Abnormal Gyral Complexity in First-Episode Schizophrenia

Katherine L. Narr, Robert M. Bilder, Sharon Kim, Paul M. Thompson, Philip Szeszko, Delbert Robinson, Eileen Luders, and Arthur W. Toga

Background: *Abnormalities in the patterns and frequency of cortical folding might help identify temporal and regionally specific disturbances in normal neurodevelopmental processes that occur in association with schizophrenia. Few studies, however, have investigated gyral complexity in schizophrenia.*

Methods: *High-resolution magnetic resonance images were used to examine differences in gyral complexity, measured three-dimensionally in five separate hemispheric regions covering the entire cortical surface, in patients with first-episode schizophrenia (*n *= 50) compared with demographically matched healthy comparison subjects (*n *= 50). The modulating effects of gender and hemisphere were also examined.*

Results: *Significant increases in cortical folding were observed in the right superior frontal cortex in male schizophrenic patients compared with male control subjects, but not between female diagnostic groups. Significant main effects of hemisphere were found in frontal, parietal, and occipital regions in directions complementary to cerebral torques.*

Conclusions: *Results support previous findings of right frontal hypergyria in male schizophrenic patients and suggest that these abnormalities predate illness onset and are of neurodevelopmental origin. Therefore, in schizophrenia, sexually dimorphic developmental processes and differences in hemispheric connectivity, which have been shown to influence the organization and/or frequency of cortical folding, seem to be disturbed during gyral formation in utero.*

Key Words: Cortical folding, neurodevelopment, gyrification, fissurization, magnetic resonance imaging, complexity

The ontogeny and function of gyrification have been studied since the beginning of the past century, but only recently have gyral patterns been examined in schizophrenia. The normative literature shows that there is a temporal as well as a regional organization to gyral development. Gyral formation begins at approximately 16 weeks in utero, although most cortical folding occurs in the late second and third trimesters of pregnancy (Armstrong et al 1995; Chi et al 1977; Richman et al 1975). In utero, primary convolutions including the lateral, central, and calcarine gyri form first. The formation of secondary cortical convolutions, including the parieto-occipital, frontal, and temporal gyri, is followed by the development of tertiary convolutions (Armstrong et al 1995; Richman et al 1975). Postnatally, the ratio between brain growth and gyral complexity remains relatively stable, although an overshoot in gyral complexity has been observed shortly after birth (Armstrong et al 1995; Richman et al 1975).

If the underlying neural connections of specific cerebral regions are lesioned during neurodevelopment, disturbances in gyrification occur (Rakic 1988). Malformations in gyral complexity might represent either decreases (lissencephaly) or increases (microgyria) in cortical convolutions. These might result from pathophysiologic processes that happen at different developmental stages and affect different cortical regions (Richman et al 1975). Abnormal patterns of gyrification might thus help establish the timing of disturbances in early neurodevelopmental events that might occur in association with disease processes in schizophrenia. Furthermore, gyrification abnormalities in discrete cortical regions might point to disturbances in specific functional systems in schizophrenia.

A few previous studies have investigated the presence of disturbed gyrification in schizophrenia. For example, Jakob and Beckmann (1986) first reported abnormalities in the sulcal/gyral patterns and underlying cytoarchitecture of temporal lobe regions in schizophrenia. Kikinis et al (1994) also observed gyrification abnormalities in temporal cortices: schizophrenic patients possessed a more vertical and interrupted course of sulci compared with healthy comparison subjects in the left hemisphere. Differences in the vertical patterns or thinning of the temporal or frontal gyri, however, were not observed by Noga et al (1996) in qualitative assessments of gyral geometry between monozygotic (MZ) co-twins discordant for schizophrenia or between unaffected MZ co-twins of schizophrenic probands compared with healthy control MZ twins.

Other studies have used a gyrification index (GI), which computes the ratio between the outer (superficial) and inner (deep) perimeter of a cortical slice (Zilles et al 1988), to investigate abnormal gyrification and/or cortical complexity in schizophrenia. Magnetic resonance imaging (MRI) data showed lower GI values, indexing reductions in cortical folding, in both anterior and posterior brain regions of the left hemisphere in male schizophrenic patients compared with male comparison subjects (Kulynych et al 1997). These results, however, contrast with postmortem findings of Vogeley et al (2000), who reported increased GIs in the prefrontal right hemisphere in male schizophrenic patients compared with male control subjects. The same group replicated these findings in an imaging study comparing gyrification differences between affected and unaffected sibling pairs from families multiply affected with schizophrenia (Vogeley et al 2001). Results showed that patients possessed right frontal hypergyria compared with their healthy siblings.

In an earlier study, we applied a semiautomated three-

From the Laboratory of Neuro Imaging (KLN, SK, PMT, EL, AWT) and Ahmanson-Lovelace Brain Mapping Center (RMB), Department of Neurology (RMB) and the Department of Psychiatry and Biobehavioral Sciences (RMB), Geffen School of Medicine at University of California-Los Angeles, Los Angeles, California; and the Department of Psychiatry Research (PS, DR, AWT), The Zucker Hillside Hospital, North-Shore Long Island Jewish Health Systems, Glen Oaks, New York.

Address reprint requests to Arthur W. Toga, Ph.D., UCLA School of Medicine, Department of Neurology, Division of Brain Mapping, Laboratory of Neuro Imaging, 710 Westwood Plaza, Los Angeles, CA 90095-1769.

Received October 7, 2003; revised December 29, 2003; accepted December 30, 2003.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2003.12.027

dimensional (3D) approach to measure the frequency of sulcal/gyral convolutions relative to the surface area of discrete cortical regions in patients with chronic schizophrenia compared with healthy subjects (Narr et al 2001). A significant reversal of asymmetry in gyral complexity was observed in superior frontal regions in schizophrenia, and patients exhibited mean increases in cortical folding. To estimate differences in hemispheric folding in schizophrenia, Yucel et al (2002) used a fissurization index (FI). The FI uses thresholding and edge detection techniques to compute the ratio of surface voxels to total brain voxels in MR data, thus also providing a semiautomated estimate of cortical folding. Results also showed a significant hemisphere × diagnostic group interaction for fissurization, although this effect was attributable to reduced cortical folding in the left hemisphere (as opposed to increased right hemisphere folding) in schizophrenic patients compared with control subjects. Although the FI was used to assess disturbances in the anterior cingulate cortex, more regional differences in cortical folding were not examined on the lateral surfaces of the cerebral hemispheres.

