfaces and cortical labels from all the subjects were averaged to create the left and right study-specific average gray matter surface template, labeled into the 32 regions. Before averaging, the accuracy of the labeling was checked in native space and manually edited if necessary.

The normalized maps containing the cortical thickness values of each subject were smoothed with a full-width at half-maximum (FWHM) kernel of 10 mm for statistical analyses.

The Degree of Cortical Folding. The degree of cortical folding has traditionally been estimated by computing a ratio between the gray matter surface contour and an outer contour in successive coronal sections (13,31). Schaer et al. (32) extended these ideas to obtain a local estimate of the degree of cortical folding. With the reconstructed gray matter surfaces, we measured the degree of cortical folding with the method by Schaer et al. (32). This method has been previously validated in a juvenile clinical population (32). The degree of cortical folding was only studied in regions where cortical thinning was detected, to provide maximum information about those regions.

**Statistical Analyses**

Demographic and Clinical Data. Data were checked for normality and outliers. If the results were not normal, the values were transformed with a logarithmic transformation. To test for group differences in the demographic and clinical data, the Student t test was used for the normally distributed continuous variables, and χ² was used for discrete categorical variables.

Confounds; Age and Intracranial Volume. For analyses of cortical thickness, surface, volume, and folding, age was entered a priori as a covariate, because age seems to be related to these SBM variables (33,34). In analyses of surface and volume, we also controlled for intracranial volume (35). For cortical thickness and folding, the relationship with intracranial volume is not clear (35). The results for cortical thickness and folding did not change after including intracranial volume as a covariate; the results without controlling for intracranial volume are reported here.

Analysis of Thickness, Surface, Folding, and Volume. Step One: Comparison of Cortical Thickness Maps. In step one, we did two analyses. In the first analysis cortical thickness (not divided in gyri and sulci) maps for each hemisphere were compared between patients and control subjects at every vertex over the whole cortex. For the second analysis the comparison between patients and control subjects was made in the frontal and temporal regions only (see Figure 2 for the included cortical frontal and temporal regions). These regions were a priori selected on the basis of previous literature showing significant structural deficits in adolescent patients with psychosis (8,15,36).

![Figure 1. (A) The inflated right hemisphere of the study-specific average gray matter surface template overlayed with a thresholded curvature map. The curvature threshold was fixed at 0, the surface point of inflexion between gyri and sulci (dark gray). This is the point where the cortical surface passed from convex to concave or vice versa. Sulci contain, effectively, both sulcal wall and fundus. The superior frontal cluster (red) in which cortical thinning was detected. (B) On the basis of the thresholded curvature map, the cluster of cortical thinning was divided in sulcal (blue) and gyral (yellow) region. Thereafter, we compared mean sulcal and gyral cortical thickness between patients and control subjects (see Results).](image-url)
In the second analysis we then compared cortical thickness maps at every vertex over the combined frontal and temporal cortex only. A General Linear Model was used in both the first and second analysis.

**Step One: Correction for Multiple Comparisons.** In both the whole cortex and the combined frontal and temporal cortex analysis, we corrected for multiple comparisons by using Monte Carlo permutation testing. Monte Carlo permutation cluster analyses were performed with a vertex-wise threshold of .05 and a cluster threshold of .05. The Monte Carlo simulations were used to investigate whether the vertex-wise threshold confirmed the cluster threshold criteria used in the analyses. This statistical approach and cluster threshold has been used previously in studies investigating psychosis (37).

**Step 2: Within-Cluster Analysis of Mean Thickness, Surface, the Degree of Folding, and Volume.** In this step we compared, group-wise, the mean gyral and sulcal thickness (Figure 2), surface, degree of cortical folding, and volume over the clusters of vertices that differed significantly between the groups in step one. Thus for each significant cluster from step one of the analysis and for every subject, gyral and sulcal thickness, surface, degree of folding, and volume were averaged over all vertices. Group differences for these variables were assessed by using analysis of covariance; we report both the \( \alpha \) and the effect size (ES) (partial \( H^2 \)).

**Relationship of the Results with Treatment and Estimated IQ**

To investigate whether group differences were correlated with dose of CPE or estimated IQ, we performed partial correlations within the patient group between the thickness, surface, folding, and volume variables and the dose of CPE and estimated IQ, controlling for age and intracranial volume.

**Results**

**Demographic and Clinical Data**

There were no significant group differences in handedness, years of education, and parental socioeconomic status (Table 1). Age was slightly higher in the control group (.7 years, \( p = .06 \)). Patients had significantly lower estimated IQ compared with healthy control subjects (38,39), as expected from previous studies.

