The nature and extent of callosal morphological alterations in schizophrenia remain unresolved. A parametric surface modeling approach using magnetic resonance (MR) images was employed. This provided spatially accurate representations of midsagittal callosal surfaces in schizophrenic patients (n = 25; 15 males) and normal controls (n = 28; 15 males). Areas of functionally relevant callosal channels and measures reflecting callosal shape were visualized and compared across groups. To register neuroanatomical landmarks surrounding the corpus callosum, each three-dimensional MR volume was scaled according to Talairach AC–PC distance, and raw distances included as covariates in multivariate analyses. Results revealed: (i) a marked vertical displacement of the corpus callosum in patients (P < 0.01); (ii) increases in curvature of superior and inferior callosal surfaces (P < 0.001); and (iii) significant increases in maximum widths in anterior and posterior regions in male patients compared to male controls; as well as (iv) increased patterns of callosal variability in female patients but no effects of diagnosis between female groups. These findings demonstrate a clear index of structural neuropathology in male schizophrenic patients. Displacement and curvature increases were highly correlated with structural differences in surrounding neuroanatomical regions, including increased volume of the lateral ventricles (P < 0.01).

Introduction

The corpus callosum plays an integral role in relaying sensory, motor and cognitive information from homologous regions in the two cerebral hemispheres. Given that cognitive impairments and both bilateral and unilateral neuroanatomic structural abnormalities are characteristic in schizophrenia, the morphology of the corpus callosum has stimulated much research (Nasrallah et al., 1986; Umematsu et al., 1988; Rossi et al., 1989; Woodruff et al., 1993, 1997; Jacobsen et al., 1997). Most investigations have used ‘region of interest’ analyses to assess differences in midsagittal area, callosal length and width (Woodruff et al., 1995), while few have investigated group differences in callosal shape or in three-dimensional location (Casanova et al., 1990; DeQuardo et al., 1996). Volumetric methods are less sensitive to across-subject variability and likely capture subtle differences in anatomy between groups. Probabilistic brain atlases using magnetic resonance (MR) images retain quantitative information on interindividual neuroanatomical variability. In these approaches three-dimensional brain volumes are registered (realigned) in a standardized coordinate system to allow cross-group comparisons while preserving subtle intragroup variability patterns (Mazziotta et al., 1995; Thompson et al., 1997, 1999a,b).

Several observations motivate the study of the corpus callosum in schizophrenia (Thompson et al., 1999a): (i) callosal pruning and myelination as well as interhemispheric coherence continue to develop into early adulthood, a factor that may be relevant to age of onset in schizophrenia (Njioiktjien et al., 1994); (ii) impairments in callosal transfer have been reported in patients (David et al., 1994), implicating alterations in callosal connectivity; (iii) structural alterations in asymmetric perisylvian regions linked by the callosum have been reported (Kikinis et al., 1994; Bart et al., 1997); (iv) callosal myelination begins prenatally and is susceptible to malnutrition, asphyxia and toxins of infectious origin; also, these same events are linked with aberrant neurodevelopmental events in schizophrenia (Njioiktjien et al., 1994; Bishop and Wahlsten, 1997; Hock et al., 1998); (v) the corpus callosum forms the roof of the superior horns of the lateral ventricles, which are enlarged in schizophrenic patients (Sharma et al., 1997, 1998). In spite of evidence linking callosal abnormality to schizophrenia, imaging studies assessing alterations in callosal morphometry as well as in other cortical and subcortical structures have produced surprisingly mixed results (Woodruff et al., 1995). Interpretation of these results is further obscured by the failure of many studies to control for brain size in patient and normal populations. Since callosal size and brain size are correlated (Rauch and Jinkins, 1994; Jäncke et al., 1997), and brain size is reported to be decreased in MR studies of schizophrenic patients (Zipursky et al., 1992; Lawrie and Abukmeil, 1998), it is clear head size corrections are necessary.