Although relatively few studies have examined regional cortical folding abnormalities in schizophrenia, disturbances in the right frontal (Narr et al 2001; Vogeley et al 2000, 2001) and left temporal lobes (Jakob and Beckmann 1986; Kikinis et al 1994) seem most implicated. Small sample sizes and methodologic differences, however, make comparisons between previous studies tenuous. For example, some investigators have relied on qualitative assessments of gyrification, whereas others have compared gyrification patterns within only a single set of sectioning planes and/or from only a few brain slices in one cortical region. Furthermore, several existing studies have compared only male subjects. Enormous variation exists in normal brain structure that has been linked with individual differences, including gender, age, and handedness, as well as the unique contributions of genes and environment (Geschwind et al 2002; Narr et al 2003; Thompson et al 2001a). Furthermore, changes in gyrification that might be associated with these factors might also interact with the pathophysiologic mechanisms contributing to schizophrenia. Larger sample sizes and the investigation of relationships with other demographic variables might thus be necessary to better characterize gyrification abnormalities in schizophrenia.

To clarify previous findings of disturbed cortical complexity in schizophrenia, we measured gyral complexity in 3D, using cortical surface models extracted from high-resolution MRI volumes obtained from each subject (Blanton et al 2001; Narr et al 2001). Gyral complexity, defined as the frequency of sulcal/gyral convolutions relative to the surface area measured from five distinct hemispheric regions, was then compared between patients with first-episode schizophrenia and healthy control subjects similar in age. Previous evidence suggests that cortical complexity increases in association with brain growth until late adolescence but remains relatively stable in adulthood (Armstrong et al 1995; Blanton et al 2001; Chi et al 1977). We therefore predicted that gyrification abnormalities, if present, would predate the onset of schizophrenia and manifest in patients experiencing their first episode. Furthermore, on the basis of findings of at least four prior investigations (Kikinis et al 1994; Narr et al 2001; Vogeley et al 2000, 2001), we hypothesized that schizophrenia patients would exhibit increased gyral complexity primarily in right frontal and left temporal lobe regions. As a second major goal, we sought to assess whether the pathophysiologic mechanisms contributing to gyrification abnormalities in schizophrenia are associated with sexually dimorphic developmental processes (Davatzikos and Resnick 1998; Good et al 2001; Harasty et al 1997; Yucel et al 2001) and hemispheric asymmetries (Beaton 1997; DeLisi et al 1997; Falkai et al 1995).

Methods and Materials

Subjects

Subjects included 50 patients (33 male, 17 female) experiencing their first episode of schizophrenia and 50 healthy comparison subjects (33 male, 17 female), group-matched for age (patients: 25.5 ± 4.5 years [mean ± SD]; control subjects: 27.8 ± 7.3 years). A structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott 1978) and the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID; Spitzer et al 1995) were used to determine patients' diagnostic status. Patients were assessed longitudinally to confirm diagnoses made at the initial episode. Before the initial episode, age of presentation of first psychotic symptoms for patients was 22.1 ± 4.3 years (this information was unavailable for three subjects). Psychopathology was assessed according to the Schedule for Affective Disorders and Schizophrenia Change Version and the Scale for the Assessment of Negative Symptoms (Andreasen 1984). The interval between admission into the study and date of scanning for all subjects was 11.7 ± 35.7 days. Thirty-two patients were drug-free at the time of scanning. The median number of weeks of antipsychotic medication received by the remaining 18 patients before scanning was 1 (range: <1–26 weeks).

Healthy comparison subjects had no history of psychiatric illness as determined by clinical interview with the SCID (nonpatient version). Exclusion criteria for all subjects included serious neurologic or endocrine disorders, any medical condition or treatment known to affect the brain, or meeting DSM-IV criteria for mental retardation. The North Shore-Long Island Jewish Health System institutional review board approved all procedures, and written informed consent was obtained from all subjects.

Image Acquisition and Preprocessing

High-resolution 3D spoiled gradient MR images were obtained on a GE 1.5 Tesla scanner (General Electric, Milwaukee, Wisconsin) as a series of 124 contiguous 1.5-mm coronal brain slices (256 × 256 matrix, .86 mm × .86 mm in-plane resolution). Image volumes were corrected for magnetic field inhomogeneities (Sled and Pike 1998; Zijdenbos and Dawant 1994), and nonbrain tissue, including the scalp, bone, and meninges were manually removed from each brain slice (interrater reliability for scalp editing procedures, r_I = .99). Measures of total brain volume were obtained from the scalp-edited brain volumes in native scanner space. Image volumes were then resampled into 1-mm isotropic voxels and placed into the standard coordinate system of the ICBM-305 average brain (Mazziotta et al 1995) with a three-translation and three-rotation rigid-body transformation with no scaling (Narr et al 2002a; Sowell et al 1999). This procedure corrects for differences in head alignment (but not size) between subjects.

Cortical surfaces representing the gray matter/external cerebrospinal fluid boundaries were extracted from each MR volume with a 3D active surface algorithm that successively deforms a spherical mesh onto the cortex, thus resolving the gyral pattern of each individual (MacDonald et al 1994). The parametric models of the cortex, consisting of a mesh of discrete triangular elements, were then used to outline the primary cortical sulci/

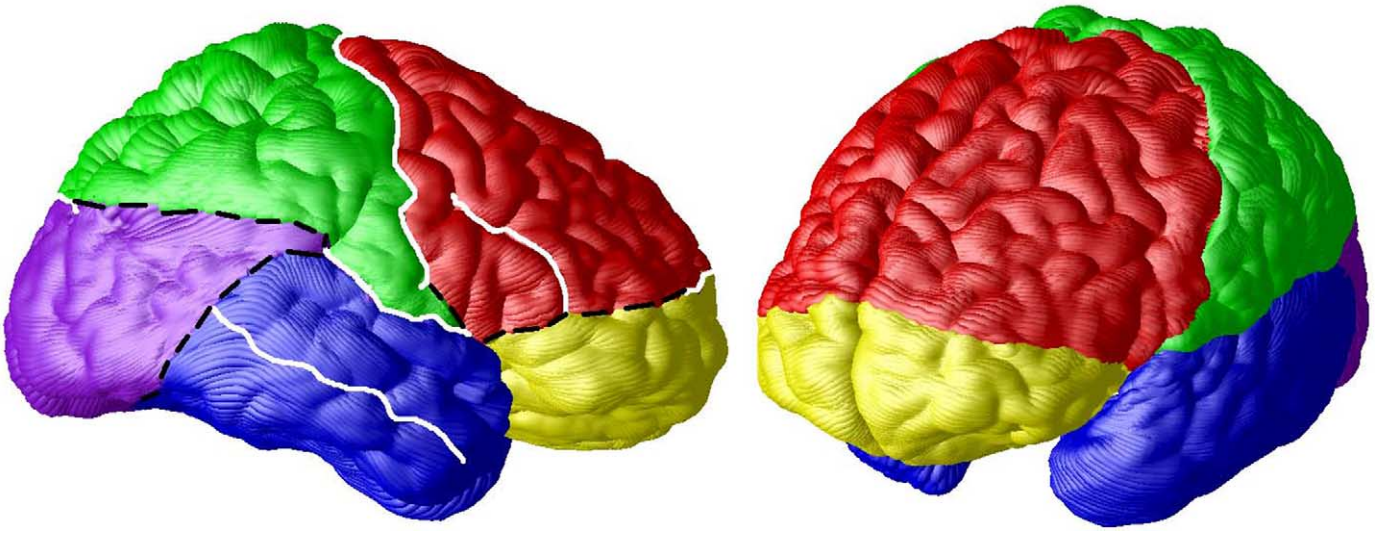

Figure 1. The termination points of specific sulci (shown in white) were used as guides to divide the hemispheric surface meshes into five homologous cortical regions in each individual. The five cortical surface meshes are shown in color in the right and left hemispheres.