**Analysis of Thickness, Surface, Folding, and Volume**

**Left Hemisphere.** **Step One: Comparison of Cortical Thickness Maps.** A comparison of the cortical thickness maps between patients and control subjects over the whole left hemispheric cortex yielded two clusters where patients showed thinner cortex compared with control subjects (Figure 3). One cluster was located in the inferior/middle frontal cortex (corrected cluster-based \( p = .01 \), surface area 1167 mm\(^2\)), and the other cluster was located in the superior temporal region (corrected cluster-based \( p = .005 \), surface area 1290 mm\(^2\)).

Comparing the cortical thickness maps between patients and control subjects over the combined left frontal and temporal cortex only (see Figure 2 for the included frontal and temporal regions) did not lead to the identification of any new clusters. There were no clusters detected where patients had increased cortical thickness relative to control subjects.

**Step 2: Within-Cluster Analysis of Mean Thickness, Surface, the Degree of Folding, and Volume.** In the superior temporal cluster, both mean gyral (ES = .2) and sulcal (ES = .3) thickness as well as volume (ES = .1) were decreased in patients (Table 2). In the inferior/middle frontal cluster, mean gyral (ES = .2) and sulcal (ES = .1) thickness of the cortex were decreased and surface area (ES = .05) were increased in patients, effectively canceling out a volume effect (Table 3). No cluster showed a significant group difference in the degree of cortical folding.

**Right Hemisphere.** **Step One: Comparison of Cortical Thickness Maps.** When comparing the cortical thickness maps between the patients and control subjects over the whole right hemisphere, three clusters where patients had thinner cortex—compared with control subjects—survived correction for multiple comparisons (Figure 3). One was located in the superior frontal gyrus (corrected cluster-based \( p = .0002 \), surface area 2006 mm\(^2\)), another was located in the medium orbitofrontal area (corrected cluster-based \( p = .01 \), surface area 1137 mm\(^2\)), and the third was located in the occipital lobe (corrected cluster-based \( p = .002 \), surface area 1440 mm\(^2\)).

Comparing the cortical thickness maps over the combined right frontal and temporal cortex (Figure 2) led to the detection of two additional clusters: one located in the inferior/middle frontal cortex (corrected cluster-based \( p = .01 \), surface area 834 mm\(^2\)), and the other in the superior temporal region (corrected cluster-based \( p = .02 \), surface area 799 mm\(^2\)). The fact that these two clusters were detected only after comparison of groups over the combined frontal and temporal cortex indicates that these clusters were statistically less strongly different between the groups compared with the superior frontal, medium orbitofrontal, and occipital clusters detected in the group comparison over the whole right hemisphere. There were no clusters detected where patients had increased cortical thickness relative to control subjects.

**Step 2: Within-Cluster Analysis of Mean Thickness, Surface, the Degree of Folding, and Volume.** For the superior frontal (ES gyral = .2, sulcal = .2, volume = .2), medium orbitofrontal (ES
gyral = .2, sulcal = .1, volume = .1), occipital (ES gyral = .2, sulcal = .2, volume = .1), and superior temporal (ES gyral = .2, sulcal = .1, volume = .2) clusters, both mean gyral and sulcal thickness as well as volume were significantly decreased in patients (Table 2). For the inferior/middle frontal cluster, gyral thickness was significantly thinner in patients (ES .1), whereas sulcal thickness was not. In the superior frontal cluster, patients had a nearly significant lower degree of cortical folding with a small ES (p = .06, ES = .05, Table 3).

Relationship of the Results with Treatment and Estimated IQ

No significant partial correlations between any of the SBM variables with dose of CPE or estimated IQ were found.

Discussion

The main findings of this study were, firstly, that male adolescents with first-episode EOP showed decreased bilateral gyral and sulcal thickness and volume deficits in prefrontal and

Table 2. Gyral and Sulcal Cortical Thickness in Clusters of Decreased Cortical Thickness