A surface deformation-based approach was employed in this study to allow quantification of standard callosal parameters such as area, length and width in addition to other parameters indexing shape (Thompson et al., 1996a,b, 1997). This approach was aimed at providing information about structural alterations in surrounding brain regions in addition to assessing callosal abnormalities. After some initial scaling to bring callosal surfaces into register and to correct for differences in overall brain dimensions, curves and points from the callosal surfaces of subjects in each group were matched and variability information from each individual surface warp retained. The scaling ratios used to align the corpus callosum across subjects can be factored out either by converting measures back into native space or by using them as covariates in a multivariate analysis, thereby ensuring that callosal measures are not affected by brain volume. These techniques allow a comprehensive analysis of callosal structure in schizophrenic patients and normal controls and provide the ability to quantify and visualize any structural differences as they relate to diagnosis and sex in a three-dimensional coordinate system in standardized and native scanner space. Furthermore, callosal shape renderings from Alzheimer’s patients (n = 10 males) acquired using the same methods in an earlier study (Thompson et al., 1998) were compared with the callosal shape renderings of male schizophrenic patients and controls to evaluate whether callosal shape profiles in schizophrenia are disease specific.
Hypotheses
We set out to detect a modest decrease in midsagittal area in schizophrenic patients, looking specifically for area differences implicating involvement of specific callosal channels as defined by Witelson et al. (Witelson et al., 1989) and Clarke et al. (Clarke et al., 1994). Furthermore, we were interested in assessing alterations in callosal shape measured by curvature and displacement in three-dimensional space in patients versus controls, which would provide further hypotheses concerning structural differences in surrounding anatomical regions. Specifically, relationships between callosal displacement and lateral and third ventricular enlargement were assessed.

Materials and Methods

Subjects
Twenty-five chronic schizophrenic patients (15 male/10 female; mean age 31.1 ± 5.6 years) and 28 normal controls (15 male/13 female; mean age 30.5 ± 8.7 years) were included in the study. Subjects were scanned at the Institute of Psychiatry, London, UK. Groups did not differ significantly in age, years of education, height or parental socio-economic class. Socio-economic status was derived from UK census data (Office of Population Censuses and Surveys, 1993), using details of 'best-ever' parental occupation. There were two left-handed subjects in each group as defined by the Annett Handedness Scale (Annett, 1970).

All schizophrenic patients met DSM-III-R (American Psychiatric Association, 1987) criteria and were receiving regular antipsychotic medication. Control subjects were screened for any personal or family history of psychiatric illness. Exclusion criteria for both patients and controls included head trauma, drug abuse and hereditary neurological disorders. All subjects gave informed written consent for their participation in this study with ethical permission obtained from the Bethlem and Maudsley Ethical Committee (Research).

Image Analysis Procedures
High-resolution three-dimensional SPGR MR images (256 × 256 matrix; 20 cm FOV) were acquired using a GE Signa 1.5 T scanner for each subject as a series of 124 contiguous 1.5 mm coronal slices. Images were resliced in the sagittal plane at 0.5 mm. To correct for head position and brain length and to allow for morphometric comparison of the corpus callosum between subjects, each brain volume was scaled and placed into the standardized Talairach and Tournoux stereotaxic coordinate system (Talairach and Tournoux, 1988). In the scaling procedure, the uniformly redigitized grid points in pixel coordinates translated into all three-dimensional extents of the corpus callosum were obtained from the Talairach and Tournoux stereotaxic coordinate system. Regional displacement of average callosal surfaces between groups, present within each group (Figs 1–4; Fig. 6). To visualize and quantify regional displacement of average callosal surfaces between groups, algorithms were used whereby corresponding grid points were matched and the discrepancy in distance calculated as three-dimensional displacement vectors between points (Fig. 5). Callosal meshes were divided into superior and inferior pieces to generate surface mesh variability and displacement maps. Measures of length, width, curvature and all three-dimensional extents of the corpus callosum were obtained from the uniformly redigitized grid points in pixel coordinates translated into millimeters.