gyri in each hemisphere according to validated anatomic delineation protocols (www.loni.ucla.edu/~esowell/new_sulcvar-.html) (Narr et al 2001; Sowell et al 2002; Thompson et al 2001b). Interrater reliability of manual outlining was measured as the 3D root mean square difference in millimeters between 100 equidistant points from each sulcal landmark in six test brains that were traced by one rater (SK) and compared with a gold standard arrived at by a consensus of raters. The 3D root mean square distance was <2 mm, and on average <1 mm, for all landmarks relative to the gold standard.

Sulcal/gyral landmarks and the cortical surface models were then used to compute a 3D vector deformation field, relating the amount of x, y, and z coordinate shift (or deformation) between equivalent surface locations on the cortical surface of each individual to homologous point locations on a cortical surface model averaged for the entire sample. Cortical pattern-matching procedures, used to spatially relate cortical folding patterns between subjects, have been detailed previously (Thompson et al 2000, 2001a, 2001b). Cortical matching is necessary to make the cortical surface meshes uniform and spatially homologous but to leave the configuration of gyral anatomy intact in each individual. The group-averaged cortical surface, composed of a parametric mesh, is used only to reference the same cortical locations between cortical surface meshes from each individual that remain in native scanner space. The main reason that the cortical matching is performed is so that, in every subject, an identical parametric mesh with the same number of nodes can be adapted to the lobar anatomy of each subject. Certain manually delineated sulcal landmarks were then chosen to divide the cortex into five separate surface meshes per hemisphere, to allow gyral complexity to be measured in five distinct neuroanatomic regions. The matching of sulcal features at the boundaries of the lobes also allows the parametric meshes to be adjusted precisely to fit the anatomic boundaries of each subject, which are highly variable across subjects.

The five hemispheric meshes included 1) superior frontal (dorsolateral); 2) inferior frontal (orbitofrontal); 3) temporal; 4) parietal; and 5) occipital regions in each hemisphere (Figure 1). Superior frontal regions included cortex anterior to the central sulcus. Inferior boundaries extended from the intersection of the central sulcus and Sylvian fissure to the inferior points of the inferior frontal and frontomarginal sulci. Inferior frontal regions included orbitofrontal cortices bordered by superior frontal region boundaries. Temporal regions were defined to include cortex inferior to the Sylvian fissure. Posterior boundaries followed a line from the posterior extrema of the Sylvian fissures (horizontal ramus) to the posterior extrema of the inferior temporal sulci and the collateral sulci on the inferior surface of the brain. The occipital notch was not included as a landmark because it is not reliably distinguishable on the hemispheric surfaces. Parietal regions were defined to include cortices posterior to the central sulci and anterior to the parietal–occipital fissure. Temporal region boundaries were used as the inferior boundaries. Occipital regions included cortex bordered by parietal and temporal regions anteriorly.

Gyral Complexity

Gyral complexity (and/or fractal dimension) was defined as the rate at which the surface area of the cortical surface increases relative to increases in the spatial frequency of the surface used to represent it (Thompson et al 1996). The frequency of cortical folding was estimated in 3D, whereby the rate of gyrification was computed by gridding each of the hemispheric surface meshes at many different resolutions. Ordered hierarchies of parametric meshes were thus obtained for each cortical region with variable resolution, where each cortical mesh is represented as $I \times J$ mesh points. Resolution was varied by allowing I to range from 2 to 100 while holding J fixed. If $A\{M_{IJ}\}$ represents the surface area of the cortical surface mesh M_{IJ}, the fractal dimension or complexity is computed by $Dim_F = 2-\{\partial \ln A\{M_{IJ}\}/\partial \ln (1/I)\}$. The gradient of the multifractal plot is obtained by the least squares regression of the function $\ln A\{M_{IJ}\}$ against $\ln (1/I)$, over the range $2 \leq I \leq 100$ (Thompson et al 1996). The highest resolution of the surface mesh sampling is similar to the image resolution (1 mm^3) and sufficient to capture the details of cortical surface folding patterns. The average area per mesh node on the brain surface at the highest mesh resolution = 1.63 mm^2, range .71–2.29 across all cortical regions. Therefore, to obtain complexity measures for each hemispheric subregion, the logarithmic least squares regression of surface area was plotted against the log of spatial

Table 1. Brain Volumes (cm^3) and Gyral Complexity Measures in Groups Defined by Diagnosis and Gender

	First Episode Patients		Normal Control Subjects	
	Male ($n = 33$)	Female ($n = 17$)	Male ($n = 33$)	Female ($n = 17$)
Intracranial Volume	1267.1 (132.7)	1104.2 (134.9)	1274.8 (93.7)	1142.9 (68.4)
Left Temporal	2.156 (.0046)	2.154 (.0027)	2.155 (.0044)	2.154 (.0034)
Right Temporal	2.155 (.0045)	2.155 (.0042)	2.156 (.0059)	2.170 (.0644)
Left Superior Frontal	2.174 (.0093)	2.170 (.0058)	2.170 (.0097)	2.166 (.0065)
Right Superior Frontal	2.173 (.0326)	2.159 (.0102)	2.157 (.0098)	2.162 (.0155)
Left Occipital	2.165 (.0042)	2.165 (.0071)	2.163 (.0063)	2.163 (.0048)
Right Occipital	2.171 (.0146)	2.167 (.0084)	2.164 (.0046)	2.181 (.0593)
Left Parietal	2.162 (.0046)	2.164 (.0072)	2.162 (.0047)	2.164 (.0061)
Right Parietal	2.166 (.0062)	2.165 (.0088)	2.165 (.0047)	2.167 (.0058)
Left Inferior Frontal	2.159 (.0078)	2.158 (.0090)	2.159 (.0068)	2.157 (.0062)
Right Inferior Frontal	2.162 (.0087)	2.158 (.0091)	2.159 (.0079)	2.156 (.0060)

Data are presented as mean (SD).

frequency for regional surface meshes. The slopes of these plots were derived and added to 2.00. For a flat surface, the slope is zero and the dimension is 2.00, with no additional detail added by representing the surface at a higher spatial frequency. Complexity values larger than 2.00 indicate more cortical convolutions; a surface with a complexity value of 3.00 would fill nearly all of 3D space. Gyral complexity measures thus range between 2.00 and 3.00.

