Folding of the Prefrontal Cortex in Schizophrenia: Regional Differences in Gyrification

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Background: Anatomy of prefrontal cortex in schizophrenia has been studied previously by quantifying the degree of gyrification. Conflicting results exist, with some studies showing hypergyria and others showing hypogyria. It is likely that regional variations in cortical folding exist within the prefrontal cortex that could be explored by studying the anatomical subdivisions formed by the sulci and gyri. With surface reconstructions from magnetic resonance imaging, we studied the gyrification within anatomically meaningful subdivisions of prefrontal cortex in schizophrenia.

Methods: Prefrontal cortex was studied with an automated method to obtain Local Gyrification Index, reflecting the degree of cortical surface reconstructions from magnetic resonance imaging, we studied the gyrification within anatomically meaningful subdivisions of prefrontal cortex in schizophrenia.

Results: Patients with schizophrenia had significant hypogyria in most prefrontal regions except the frontomarginal region, which showed hypergyria. The normal left > right pattern of prefrontal gyrification was reversed in schizophrenia. Patients with schizophrenia also showed significant age-related reduction in gyrification at the hypogyrpic regions.

Conclusions: The differences between reported findings regarding prefrontal gyrification might reflect regional variation in the nature of the abnormal process of gyrification in schizophrenia. Prefrontal gyrification is significantly influenced by age in schizophrenia, in addition to the influence of neurodevelopmental factors.

Key Words: Cortical folding, gyrification index, neuroimaging, prefrontal cortex, schizophrenia, surface based morphometry

During development, human brain comes under two distinct sets of challenges. Being one of the largest brains among primates, it requires substantial development in utero. But mechanical limits of parturition necessitate a finite restraint to the brain size to facilitate passage through birth canal. In part, significant increase in brain surface area without necessitating an attendant increase in head size becomes possible due to the remarkable folding capacity of the developing brain (1). In human brain, the process of gyrification that accompanies significant increase in brain area is thought to be well-orchestrated during early development (2). Substantial variability in degree and pattern of gyrification is noted both between and within individuals (3,4). A disturbance in the process of gyrification is of potential interest in the study of schizophrenia due to its close relationship with neuronal differentiation and migration. In addition, the folding of a brain region is also influenced by underlying intracortical, axonal connections (5), making cortical gyrification a morphological entity that is crucial for understanding the pathophysiology of schizophrenia.

Prefrontal cortex undergoes significant expansion in both ontogenetic and phylogenetic development and remains a region of significant interest in attempts to understand and treat schizophrenia (6). Analysis of prefrontal cortex structure (7) and gene expression (8) suggests that changes seen in schizophrenia might be similar to processes associated with aging. Studies exploring prefrontal cortical folding in schizophrenia report conflicting results; some report increased prefrontal gyrification (9–11), whereas other studies report reduced gyrification (12–15) or no difference (16) from healthy control subjects. Such discrepancy could be due to various factors: 1) all the previous studies employed measures of gyrification in two-dimensional space that could be influenced by various imaging parameters such as slice thickness and orientation; 2) prefrontal cortex is a heterogeneous region comprising multiple subregions with notable structural and functional dissimilarities; most of the previous studies have reported the degree of gyrification for whole of the prefrontal cortex; it is possible that regional differences exist in prefrontal gyrification that are hitherto unexplored; and 3) none of the previous studies have explored regional differences in gyrification across meaningful boundaries of anatomically defined gyri and sulci of a region. Nonetheless, there is a consistent trend for studies to report hypergyria in the most anterior regions (9,12) suggesting that there are consistent regional differences. In addition, the effect of age on prefrontal gyrification in schizophrenia is unclear.

In the present study, we computed the degree of prefrontal cortical folding with a recently developed method for measuring Gyrification Index in three-dimensional surface reconstructions. We investigate the regional differences and the effect of age on prefrontal gyrification along the major sulcogyrical regions in patients with schizophrenia. We hypothesized, given the previous findings, that regions with increased gyrification (hypergyria) will be present alongside regions with reduced gyrification (hypogyria) in the prefrontal cortex.