Finally, midsagittal callosal renderings were divided into five vertical partitions representing the (i) anterior third, (ii) anterior body, (iii) posterior body, (iv) isthmus and (v) splenium (Fig. 7) (Witelson et al., 1989; Clarke and Zaidel, 1994). Midsagittal areas were obtained in mm² for the entire callosum and for each midsagittal segment.

Brain and Ventricle Volume
Total brain volume and volumes of the lateral and third ventricles were acquired by segmenting each three-dimensional image set into gray and white matter, cerebrospinal fluid (CSF) and background. Briefly, image data (16 bit) was processed using a number of steps that included: (i) correction for signal intensity inhomogeneities; (ii) tissue classification by choosing representative signal intensity values for the different tissue types from 120 predefined regions across the entire brain volume (Sowell et al., 1999); (iii) removal of the skull, cerebellum and extracortical CSF; and (iv) calculation of brain volume in native space. Reliability of selection for representative tissue type intensity values was evaluated by classifying 10 different brains and computing intensity errors (reliability > 94% for all tissue types). Volume of the lateral and third ventricles were measured by outlining the regions of interest in consecutive tissue segmented coronal slices by following anatomical landmarks and restricted to boundaries between CSF and other tissue types (Fig. 8).

Alzheimer’s Data
To compare the shape profiles of midsagittal callosal surface renderings between male schizophrenic patients (n = 15), adult controls (n = 15) and Alzheimer’s patients (n = 10), Alzheimer’s data was included from a study assessing cortical variability in normal aging and Alzheimer’s disease (Thompson et al., 1998). Image analysis procedures employed in this study were identical to those used here and callosal shape parameters were measured in the same stereotaxic coordinate system. The rationale for including this data was to evaluate whether Alzheimer’s patients exhibit similar differences in callosal shape profiles given that Alzheimer’s patients show ventricular enlargement and decreases in brain size that are similarly reported in schizophrenia (Lawrie and Abukmeil, 1998). Callosal renderings from all male groups are overlaid for comparison in Figure 9.

Statistical Analyses
Differences in discrete callosal areas and morphometric shape parameters obtained from the mesh pieces were compared within and between groups using multivariate analyses of covariance (MANCOVAs) and, when appropriate, followed by univariate analyses. Multivariate test statistics control for type I error by adopting a strict criterion for significance. In order to control for type I error, tests of independent dependent variables were only performed if the corresponding multivariate tests were found significant. In these analyses sex and Diagnosis were used as independent variables, while curvature and superior and inferior extents of top and bottom callosal surfaces, length, width and area measures were used as dependent variables. Talairach scaling ratios used to normalize AC-PC distance and brain volume were assessed as potential covariates. Results of these analyses, summarized in Table 1, are described below.

Results
Several striking trends emerged in the callosal morphometric...
analyses between groups: (i) different patterns of variability were observed in each group with female schizophrenic patients showing the highest variability overall; (ii) significant vertical displacement of the corpus callosum was observed in male patients compared to controls; (iii) male patients exhibited a significant increase in curvature for superior and inferior callosal surfaces; and (iv) increases in callosal thickness were identified in anterior and posterior callosal regions in male patients versus male controls. Finally, callosal shape measures were significantly related to lateral ventricle enlargement.