Statistical Analyses

To examine differences in gyral complexity, 2 (gender) × 2 (diagnosis) × 2 (hemisphere) analyses of variance (ANOVAs) were used. Gender and diagnosis were treated as between-subject variables, and right and left hemispheric measures from the five cortical subregions were used as repeated measures (within-subject variables). All main effects and interactions were included in the model. Effects of hemisphere (asymmetries) and interactions between hemisphere and gender and diagnosis were thus also included. Type I error was controlled by adopting Bonferroni corrections for the five separate ANOVAs ($p < .01$). Simple interactions and/or univariate tests of simple effects were performed only in the presence of significant omnibus results. Dependent measures were not corrected for brain size because the frequency of gyral folding is computed relative to the surface area of the subregion, so the magnitude of the surface area is already factored out of the measure. A previous study using similar methodology, however, found raw brain volumes to be significantly associated with complexity measures as a biological effect in scaled brain volumes (Narr et al 2001). Therefore, to ensure that brain volume did not contribute significantly to the variance, we examined relationships between brain volume and complexity measures. Finally, to examine whether the groups defined by gender and diagnosis differed with respect to global brain volumes, we used a 2 (gender) × 2 (diagnosis) ANOVA.

Results

A significant gender effect was found for raw brain volume [$F(1,96) = 38.68$, $p < .001$], with men exhibiting greater brain volumes than women. No significant effects of diagnosis [$F(1,96) = .96$, $p > .1$] or gender × diagnosis interactions [$F(1,96) = .43$, $p > .1$] were detected. Means and SDs for raw brain volume within each group are shown in Table 1. Significant relationships were absent between gyral complexity and raw brain volume across all groups (median Pearson's $r = .07$; range $-.1$ to .19, $p > .1$). Overall, these relationships were also absent within groups defined by gender (men: median $r = -.03$; range $-.16$ to .02; women: median $r = .08$; range $-.06$ to .41) or diagnosis (patients: median $r = .01$; range $-.18$ to .23; control subjects: median $r = .14$; range $-.26$ to .19). Brain volume was thus not included as a covariate in subsequent analyses.

Main effects of diagnosis were absent for all of the regional complexity measures. A significant diagnosis × gender × hemisphere interaction, however, was present for the superior frontal region [$F(1,96) = 5.71$, $p < .01$]. Follow-up analyses showed significant diagnosis [$F(1,64) = 6.87$, $p < .01$] and diagnosis × hemisphere effects in comparisons between male subjects for superior frontal gyral complexity [$F(1,64) = 5.21$, $p < .02$] but not between female diagnostic groups. Examination of simple effects revealed that gyral complexity was increased in the right hemisphere [$F(1,64) = 6.98$, $p < .01$] in male schizophrenic patients compared with male comparison subjects but not in the left hemisphere [$F(1,64) = 1.04$, $p > .1$].For right superior frontal complexity, however, the male patient group variance divided by the male control within-group variance = 3.32 (F_{max}). Levene's equality of variance test showed that variances between the two male groups were significantly different [$F(1,64) = 19.36$, $p < .001$]. Importantly, comparisons of right hemisphere superior frontal complexity between male patients and male control subjects remained significant after the use of unequal variance assumptions in the univariate test [$F(1,37.8) = 2.64$, $p < .01$]. Figure 2 shows brains exhibiting increased and decreased gyral complexity in the right superior frontal cortices as compared with the mean gyral complexity. Figure 3 plots gyral complexity measures from the superior frontal lobe in both hemispheres in groups defined by gender and diagnosis.

No additional interactions with diagnosis were significant for any of the remaining regional gyral complexity measures; however, a trend toward a significant diagnosis × gender × hemisphere interaction was observed for occipital lobe gyral complexity [$F(1,96) = 4.0$, $p < .05$], but this effect did not survive Bonferroni correction. Means for the five gyral complexity measures are shown in Table 1 for each hemisphere in groups defined by gender and diagnosis. Table 2 shows the magnitude of diagnostic group effects (Cohen's d) within groups defined by gender for each hemisphere. Cohen's d (Cohen 1988) is the standardized mean difference between groups, by which effect sizes can be categorized as small ($d = .2$), medium ($d = .5$), or large ($d = .8$). Effect sizes show that diagnostic group differences

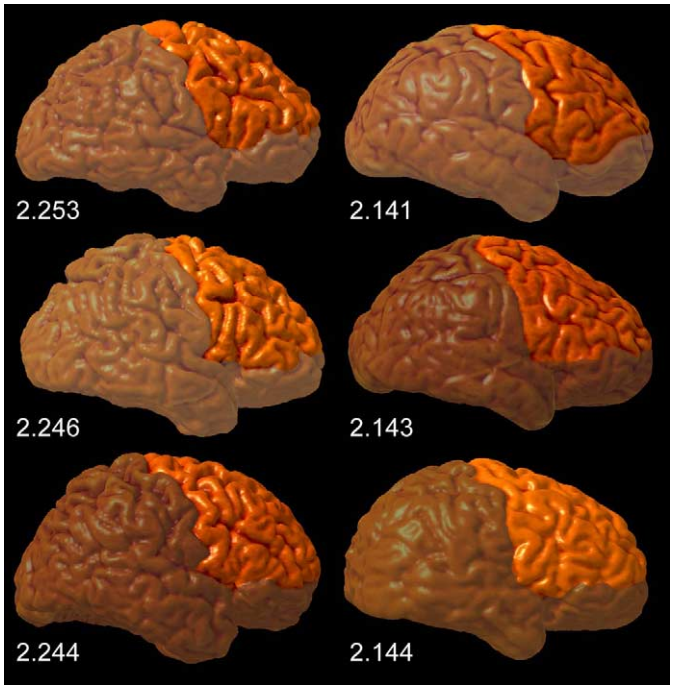

Figure 2. Cortical surface models highlighting the right superior frontal region to illustrate interindividual differences in gyral complexity. Examples of brains exhibiting increased (left) and decreased (right) gyral complexity in superior frontal cortices as compared with the mean. Gyral complexity indices are shown below each cortical surface model.

between men for the right occipital region are only slightly smaller in magnitude compared with the significant result observed for the right superior frontal region. Left hemisphere

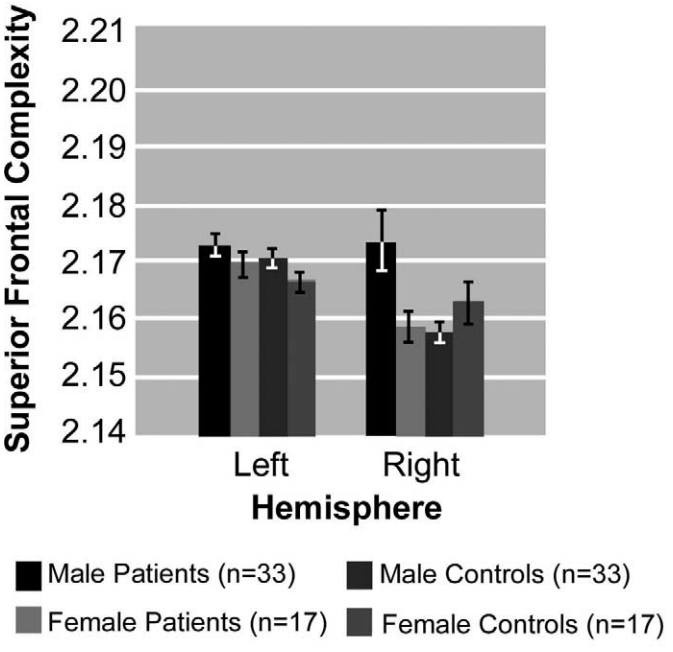

Figure 3. Gyral complexity indices and standard errors for the right and left superior frontal cortex in groups defined by gender and diagnosis. The left hemisphere is more complex overall ($p < .002$), although gyral folding is increased in male patients compared with male control subjects in the right hemisphere ($p < .01$).

superior frontal complexity also shows a medium effect size when female diagnostic groups are contrasted (Cohen 1988).