Methods and Materials

Participants

A sample of 57 patients satisfying DSM-IV criteria (17) for schizophrenia and 42 healthy control subjects was recruited. Regional ethics committees (Nottinghamshire and Derbyshire) approved the study, and all participants provided written informed consent. Patients were initially referred by clinicians attached to community mental health teams and rehabilitation services. The diagnosis of schizophrenia was made in a clinical consensus meeting among a team of research psychiatrists (PFL, PM, or VJ) in accordance with...
Leckman et al. (18), with all available information, including a review of case files and a standardized clinical interview (Signs and Symptoms of Psychotic Illness) (19). The predominant subtypes of schizophrenia in the sample included Paranoid (DSM-IV 295.30) (n = 47), Undifferentiated (DSM-IV 295.90) (n = 7), and Disorganized (DSM-IV 295.10) (n = 3). All patients were in a stable phase of schizophrenia (defined as a change of no more than 10 points in their Global Assessment of Function [DSM-IV] [17] score, assessed 6 weeks prior and immediately before study participation), and the mean duration of illness was 4.3 years. Subjects with neurological disorders, current substance dependence, IQ < 70 with Quick Test (20), and diagnosis of any other axis I disorder were excluded. All patients were receiving treatment with antipsychotic medications and had no change in their prescriptions for the 6 weeks preceding the scan. The average dose in chlorpromazine equivalents was 288.7 mg (range: 100–1200 mg). Chlorpromazine equivalent doses were computed for oral antipsychotic medication with data presented by Woods (21). In the case of risperidone Consta injection, 25 mg Consta injection every 14 days was taken to equate to 4 mg oral risperidone/day, in accordance with the recommendation of the British National Formulary (22). Healthy control subjects were recruited from the local community via advertisements and included 42 subjects free of any psychiatric or neurological disorder, matched in age (± 3 years) and socioeconomic status (measured with National Statistics—Socio-Economic Classification) (23) with the patient group. Control subjects had exclusion criteria similar to patients; in addition subjects with history of psychotic illness in first-degree relatives were excluded. One control subject was excluded in the final analysis due to a movement artifact in the magnetic resonance imaging image that precluded volumetric computations.

**Image Acquisition**

Magnetic resonance scans were collected with Philips 3-T imaging system equipped with 8-channel phased array head coil. The scanning protocol included a single high-resolution three-dimensional T1-weighted magnetization prepared rapid gradient echo volume of isotropic voxel size $1 \times 1 \times 1$ mm$^3$, flip angle 8°, field of view 256 $\times$ 256 $\times$ 160 mm$^3$. One hundred sixty slices of 1 mm thickness each were collected in an acquisition matrix $256 \times 256$ mm and in-plane resolution $1 \times 1$ mm$^2$.

**Surface Extraction**

Surface extraction and cortical parcellation were carried out with FreeSurfer version 4.5.0 (24); the preprocessing was carried out according to the description available at [http://surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/). Briefly, after skull-stripping and intensity correction, the gray–white matter boundary for each cortical hemisphere was determined with tissue intensity and neighborhood constraints. The resulting surface boundary was tessellated to generate multiple vertices across the whole brain before inflating. All surfaces were visually inspected after an automated topology fixation procedure, and remaining minor defects were manually corrected as recommended by the software guidelines. The expansion of the resulting gray–white interface created the pial surface with a point-to-point correspondence. This was followed by spherical morphing and spherical registration. Finally, the parcellations were obtained by inverting spherical morphing procedure to map back the average spherical representation onto the inflated surface of each subject. The parcellations were obtained with Destrieux sulcogyral-based atlas, which follows the anatomical conventions of Duvernoy (25). The six combined sulcogyr regions selected a priori include frontomarginal region; orbital frontal region (including H-shaped orbital sulcus); inferior, middle, and frontal regions (both gyri and sulci); and frontal pole (comprising transverse frontopolar gyrus and sulcus). Anatomical boundaries of each individual region are described by Destrieux et al. (25). Figure S1 in Supplement 1 displays the selected sulcogyr regions.

**Gyrification Index**

Local gyrification indices (LGI) were obtained with the method of Schaer (26) with images reconstructed through the Freesurfer pipeline. Schaer’s method is a vertex-wise extension of Zilles’ gyrification index, which gives a ratio of the inner folded contour to the outer perimeter of the cortex (27). Schaer’s method has been employed to study gyrification across various conditions such as first episode psychosis (28), depression (29), mental retardation (30), and 22q11 deletion (31). With the gray–white interface constructed via surface registration and cortical inflation from the Freesurfer workflow, a pial surface is first obtained by constructing a set of lines perpendicular to the gray–white interface. A morphological closing operation is then performed by smoothing to ensure that the local curvature at all points on the smoothed pial surface (the “hull” surface) is less than the curvature of a 15-mm radius sphere. The chosen radius of 15 mm for the closing operation ensures that the hull surface does not dip into the sulci and remains tight but external to the sulcal dips.