Table 1

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Effect</th>
<th>Mean ± SEM</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raw brain volume (univariate effects)</strong></td>
<td>Sex</td>
<td>F: 1.165 ± 18.1</td>
<td>M: 1270.9 ± 21.5</td>
</tr>
<tr>
<td></td>
<td>w/ covariate</td>
<td>Sex</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>AC-PC distance (univariate effects)</strong></td>
<td>Sex</td>
<td>M: 26.83 ± 0.24</td>
<td>F: 25.68 ± 0.29</td>
</tr>
<tr>
<td><strong>Mid sagittal area (univariate effects)</strong></td>
<td>AC-PC-covariate</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Shape parameters (multivariate effects)</strong></td>
<td>Diagnosis</td>
<td></td>
<td>&lt; 0.053</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Shape variable</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex × Shape</td>
<td></td>
<td>&lt; 0.008</td>
</tr>
<tr>
<td></td>
<td>AC-PC</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>AC-PC by Shape</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Length (univariate effects)</strong></td>
<td>AC-PC Distance</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Top superior boundary</strong></td>
<td>AC-PC distance</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>NC: 24.84 ± 0.62</td>
<td>SZ: 26.78 ± 0.58</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td></td>
<td>Male patients &gt; male controls</td>
<td>NC: M: 23.27 ± 0.56</td>
<td>SZ: M: 27.38 ± 0.67</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex w/ Covariate</td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Bottom superior boundary</strong></td>
<td>AC-PC distance</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>NC: 19.67 ± 0.57</td>
<td>SZ: 21.44 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.008</td>
</tr>
<tr>
<td></td>
<td>Male patients &gt; male controls</td>
<td>NC: M: 18.29 ± 0.52</td>
<td>SZ: M: 22.03 ± 0.73</td>
</tr>
<tr>
<td><strong>Inferior rostrum</strong></td>
<td>Diagnosis</td>
<td>NC: 2.78 ± 0.28</td>
<td>SZ: 2.84 ± 0.34</td>
</tr>
<tr>
<td><strong>Top curvature</strong></td>
<td>Diagnosis</td>
<td>NC: 1.29 ± 0.01</td>
<td>SZ: 1.33 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.004</td>
</tr>
<tr>
<td></td>
<td>Male patients &gt; male controls</td>
<td>NC: M: 1.50 ± 0.02</td>
<td>SZ: M: 1.63 ± 0.02</td>
</tr>
<tr>
<td><strong>Width (multivariate effects)</strong></td>
<td>AC-PC distance</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>NC: 19.88 ± 0.72</td>
<td>SZ: 21.94 ± 0.82</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.016</td>
</tr>
<tr>
<td></td>
<td>Male patients &gt; male controls</td>
<td>NC: M: 18.63 ± 0.76</td>
<td>SZ: M: 22.71 ± 0.73</td>
</tr>
<tr>
<td><strong>Ventricle volume (multivariate effects)</strong></td>
<td>Diagnosis</td>
<td></td>
<td>&lt; 0.016</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.009</td>
</tr>
<tr>
<td></td>
<td>Male patients &gt; male controls</td>
<td>NC: M: 15.05 ± 0.16</td>
<td>SZ: M: 16.70 ± 0.56</td>
</tr>
<tr>
<td><strong>Anterior segment (univariate effects)</strong></td>
<td>Diagnosis</td>
<td>NC: 5.97 ± 0.25</td>
<td>SZ: 7.07 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.004</td>
</tr>
<tr>
<td></td>
<td>Male patients &gt; male controls</td>
<td>NC: M: 10.70 ± 1.60</td>
<td>SZ: M: 20.17 ± 2.65</td>
</tr>
<tr>
<td><strong>Prior ventricle (univariate effects)</strong></td>
<td>Diagnosis</td>
<td>NC: 1.86 ± 0.13</td>
<td>SZ: 2.58 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Lateral ventricle</strong></td>
<td>Diagnosis</td>
<td>NC: M: 10.70 ± 1.60</td>
<td>SZ: M: 20.17 ± 2.65</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Splenium</strong></td>
<td>Diagnosis</td>
<td>NC: M: 1.86 ± 0.13</td>
<td>SZ: M: 2.58 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Posterior midbody</strong></td>
<td>Diagnosis</td>
<td>NC: M: 10.70 ± 1.60</td>
<td>SZ: M: 20.17 ± 2.65</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Third ventricle</strong></td>
<td>Diagnosis</td>
<td>NC: M: 1.86 ± 0.13</td>
<td>SZ: M: 2.58 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × Sex</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

SZ, schizophrenic patients; NC, normal controls; M, males; F, females. Multivariate analyses were performed with Sex and Diagnosis as factors, and included callosal areas, shape parameters or ventricular volumes as dependent variables using AC-PC distance or raw brain volume as covariates. Univariate analyses were only performed if the corresponding multivariate test was significant.