Finally, significant main effects of hemisphere (asymmetry) were observed in the omnibus ANOVAs performed for the five hemispheric cortical complexity measures. Main effects of asymmetry were detected for the superior frontal cortices [$F(1,96) = 10.06$, $p < .002$], with the left hemisphere showing increased gyral complexity across all groups (Figure 3). Occipital [$F(1,96) = 5.68$, $p < .01$] and parietal regions [$F(1,96) = 20.35$, $p < .001$] also showed significant hemisphere effects, with increased gyral complexity in the right compared with the left hemisphere. No main effects of gender were observed for any of the complexity measures after Bonferroni correction.

Discussion

Gyral complexity reflects whether a cortical region of interest contains more sulcal bifurcations and captures differences in the patterns of gyral geometry as might occur during neurodevelopment and/or in association with disease (Armstrong et al 1995; Blanton et al 2001; Narr et al 2001; Thompson et al 1996, 1998). Sexually dimorphic developmental processes and differences in hemispheric connectivity contribute to the organization and/or frequency of gyrification (Bilder et al 1994; Narr et al 2001; Van Essen 1997; Yucel et al 2001, 2002). Furthermore, individual differences in the patterns of cortical folding seem to be driven by both genetic and epigenetic factors (Bartley et al 1997; Biondi et al 1998; Lohmann et al 1999; Steinmetz et al 1995; Thompson et al 2001a). By studying disturbances in gyrification, which occur after neuronal migration is complete (Beaton 1997), the temporal patterns and the biological mechanisms contributing to schizophrenia neuropathology, as well as the modulating effects of gender and hemisphere, might be elucidated (DeLisi et al 1997; Falkai et al 1995).

To confirm the presence of gyrification abnormalities in schizophrenia and to investigate interactions with gender and hemisphere, we examined gyral complexity in patients experiencing their first episode of schizophrenia compared with demographically matched healthy comparison subjects. Patients were studied at first episode and had received little or no prior medication exposure. Therefore, any observed alterations in gyrification would suggest the presence of early neurodevelopmental rather than progressive neurodegenerative disturbances. Furthermore, although some regional brain abnormalities are well replicated in schizophrenia, global changes in brain structure appear largely below the threshold of significance. These observations suggest that some functional systems are more susceptible than others to disease processes in schizophrenia (Shenton et al 2001). Relationships have been demonstrated between cortical folding patterns and the underlying cytoarchitectonic and connectional characteristics of cortical regions (Caviness 1975; Rademacher et al 1993; Rakic 1988; Shapleske et al 1999; Watson et al 1993). We therefore divided the cortex into five functionally relevant cortical regions on the lateral surface of each hemisphere to examine regional differences in 3D gyral complexity in schizophrenia.

As consistent with the results of two earlier investigations that used the GI to investigate abnormal gyrification in schizophrenia, male patients were shown to exhibit significant increases in gyral complexity in right superior frontal cortices, compared with healthy male subjects (Vogeley et al 2000, 2001). Results are also compatible with the mean gyral complexity increases reported for this region in chronic schizophrenia (Narr et al 2001),

Table 2. Magnitude of Diagnostic Group Effects (Cohen's *d*) for Regional Gyral Complexity Measures Within Groups Defined by Gender

	Male Patients ($n = 33$) Versus Male Control Subjects ($n = 33$)		Female Patients ($n = 17$) Versus Female Control Subjects ($n = 17$)	
	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere
Temporal	−.19	.22	−.32	−.02
Superior Frontal	.67	.42	−.22	.64
Occipital	.64	.37	−.33	.33
Parietal	.18	.09	−.26	−.10
Inferior Frontal	.36	.01	.25	.12

Positive values indicate increases in gyral complexity in schizophrenia patients compared with healthy comparison subjects. Negative values indicate increases in gyral complexity in healthy comparison subjects relative to patients.

although interactions between diagnosis and gender were below the threshold of significance. Results, however, contrast with findings of significant decreases in left hemisphere GIs in anterior (cortex rostral to the coronal section where the temporal lobe first appears) and posterior brain regions in male patients with schizophrenia ($n = 9$) compared with male control subjects ($n = 9$) (Kulynych et al 1997). Right hemisphere effects and relationships with gender (only male subjects were examined) were not assessed, however, which prevented comparisons of right hemisphere findings. Furthermore, the GI was quantified in coronal sections that were 4 mm apart, perhaps accounting for differences in left hemisphere findings. Our results also differ from those of Yucel et al (2002), who used the FI to determine the rate of cortical folding in each hemisphere as well as in anterior cingulate regions. Findings included decreased fissurization in the left hemisphere and within anterior cingulate cortices in male schizophrenic patients compared with male control subjects. Yucel et al (2002), however, did not examine regional differences in gyral complexity on the lateral hemispheric surfaces, and gyral complexity was not measured on the medial hemispheric surfaces in our investigation.

In contrast to previous findings of increased gyral vertical orientation and sulcal interruptions in left temporal cortices in schizophrenia (Kikinis et al 1994), we failed to detect significant changes in gyral complexity in temporal lobe regions in first-episode patients. Different features of gyral anatomy were studied, however, which perhaps explains discrepancies in results. Our findings suggest that gray matter deficits, as widely observed in lateral and medial temporal lobe regions in schizophrenia (Narr et al 2002b; Narr et al, in press; Shenton et al 2001), are not accompanied by changes in gyral frequency; however, the cortical surfaces, obtained from deforming a spherical mesh to fit the signal intensity thresholds between cortical gray matter and extracortical cerebrospinal fluid, do not extend into the deep surfaces of individual sulci (or into insula cortex). Therefore, abnormalities in the folding patterns of Heschl's gyri and/or the planum temporale (Gur and Chin 1999; Kwon et al 1999) might have remained undetected. Furthermore, the width and depth of cortical sulci might influence the complexity metric, such that more atrophied brains might exhibit increases in gyral complexity. In our study, groups were similar in age, and brain sizes were not significantly different in schizophrenic patients. Therefore, diagnosis-specific reductions in global brain tissue do not explain the increased gyral complexity observed in patients; however, it is possible that focal areas of atrophy might affect complexity measurements made at the regional level, such as in superior frontal cortices. Although gender × diagnosis interactions were absent for the four remaining cortical regions studied, a trend also suggested increased right hemisphere gyral complexity in male patients for the occipital region (Table 2). Additionally, left superior frontal complexity was larger in female patients compared with female control subjects (Table 2), although this effect was not identified as significant in statistical tests.