This hull surface acts as the outer perimeter, whereas original pial surface provides the inner perimeter. Both inner and outer surfaces are tessellated with numerous vertices that are formed by the meeting points of triangles. For each vertex $j$ on the outer surface, a spherical region of interest is created with the vertex as the center point and a standard 25-mm radius. This sphere yields two area measures for each vertex. The outer measure (Area$_o$) is area of that part of the hull defined by the intersection of this sphere with the hull surface. To measure the corresponding pial surface area, the respective pial region of interest for the given vertex on outer hull surface is determined as follows. Initially all vertices within Area$_o$ (on the hull surface) are identified. After this, the nearest pial vertex to each of these hull vertices is identified. These pial vertices define the outline of pial mesh, whose area is then calculated with sum of areas of all included triangular tessellations (Area$_p$). The ratio of the pial surface area to the outer surface area gives the LGI for each vertex on the outer surface (Area$_p$/Area$_o$). These outer surface values are redistributed to the pial surface with a weighted sum of all outer surface LGIs to which each pial vertex contributed during the prior computation. The weighting was inversely proportional to the distance of the hull vertex from the pial vertex. Thus, the LGI for each vertex on pial surface reflects the amount of cortex buried in its locality.

The mean LGI calculated with all vertices present within a predefined sulcogyr region of the atlas is used as the LGI of that anatomical subregion. Thus, six LGI values were obtained for each hemisphere for further analysis.

**Statistical Analysis**

All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS16.0, SPSS, Chicago, Illinois). Logarithmic transformation was applied to age to account for non-normal distribution. Statistical analysis of prefrontal LGI was carried out with a General Linear Model repeated-measure analysis of covariance, with hemisphere (left and right) and regions (superior frontal, middle frontal, inferior frontal, orbitofrontal, frontomarginal, and frontopolar) as within-subject factors and diagnosis as between-subjects factor. Age and total brain volume were used as covariates. Follow-up tests comparing regional LGIs between the
two groups were carried out with independent-measure $t$ tests with Bonferroni correction for multiple testing. Significant two-way interactions were studied with Bonferroni-corrected partial correlations.

**Results**

There were no significant differences in demographic features such as age [$t(1,96) = -1.32, p = .17$] or parental socioeconomic status (Mann–Whitney $U$ test, $Z = -1.94, p > .05$) between the two groups. The mean total symptom score on the Signs and Symptoms of Psychotic Illness was 10.28 of a maximum of 80 (range: 0–29), indicating a low symptom burden and consistent with recruitment in a stable phase of illness. The mean score on Reality Distortion (Delusions and Hallucinations) among the patient group was three in a stable phase of illness. The mean score on Psychomotor Poverty dimension was 2.86 (range: 0 to 9) and on Disorganization dimension was .74 (range: 0 to 4). The demographic features of the sample are shown in Table 1.

**Altered Gyrification in Schizophrenia**

There was a significant effect of diagnosis on the prefrontal LGI $F(1,94) = 4.71, p = .03$. Both age $F(1,94) = 7.33, p = .008$ and total brain volume $F(1,94) = 5.52, p = .021$ were significant covariates. Hemisphere $\times$ diagnosis interaction was statistically significant $F(1,94) = 4.39, p = .039$ (Figure 1). A significant diagnosis $\times$ regions interaction $F(5,470) = 29.79, p < .001$ was also seen in addition to significant age $\times$ regions interaction $F(5,470) = 9.91, p < .001$. The effect of diagnosis was unaltered, even after removing the total brain volume covariate $F(1,95) = 5.34, p = .02$.

Independent-measures $t$ tests revealed significant hypogyria at left middle frontal, left superior frontal, left inferior frontal, left frontopolar, right superior frontal, and right frontopolar regions in patients. Significant hyperyria was seen in left and right frontomarginal regions. Significant trends toward hypogyria not reaching statistical significance were noted for left orbital, right orbital, right inferior frontal, and right middle frontal regions in patients with schizophrenia. The regional differences are presented in Table 2.

**Effect of Age on Prefrontal Gyrification**

Correlations between regional LGIs and age in the whole sample are presented in Table 3. To explore the influence of age on hypergyric and hypogyric regions separately across the two groups, we computed average LGI for left and right hypogyric regions with the marginal regions (left hemisphere) and right hypergyric (right frontomarginal) regions as dependent measures— with diagnosis as fixed factor and age as covariate of interest— revealed significant age $\times$ diagnosis interaction for hypogyric [left hemisphere $F(1,93) = 9.05, p = .003$; right hemisphere $F(1,93) = 6.16, p = .01$] but not the hypergyric regions [left hemisphere $F(1,94) = .01, p = .91$; right hemisphere $F(1,94) = 1.20, p = .28$]. Bonferroni-corrected post hoc analysis revealed significant partial correlations between LGI and age, corrected for total brain volume for the hypogyric regions (left hemisphere $r = -.57, p < .01$; right hemisphere $r = -.56, p < .01$) but not for the hypergyric frontomarginal regions (left hemisphere $r = .13, p > .05$; right hemisphere $r = .24, p > .05$) in patients. None of the partial correlations were significant in control subjects (left hypogyric $r = .06, p > .05$; right hypogyric $r = -.11, p > .05$; left hypergyric $r = .34, p > .05$; right hypergyric $r = -.13, p > .05$). Figure 2 shows scatter plots of the age effect on hypogyric regions.