<table>
<thead>
<tr>
<th>Cluster</th>
<th>% Verticesb</th>
<th>Thicknessa</th>
<th>Gyrus</th>
<th>Sulcus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal</td>
<td>75</td>
<td>75</td>
<td>2.28</td>
<td>.21</td>
</tr>
<tr>
<td></td>
<td>2.48b .23</td>
<td></td>
<td>2.12</td>
<td>.12</td>
</tr>
<tr>
<td>Inferior middle frontal</td>
<td>41</td>
<td>41</td>
<td>2.42</td>
<td>.19</td>
</tr>
<tr>
<td></td>
<td>2.66b .23</td>
<td></td>
<td>2.25</td>
<td>.21</td>
</tr>
<tr>
<td>Right Hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal</td>
<td>48</td>
<td>48</td>
<td>2.63</td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>2.86b .23</td>
<td></td>
<td>2.42</td>
<td>.23</td>
</tr>
<tr>
<td>Medium orbitofrontal</td>
<td>48</td>
<td>48</td>
<td>2.56</td>
<td>.27</td>
</tr>
<tr>
<td></td>
<td>2.83b .25</td>
<td></td>
<td>2.41</td>
<td>.25</td>
</tr>
<tr>
<td>Occipital</td>
<td>59</td>
<td>55</td>
<td>1.79</td>
<td>.16</td>
</tr>
<tr>
<td></td>
<td>1.95b .21</td>
<td></td>
<td>1.70</td>
<td>.13</td>
</tr>
<tr>
<td>Superior temporald</td>
<td>21</td>
<td>22</td>
<td>2.49</td>
<td>.23</td>
</tr>
<tr>
<td></td>
<td>2.71b .21</td>
<td></td>
<td>2.29</td>
<td>.31</td>
</tr>
<tr>
<td>Inferior middle frontald</td>
<td>27</td>
<td>28</td>
<td>2.70</td>
<td>.26</td>
</tr>
<tr>
<td></td>
<td>2.81b .28</td>
<td></td>
<td>2.39</td>
<td>.33</td>
</tr>
</tbody>
</table>

CS, control subjects.

aCortical thickness in millimeters.
bPercentage of total number of cluster vertices belonging to gyral part of cluster.
cClusters detected after combined frontal and temporal cortex analysis (see Figure 2 for included frontal and temporal regions).
dp < .001.
ep < .05.
superior temporal regions and in a right occipital region. There was one exception: a right inferior-middle frontal region where gyral thickness was affected, whereas sulcal thickness was not. Secondly, in a right superior frontal region, decreased cortical thickness overlapped with a decreased degree in cortical folding (which was not significant but was close to significance) in our sample of male EOP patients.

The results of the current study are consistent with previous studies reporting cortical thinning and volume deficits in prefrontal, temporal, and occipital subregions, in adolescents with psychosis (8,16) and in children and adults with first episode and chronic schizophrenia (1–3,15,40,41). One recent study used the same methodology for measuring cortical thickness as the current study but reported more widespread thinning in patients (16). This might be due to important differences between the study by Voets et al. (16) and the current one. Patients in the study by Voets et al. had a considerably longer mean disease duration compared with the patients in the current study (1.4 years vs. 13 weeks) and constituted a mixed gender sample. In addition, the acquisition protocol used by Voets et al. was optimized for SBM, which could have improved the sensitivity of their SBM analysis.

Our results suggest that in male subjects with EOP, decreased thickness in both gyral and sulcal regions—more than a decrease in surface area—might underlie the volumetric deficits in these regions. For a left middle frontal region we found decreased thickness and increased surface area that effectively canceled out a patient/control difference in volume. This illustrates the power of decomposing volume into thickness and surface area. Furthermore, in a right inferior-middle frontal region, gyral thickness was more affected in patients compared with sulcal thickness. This is a provisional finding that needs replication. Morphological surface-based abnormalities in sulci have been reported in adult and adolescent patients with schizophrenia (5), but it was unclear whether these abnormalities overlapped with cortical thinning (5,12). Our finding suggests that for some cortical regions in male adolescents with EOP, cortical thinning is not uniform but might depend upon the relative gyral and sulcal presence in that region.

The bilateral dorsolateral prefrontal and superior temporal regions where patients had decreased thickness include neural circuitry related to diverse cognitive functions. For the right hemisphere, the dorsolateral prefrontal cortex has been strongly associated with executive, attentional, and working memory function, and the orbitofrontal cortex is known to play an important role in affective decision making (42). For the left hemisphere, our findings indicate cortical thinning in language-related regions (43). In adolescents with psychosis, language function might be impaired (44,45). In addition, functional as well as structural MRI studies have found abnormalities in brain structures belonging to the language network in adult and adolescent patients with psychosis (46–48).