Structural asymmetries are shown to occur before gyrification during neurodevelopment (Beaton 1997). That is, volumetric asymmetries occur early in the second trimester, whereas gyrification seems to commence toward the end of the second and during the third trimester (Armstrong et al 1995; DeLacoste et al 1991; Hering-Hanit et al 2001). Disturbances in the hemispheric patterns of gyral folding suggest that harmful environmental events and/or genetic factors contribute to interrupt neurodevelopmental processes before gyrification is complete. Reversals in the direction of asymmetry for the frequency of gyral folding in superior frontal cortices were previously documented in chronic schizophrenia (Narr et al 2001). Patients showed leftward asymmetries (i.e., increased gyrification in the left hemisphere), whereas control subjects showed rightward asymmetries. Such effects were absent in the current investigation, in which leftward asymmetries were observed in both patient and healthy comparison groups. The asymmetry of gyral frequency in control subjects and not schizophrenia patients therefore differed between studies. Discrepancies in findings might be attributable to differences in demographic characteristics or might perhaps illustrate the pitfalls of using smaller sample sizes; in the Narr et al (2001) study, the sample size was half that of the current investigation.

Main effects of hemisphere were shown in occipital and parietal regions (right GI larger than left), as well as the superior frontal lobe (left larger). Two previous investigations using the FI showed significant asymmetries in hemispheric fissurization (left larger) that were pronounced in male compared with female subjects (Yucel et al 2001, 2002). In contrast, Zilles et al (1988), who used the GI to quantify gyral frequency, did not detect significant hemispheric asymmetries in cortical folding. In a normative sample of young adults, hemispheric complexity differences were demonstrated in the same cortical regions as in our study (i.e., frontal, parietal, and occipital regions) (Luders et al, unpublished data). Given the direction of asymmetries observed for gyral folding, it is possible that increases in cortical surface area occur to compensate for the right frontal and left occipital petalias documented in human and nonhuman primates (Chiu and Damasio 1980; Hopkins and Marino 2000; Zilles et al 1996). That is, because brain growth is restricted by the size of

the intracranial cavity, and the inner skull forms asymmetries complementary to petalias (Daniel et al 1989; Faglioni and Scarpa 1989; Gundara and Zivanovic 1968; Holloway 1981), increased surface area caused by increased folding might occur in regions with smaller hemispheric volumes (left frontal and right occipital regions).

There is some evidence to suggest that gender differences exist in the frequency of cortical folding (Yucel et al 2001), although others disagree (Nopoulos et al 2000; Zilles et al 1988). Significant main effects of gender were not detected in this investigation. Gender differences, however, were not examined exclusively within healthy subjects, and the numbers of male and female subjects were not equally matched (Table 1). Using the same methodological approach, Luders et al (unpublished data) showed significant increases in gyral complexity in female subjects in parietal and superior frontal cortices bilaterally, and in left inferior frontal cortex. In our study, mean differences in the frequency of right superior frontal gyral folding were greater in male patients compared with male control subjects but larger in normal female subjects compared with female patients (Figure 3). This might support previous data suggesting that mechanisms producing normal sexual dimorphisms are disturbed in schizophrenia, particularly at the cortex (Goldstein et al 2002; Yucel et al 2002). Two prior studies using the GI failed to detect gender differences in gyral frequency between the hemispheres (Nopoulos et al 2000; Zilles et al 1988), although regional differences in gyral frequency were not examined in these prior investigations.

The hypothesis that schizophrenia is of neurodevelopmental origin is now the most widely accepted explanation for schizophrenia pathophysiology. From the neurodevelopmental perspective, schizophrenia is assumed an ongoing process resulting from a combination of genetic and harmful environmental factors occurring sometime between conception and adulthood, rather than the result of a specific static event (Harrison 1999; Woods 1998). Interestingly, both genetic and environmental factors have been shown to influence cortical folding patterns. For example, hypoxia in the second trimester might lead to lissencephaly and pachygyria (incomplete lissencephaly) (Stewart et al 1975), whereas several families of genes seem to control the production and migration of neurons toward their positions in the cortex during gyral formation (Rakic 2000). Our observations of gyrification abnormalities in first-episode schizophrenia suggest that cortical folding disturbances predate the onset of illness. More importantly, the presence of gyrification abnormalities in schizophrenia suggests that pathophysiologic mechanisms interfere with normal neurodevelopmental processes during the second and third trimester of pregnancy, when the majority of cortical folding occurs (Chi et al 1977; Huang 1991; Naidich et al 1994). Candidate mechanisms for altered gyrification might include disturbances in neurogenesis, neuronal migration, differentiation, and synaptogenesis (Jakob and Beckmann 1986). Early genetic or environmental insults, however, might lead to decreased, as opposed to increased gyrification. The events contributing to increased gyral complexity in schizophrenia might therefore occur slightly later during neurodevelopment. That is, because there seems to be a brief overshoot in cortical folding shortly after birth, mechanisms that might involve neuron and synaptic pruning and myelination (Arnold 1999) might underlie the apparent patterns of increased gyral frequency in selective cortical regions in schizophrenia.

There are many proposed models of gyrification, with some more strongly supported (Rakic 2000; Richman et al 1975; Todd 1982; Van Essen 1997; Welker 1990). Recent evidence, however, suggests that the patterns of cortical folding are influenced by functional connectivity (Van Essen 1997; Welker 1990). Therefore, misconnections in some cortical areas might lead to focal hypergyrification as was observed in the superior frontal cortices in schizophrenia (Vogeley et al 2000, 2001). Hemispheric and gender differences in the rates of normal brain maturation (Geschwind and Galaburda 1985; Yucel et al 2001) might also explain why male and not female patients show increases in gyral frequency that are hemisphere specific. For example, in the developing fetal brain, prefrontal and striate cortices seem to be the most asymmetric brain regions, with increased asymmetry in male fetuses favoring the right hemisphere. Female fetuses are likely to have two hemispheres of the same size or to exhibit subtle leftward asymmetries, which suggests that testosterone in utero might lead to a more rapid growth of the right hemisphere or, alternatively, retard the growth of the left hemisphere (DeLacoste et al 1991; Wisniewski 1998). Similar neurobiological mechanisms occurring in utero might be disturbed in schizophrenia and account for the hemisphere × gender interactions observed for gyral complexity. Only systematic investigation of the factors contributing to altered gyrification patterns, however, might help clarify exactly what neuropathologic processes are linked with this structural abnormality in schizophrenia.