**Effect of Antipsychotic Dose**

No significant correlations were noted between chlorpromazine equivalents and gyrification indexes across the hypogyric and hypergyric regions on either hemisphere (left hypogyric $r = -.22, p > .05$; right hypogyric $r = -.19, p > .05$; left hypergyric $r = -.02, p > .05$; right hypergyric $r = -.09, p > .05$).

**Discussion**

With vertex-wise computation of gyrification index within major sulcogyral regions of prefrontal cortex on three-dimensional brain reconstructions, we have shown significantly altered cortical folding pattern in schizophrenia. Our results confirm our main hypothesis that there are both hypergyric and hypogyric regions in prefrontal cortex of patients with schizophrenia when compared with healthy control subjects. Significant age-related reduction in gyrification index is observed in those regions that are hypogyric in patients with schizophrenia.

Hemispheric differences are noted in prefrontal gyrification, with overall right hemispheric LGI being higher than the left hemispheric LGI in patients, whereas the opposite is true in control subjects. Many of the previous studies of prefrontal gyrification in schizophrenia reported similar hemispheric differences (10,32,33). A preliminary report of association between protocadherin and altered cerebral gyrification in schizophrenia supports the notion

<table>
<thead>
<tr>
<th>Table 1. Demographic Features of the Sample</th>
<th>Patients with Schizophrenia</th>
<th>Healthy Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>57</td>
<td>41</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>50/7</td>
<td>39/2</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>52/5</td>
<td>34/7</td>
</tr>
<tr>
<td>Age Range, yrs (mean and SD)</td>
<td>19–47 (26.10–7.49)</td>
<td>18–44 (28.04–6.63)</td>
</tr>
<tr>
<td>Mean Parental NS-SEC (SD)</td>
<td>2.54 (1.57)</td>
<td>2.02 (1.44)</td>
</tr>
</tbody>
</table>

NS-SEC, National Statistics—Socio-Economic Status.
that disturbed cerebral torque in schizophrenia could be related to the gyrification asymmetry (34).

**Localized Hypergyria**

Sallet et al. (12) reported local hypergyria in the “anterior-most” slices of prefrontal cortex in patients with schizophrenia. Although direct comparison is not possible due to methodological dissimilarities, it is likely that these slices included frontomarginal sulcus. These findings were replicated in a later study by Harris (9), who found hypergyric slices in both right and left hemispheres.

Although the rest of the prefrontal cortex showed significant hypogyria, the frontomarginal region seems to be unique in being hypergyric in both hemispheres. Frontomarginal sulcus is one of the few regions identified as a “sulcal basin” (35). According to Lohmann’s sulcal basin model of gyrification, an entire sulcus arises from several segments that are concavities in the white matter surface (36). Such basins are more consistent than the surface folds across individuals. By comparing the volume and depth of the anteriorly located sulcal basins with the posterior regions within the prefrontal cortex, Huttner et al. (35) concluded that the anterior regions including the frontomarginal sulcus show less deterministic gyrification patterns and are likely to be both ontogenically and phylogenetically younger. This suggests that anterior prefrontal cortex including the frontomarginal region might be more susceptible to perinatal and developmental influences than other prefrontal regions. They also noted that the degree of variability in the volume of sulcal basins was higher than the variability of the neighboring sulcal regions and hypothesized the existence of an underlying mechanism to preserve overall prefrontal volume (35). In this context, an increase in frontomarginal gyrification that could result from an increase in the sulcal basin volume in this region could be construed as the result of compensation for influences that reduce either prefrontal or overall brain development in schizophrenia.