In patients, the degree of cortical folding was not abnormal in any region studied, although there was a nearly significant difference of small ES in one prefrontal region of cortical thinning. A decreased degree of cortical folding has been reported in adolescents with early-onset schizophrenia (19) and adult patients with chronic schizophrenia (4,49). Interestingly, the literature on cortical folding in those with increased genetic risk of psychosis shows predominantly increased prefrontal folding when compared with normal control subjects (50–52). These findings might suggest a change in folding around the time of symptom onset. However, this is speculative, because cortical folding seems to be developmentally invariant (53).

Although the current study did not measure the degree of cortical folding outside regions of decreased thickness, our results suggest that—in a right hemispheric superior frontal region—decreased cortical thickness might co-occur with a decreased degree of cortical folding in male adolescent patients with EOP. Few previous studies have investigated the relationship between cortical thickness and the degree of cortical folding, none of them in adolescents or adults with psychosis (54–56). None of these studies found a clear linear correlation between thickness and the degree of folding, suggesting that the relationship between them is not straightforward (54). However, we found an identical inverse correlation in patients and control subjects between right superior frontal cortical thickness and degree of cortical folding, predicted by biological theories and models of cortical folding (11,57). Neurodevelopment of the human cortical folds takes place between the fourth month of gestation and the fourth postnatal month (13). Thus, an abnormal degree of cortical folding might be a strong indication of

---

**Table 3. Cortical Surface, Volume, and the Degree of Cortical Folding in Clusters of Cortical Thinning**

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Surfacea</th>
<th>Volumeb</th>
<th>Foldingc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>CS</td>
<td>Patients</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>Left Hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior temporal</td>
<td>923.4</td>
<td>146.7</td>
<td>935.7</td>
</tr>
<tr>
<td>Inferior middle frontal</td>
<td>825.4</td>
<td>180.8</td>
<td>732.3e</td>
</tr>
<tr>
<td>Right Hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal</td>
<td>1363.6</td>
<td>209.1</td>
<td>1388.2</td>
</tr>
<tr>
<td>Medium orbitofrontal</td>
<td>783.1</td>
<td>129.9</td>
<td>795.4</td>
</tr>
<tr>
<td>Occipital</td>
<td>1017.3</td>
<td>189.9</td>
<td>1023.5</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>570.7</td>
<td>65.5</td>
<td>587.8</td>
</tr>
<tr>
<td>Inferior middle frontal</td>
<td>555.1</td>
<td>133.6</td>
<td>599.1</td>
</tr>
</tbody>
</table>

---

*aSurface in mm².  
*bVolume in mm³.  
*cFolding is unitless.  
*dP < .01.  
*eP < .05.  
*fP < .001.  
*Clusters detected after combined frontal and temporal cortex analysis (see Figure 2 for included frontal and temporal regions).
abnormal pre- and perinatal neurodevelopment. The fact that the degree of folding was generally not abnormal in regions of cortical thinning suggests that the patient-control differences in cortical thickness do not date from the period when gyri and sulci are forming. Thinning of the cortex in patients seems to stem from the later period after birth when, in healthy subjects, cortical thickness first increases and then decreases (34). The cortex might thus develop in a similar way in patients and control subjects during the (pre- and postnatal) period, with the net tissue loss in patients resulting from events that happen during a later period.

There are several caveats based on limitations of this study. Firstly, we did not have access to full-scale premorbid and current IQ for the patients. Patients underwent extensive neuropsychological testing. To reduce the time of assessment, we estimated IQ on the basis of two Wechsler Adult Intelligence Scale subtests. Secondly, brain changes due to antipsychotic treatment cannot be ruled out (58). However, a strength of the current study is the short mean duration of exposure to antipsychotics. Given the magnitude of the anatomical ES we found and the relative short period of drug exposure, it is biologically unlikely that all of these differences are secondary to this confounding variable. Furthermore, we found no correlation within patients between anatomical variation in the relevant brain areas where significant group differences were found and dose of chlorpromazine equivalents used. Thirdly, our acquisition protocol was not optimized for SPM analyses (e.g., our scans did not have isotropic 1-mm voxel-resolution), which might have decreased the sensitivity of SPM. Fourthly, we analyzed cortical folding only in regions where differences in thickness were detected, which does not exclude the possibility of differences in folding in other areas of the cortex.

This study is supported by CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, and the Juan de la Cierva Programme of the Spanish Ministry of Science and Innovation; CIBER CB06/01/0079, CDTTEAM Programa CÉNT of the Spanish Ministry of Industry, the Fundación Alicia Koplowitz, and Caja Navarra. EB was supported by a Banco Bilbao Vizcaya Argen-}