This work was generously supported by research grants from the National Center for Research Resources (2 P41 RR13642 and 2 M01 RR00865), the National Institute of Mental Health (NIMH) (RO1-MH-60374), the National Library of Medicine (5 R01 LM05639), the National Institute for Biomedical Imaging and Bioengineering (EB 001561), a NIMH National Research Service Award Training Grant (MH14584), and a National Alliance for Research on Schizophrenia and Depression Young Investigator Award.

Andreasen NC (1984): *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Iowa: The University of Iowa.

Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K (1995): The ontogeny of human gyrification. *Cereb Cortex* 1:56–63.

Arnold SE (1999): Neurodevelopmental abnormalities in schizophrenia: Insights from neuropathology. *Dev Psychopathol* 11:439–456.

Bartley AJ, Jones DW, Weinberger DR (1997): Genetic variability of human brain size and cortical gyral patterns. *Brain* 120(pt 2):257–269.

Beaton AA (1997): The relation of planum temporale asymmetry and morphology of the corpus callosum to handedness, gender, and dyslexia: A review of the evidence. *Brain Lang* 60:255–322.

Bilder RM, Wu H, Bogerts B, Degreef G (1994): Absence of regional hemispheric volume asymmetries in first-episode schizophrenia. *Am J Psychiatry* 151:1437–1447.

Biondi A, Nogueira H, Dormont D, Duyme M, Hasboun D, Zouaoui A, et al (1998): Are the brains of monozygotic twins similar? A three-dimensional MR study. *Am J Neuroradiol* 19:1361–1367.

Blanton RE, Levitt JG, Thompson PM, Narr KL, Capetillo-Cunliffe L, Nobel A, et al (2001): Mapping cortical asymmetry and complexity patterns in normal children. *Psychiatry Res* 107:29–43.

Caviness VS Jr (1975): Mechanical model of brain convolutional development. *Science* 189:18–21.

Chi JG, Dooling EC, Gilles FH (1977): Gyral development of the human brain. *Ann Neurol* 1:86–93.

Chiu HC, Damasio AR (1980): Human cerebral asymmetries evaluated by computed tomography. *J Neurol Neurosurg Psychiatry* 43:873–878.

Cohen J (1988): *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, New Jersey: Lawrence Erlbaum.

Daniel DG, Myslobodsky MS, Ingraham LJ, Coppola R, Weinberger DR (1989): The relationship of occipital skull asymmetry to brain parenchymal measures in schizophrenia. *Schizophr Res* 2:465–472.

Davatzikos C, Resnick SM (1998): Sex differences in anatomic measures of interhemispheric connectivity: Correlations with cognition in women but not men. *Cereb Cortex* 8:635–640.

DeLacoste MC, Horvath DS, Woodward DJ (1991): Possible sex differences in the developing human fetal brain. *J Clin Exp Neuropsychol* 13:831–846.

DeLisi LE, Sakuma M, Kushner M, Finer DL, Hoff AL, Crow TJ (1997): Anomalous cerebral asymmetry and language processing in schizophrenia. *Schizophr Bull* 23:255–271.

Faglioni P, Scarpa M (1989): Skull asymmetries bear no relation to the occurrence of apraxia. A clinical and CT-scan study in patients with unilateral brain damage. *Cortex* 25:449–459.

Falkai P, Bogerts B, Schneider T, Greve B (1995): Disturbed planum temporale asymmetry in schizophrenia: A quantitative post-mortem study. *Schizophr Res* 14:161–176.

Geschwind DH, Miller BL, DeCarli C, Carmelli D (2002): Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. *Proc Natl Acad Sci U S A* 99:3176–3181.

Geschwind N, Galaburda AM (1985): Cerebral lateralization: Biological mechanisms, associations, pathology: II. A hypothesis and a program for research. *Arch Neurol* 42:521–552.

Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al (2002): Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Arch Gen Psychiatry* 59:154–164.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001): A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21–36.

Gundara N, Zivanovic S (1968): Asymmetry in east African skulls. *Am J Phys Anthropol* 28:331–337.

Gur RE, Chin S (1999): Laterality in functional brain imaging studies of schizophrenia. *Schizophr Bull* 25:141–156.

Harasty J, Double KL, Halliday GM, Kril JJ, McRitchie DA (1997): Language-associated cortical regions are proportionally larger in the female brain. *Arch Neurol* 54:171–176.

Harrison PJ (1999): The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 122:593–624.

Hering-Hanit R, Achiron R, Lipitz S, Achiron A (2001): Asymmetry of fetal cerebral hemispheres: In utero ultrasound study. *Arch Dis Child Fetal Neonatal Ed* 85:F194–F196.

Holloway RL (1981): Volumetric and asymmetry determinations on recent hominid endocasts: Spy I and II, Djebel Ihroud I, and the sale Homo erectus specimens, with some notes on Neanderthal brain size. *Am J Phys Anthropol* 55:385–393.

Hopkins WD, Marino L (2000): Asymmetries in cerebral width in nonhuman primate brains as revealed by magnetic resonance imaging (MRI). *Neuropsychologia* 38:493–499.

Huang CC (1991): Sonographic cerebral sulcal development in premature newborns. *Brain Dev* 13:27–31.

Jakob H, Beckmann H (1986): Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *J Neural Transm* 65:303–326.

Kikinis R, Shenton ME, Gerig G, Hokama H, Haimson J, O'Donnell BF, et al (1994): Temporal lobe sulco-gyral pattern anomalies in schizophrenia: An in vivo MR three-dimensional surface rendering study. *Neurosci Lett* 182:7–12.

Kulynych JJ, Luevano LF, Jones DW, Weinberger DR (1997): Cortical abnormality in schizophrenia: An in vivo application of the gyrification index. *Biol Psychiatry* 41:995–999.

Kwon JS, McCarley RW, Hirayasu Y, Anderson JE, Fischer IA, Kikinis R, et al (1999): Left planum temporale volume reduction in schizophrenia. *Arch Gen Psychiatry* 56:142–148.

Lohmann G, von Cramon DY, Steinmetz H (1999): Sulcal variability of twins. *Cereb Cortex* 9:754–763.

MacDonald D, Avis D, Evans AC (1994): Multiple surface identification and matching in magnetic resonance imaging. *Proc SPIE* 2359:160–169.

Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J (1995): A probabilistic atlas of the human brain: Theory and rationale for its development (ICBM). *Neuroimage* 2:89–101.

Naidich TP, Grant JL, Altman N, Zimmerman RA, Birchansky SB, Braffman B, Daniel JL (1994): The developing cerebral surface. Preliminary report on the patterns of sulcal and gyral maturation—anatomy, ultrasound, and magnetic resonance imaging. *Neuroimaging Clin N Am* 4:201–240.