**Table 2. Regional Differences in Gyrification Index**

<table>
<thead>
<tr>
<th>Regions</th>
<th>Control Subjects, Mean (SD)</th>
<th>Patients, Mean (SD)</th>
<th>t</th>
<th>Control Subjects, Mean (SD)</th>
<th>Patients, Mean (SD)</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital</td>
<td>2.55 (.13)</td>
<td>2.47 (.14)</td>
<td>2.69</td>
<td>2.50 (.16)</td>
<td>2.44 (.13)</td>
<td>2.11</td>
</tr>
<tr>
<td>Superior Frontal</td>
<td>2.53 (.11)</td>
<td>2.41 (.11)</td>
<td>5.07*</td>
<td>2.50 (.12)</td>
<td>2.43 (.12)</td>
<td>3.03*</td>
</tr>
<tr>
<td>Middle Frontal</td>
<td>2.92 (.13)</td>
<td>2.80 (.16)</td>
<td>3.73*</td>
<td>2.90 (.14)</td>
<td>2.82 (.16)</td>
<td>2.45</td>
</tr>
<tr>
<td>Inferior Frontal</td>
<td>4.19 (.32)</td>
<td>3.95 (.30)</td>
<td>3.78*</td>
<td>4.17 (.31)</td>
<td>4.00 (.36)</td>
<td>2.03</td>
</tr>
<tr>
<td>Frontal Pole</td>
<td>2.25 (.11)</td>
<td>2.07 (.13)</td>
<td>7.03*</td>
<td>2.27 (.12)</td>
<td>2.10 (.14)</td>
<td>6.33*</td>
</tr>
<tr>
<td>Frontomarginal</td>
<td>2.31 (.12)</td>
<td>2.52 (.23)</td>
<td>−5.01*</td>
<td>2.23 (.12)</td>
<td>2.52 (.29)</td>
<td>−5.91*</td>
</tr>
</tbody>
</table>

Results of unpaired t tests with Bonferroni corrected p values. Frontomarginal region shows hypergyria in patients (negative t values). All other significant results suggest hypogyria (positive t values).

*p < .005.

**Effect of Age**

Our results show strong negative correlation between age and gyrification index in the hypogyric regions of patients but not control subjects. Although reduced gyrification could be inferred as the result of processes related to maturational arrest in the prefrontal cortex, the negative correlation with age suggests a susceptibility of these regions to a higher degree of age-related morphometric changes in schizophrenia.

Available data suggest that 25% of variance in sulcal and gyral curvature can be explained by age in healthy control subjects (42). Although global gyration shows a positive relationship with age during neonatal period and childhood, there is a distinct drop in gyration around adolescence (8–19 years) (43). After a period of relative stability during the third and fourth decades (42), a further significant drop is seen after the fifth decade with further drop in the later ages (44). In our sample, relative stability of gyration with age in control subjects contrasts with the decrease in patients. This suggests that there is a distinct shift in the normal trajectory in patients, whereby they show either a continued postadolescent drop in gyration until the fourth decade or they show premature regression as seen in typical elderly persons. Age-related changes in gray matter have been variously attributed to synaptic pruning in adolescence and continued intracortical myelination or degenerative tissue loss in older cohorts (45).

There is some evidence that frontal myelination normally continues well into adulthood (46); this can contribute to a shift in the gray–white boundary with age, leading to a reduction in regional gray matter area and a drop in LGI. In patients with schizophrenia,
either a disruption in regional myelination or progressive degenerative
gray matter changes are likely to contribute to the observed age effect. In schizophrenia, pronounced sulcal widening and gyral “peakedness,” both of which can contribute to reduced gyrification index, have been observed (47). In contrast to rest of the prefrontal cortex in schizophrenia, the hypergyric frontomarginal regions seem to be resistant to the negative influence of age in both groups, suggesting regional variations in the maturational trajectory in the prefrontal cortex. This implies that gyrification abnormalities cannot be simply interpreted as the effect of a single pathological event early in development but rather involve abnormal maturational trajectory with regional variations in schizophrenia. Longitudinal studies will be required to further delineate the relative contributions of developmental and degenerative processes in the prefrontal structural abnormalities seen in schizophrenia.

Study Limitations
Sexual dimorphism has been noted in gyrification indexes in healthy volunteers (48); our sample is predominantly male, precluding a meaningful analysis of gender effect on prefrontal gyrification in schizophrenia. Hence the results presented here must be interpreted with caution for mixed samples. Another limitation of our study is the use of cross-sectional sample; the negative correlation between age and gyrification index is best studied in a prospective sample (49). In addition, all patients in our study were taking antipsychotic medications during participation. The effect of antipsychotics on brain structure is a matter of intense debate, with most data analyzing gray matter density and volume (50). We did not find, consistent with previous findings (51), a correlation between cortical gyrification and antipsychotic dose. However, these results should be considered cautiously until replicated in unmedicated samples.

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Supplementary material cited in this article is available online.