Narr K, Thompson P, Szesko P, Robinson D, Jang S, Woods R, et al (in press): Regional specificity of hippocampal volume reductions in first episode schizophrenia. *Neuroimage*.

Narr KL, Cannon TD, Woods RP, Thompson PM, Kim S, Asunction D, et al (2002a): Genetic contributions to altered callosal morphology in schizophrenia. *J Neurosci* 22:3720–3729.

Narr KL, Sharma T, Woods RP, Thompson PM, Sowell E, Rex D, et al (2003): Regional subarachnoid CSF increases without apparent cortical gray matter deficits in schizophrenia: The modulating effects of sex and age. *Am J Psychiatry* 160:2169–2180.

Narr KL, Thompson PM, Moussai J, Zoumalan C, Rayman J, Toga AW (2001): 3d mapping of gyral shape and cortical surface asymmetries in schizophrenia: Gender effects. *Am J Psychiatry* 158:244–255.

Narr KL, van Erp TG, Cannon TD, Woods RP, Thompson PM, Jang S, et al (2002b): A twin study of genetic contributions to hippocampal morphology in schizophrenia. *Neurobiol Dis* 11:83–95.

Noga JT, Bartley AJ, Jones DW, Torrey EF, Weinberger DR (1996): Cortical gyral anatomy and gross brain dimensions in monozygotic twins discordant for schizophrenia. *Schizophr Res* 22:27–40.

Nopoulos P, Flaum M, O'Leary D, Andreasen N (2000): Sexual dimorphism in the human brain: Evaluation of tissue composition and surface anatomy using magnetic resonance imaging. *Psychiatry Res* 98:1–13.

Rademacher J, Caviness VS Jr, Steinmetz H, Galaburda AM (1993): Topographical variation of the human primary cortices: Implications for neuroimaging, brain mapping, and neurobiology. *Cereb Cortex* 3:313–329.

Rakic P (1988): Specification of cerebral cortical areas. *Science* 241:170–176.

Rakic P (2000): Radial unit hypothesis of neocortical expansion. *Novartis Found Symp* 228:30–42.

Richman D, Stewart R, Hutchinson J, Caviness V (1975): Mechanical model of brain convolutional development. *Science* 189:18–21.

Shapleske J, Rossell SL, Woodruff PW, David AS (1999): The planum temporale: A systematic, quantitative review of its structural, functional and clinical significance. *Brain Res Brain Res Rev* 29:26–49.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001): A review of MRI findings in schizophrenia. *Schizophr Res* 49:1–52.

Sled JG, Pike GB (1998): Standing-wave and RF penetration artifacts caused by elliptic geometry: An electrodynamic analysis of MRI. *IEEE Trans Med Imaging* 17:653–662.

Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW (1999): Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9:587–597.

Sowell ER, Thompson PM, Rex D, Kornsand D, Tessner KD, Jernigan TL, Toga AW (2002): Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: Maturation in perisylvian cortices. *Cereb Cortex* 12:17–26.

Spitzer R, Gibbon M, Williams J (1995): *Structured Clinical Interview for Axis I DSM-IV Disorders (SCID)*. Washington, DC: American Psychiatric Association.

Spitzer RL, Endicott J (1978): *Schedule for Affective Disorders and Schizophrenia–Lifetime Version*. New York: New York State Psychiatric Institute, Biometrics Research.

Steinmetz H, Herzog A, Schlaug G, Huang Y, Jäncke L (1995): Brain (a) symmetry in monozygotic twins. *Cereb Cortex* 5:296–300.

Stewart RM, Richman DP, Caviness VS Jr (1975): Lissencephaly and pachygyria: An architectonic and topographical analysis. *Acta Neuropathol (Berl)* 31:1–12.

Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, et al (2001a): Genetic influences on brain structure. *Nat Neurosci* 4:1253–1258.

Thompson PM, Moussai J, Zohoori S, Goldkorn A, Khan AA, Mega MS, et al (1998): Cortical variability and asymmetry in normal aging and Alzheimer's disease. *Cereb Cortex* 8:492–509.

Thompson PM, Schwartz C, Lin RT, Khan AA, Toga AW (1996): Three-dimensional statistical analysis of sulcal variability in the human brain. *J Neurosci* 16:4261–4274.

Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, et al (2001b): Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci U S A* 98:11650–11655.

Thompson PM, Woods RP, Mega MS, Toga AW (2000): Mathematical/

computational challenges in creating deformable and probabilistic atlases of the human brain. *Hum Brain Mapp* 9:81–92.
Todd PH (1982): A geometric model for the cortical folding pattern of simple folded brains. *J Theor Biol* 97:529–538.
Van Essen DC (1997): A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 385:313–318.
Vogeley K, Schneider-Axmann T, Pfeiffer U, Tepest R, Bayer TA, Bogerts B, et al (2000): Disturbed gyrification of the prefrontal region in male schizophrenic patients: A morphometric postmortem study. *Am J Psychiatry* 157:34–39.
Vogeley K, Tepest R, Pfeiffer U, Schneider-Axmann T, Maier W, Honer WG, Falkai P (2001): Right frontal hypergyria differentiation in affected and unaffected siblings from families multiply affected with schizophrenia: A morphometric MRI study. *Am J Psychiatry* 158:494–496.
Watson JD, Myers R, Frackowiak RS, Hajnal JV, Woods RP, Mazziotta JC, et al (1993): Area v5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex* 3:79–94.
Welker WI (1990): The significance of foliation and fissuration of cerebellar cortex. The cerebellar folium as a fundamental unit of sensorimotor integration. *Arch Ital Biol* 128:87–109.
Wisniewski AB (1998): Sexually-dimorphic patterns of cortical asymmetry, the role for sex steroid hormones in determining cortical patterns of lateralization. *Psychoneuroendocrinology* 23:519–547.
Woods BT (1998): Is schizophrenia a progressive neurodevelopmental disorder Toward a unitary pathogenetic mechanism. *Am J Psychiatry* 155:1661–1670.
Yucel M, Stuart GW, Maruff P, Velakoulis D, Crowe SF, Savage G, Pantelis C (2001): Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: An MRI morphometric study. *Cereb Cortex* 11:17–25.
Yucel M, Stuart GW, Maruff P, Wood SJ, Savage GR, Smith DJ, et al (2002): Paracingulate morphologic differences in males with established schizophrenia: A magnetic resonance imaging morphometric study. *Biol Psychiatry* 52:15–23.
Zijdenbos AP, Dawant BM (1994): Brain segmentation and white matter lesion detection in MR images. *Crit Rev Biomed Eng* 22:401–465.
Zilles K, Armstrong E, Schleicher A, Kretschmann HJ (1988): The human pattern of gyrification in the cerebral cortex. *Anat Embryol* 179:173–179.
Zilles K, Dabringhaus A, Geyer S, Amunts K, Qu M, Schleicher A, et al (1996): Structural asymmetries in the human forebrain and the forebrain of non-human primates and rats. *Neurosci Biobehav Rev* 20:593–605.