Measures of volumes are reported in cm³, and distance measures in mm.

*aSignificant correlations between lateral ventricle volume and callosal shape parameters (*P* < 0.01).
Variability and Displacement Maps

Variability maps revealed distinct differences in the patterns of local variability and shape in each group (Figs 1–4). The average callosal surface mesh appeared considerably more bowed in the male schizophrenic group (Fig. 2). Overall, female schizophrenic patients displayed higher intragroup variability in callosal parameters than male patients or controls (~4.5 mm) (Figs 1 and 4). Male patients exhibited higher callosal variability compared with male controls (Fig. 2). Maximal displacement of callosal variability averages was visualized in anterior, superior and inferior midbody regions between male patients and controls, approaching 5 mm (Fig. 5).

Covariates

Raw AC–PC distances (anterior–posterior axis) and brain volume were evaluated as potential covariates to remove the effects of head size and of AC–PC scaling from the data. Preliminary analyses found AC–PC scaling to be highly correlated with midsagittal callosal area and shape parameters after normalization (average r = 0.48, P < 0.005). Brain volume, however, did not correlate significantly with any of the AC–PC scaled dependent variables (correlations did not exceed 0.15 for any variable, P > 0.3); thus only raw AC–PC distance was used as a covariate in subsequent analyses of callosal parameters.

To determine whether the four groups differed in average values on the AC–PC covariate or brain volume, the AC–PC scaling measure and brain volumes in native space were used as dependent variables in separate 2 (Sex) × 2 (Diagnosis) ANOVAs. There was a significant effect of Sex on AC–PC distance [F(1,49) = 8.42, P < 0.006], with males (mean ± SEM = 26.84 ± 0.24) having larger raw AC–PC distances compared to females (mean = 25.72 ± 0.29). There were no Diagnosis or Sex × Diagnosis interactions for brain volume. Brain volume, however, was significantly dependent upon Sex (males larger, P < 0.001).

Midsagittal Area

A 2 (Sex) × 2 (Diagnosis) MANCOVA analysis confirmed significance of the AC–PC covariate [F(1,48) = 29.68, P < 0.001]. There were no further main effects. When AC–PC was excluded as a covariate the Sex effect approached significance [F(1,50) = 3.65, P = 0.062], indicating the covariate corrected for the difference in raw AC–PC distances across Sex.

Shape Parameters

A similar MANCOVA was performed to determine whether group differences existed in parameters characterizing the shape of the corpus callosum, including top and bottom curvature, apices of the superior and inferior callosal surfaces, the most inferior part of the rostrum and callosal length as dependent variables. This analysis revealed a marginal multivariate effect of Diagnosis [F(1,48) = 3.925, P = 0.053] and a marginal multivariate Diagnosis × Sex interaction for all shape parameters (P = 0.096). The Diagnosis × Sex interaction, however, differed significantly for the shape variables [F(6,288) = 2.968, P = 0.008]. The effect of Diagnosis also differed for the dependent measures [F(6,288) = 62.489, P < 0.001]. These results justified conducting univariate F-tests to examine Diagnosis × Sex interactions separately for each variable listed above. Finally, the AC–PC multivariate effect was highly significant [F(1,48) = 25.34, P < 0.001], but the covariate interacted with the different shape parameters [F(6,288) = 13.386, P < 0.001].

Thus univariate ANOVAs were first run to determine which of the shape parameters were significantly affected by the covariate. Of these, length [F(1,48) = 22.79, P < 0.001] and the most superior limits of the top [F(1,48) = 22.24, P < 0.001] and bottom callosal surfaces, [F(1,48) = 15.76, P < 0.001], were significantly affected by AC–PC distance. Since the covariate did not account for a significant portion of the variance for curvature or inferior surface measures, use of raw AC–PC distance as a covariate was considered inappropriate for these dependent variables and they were reanalyzed using ANOVAs without the covariate, again assessing Diagnosis × Group effects.

Effects of Diagnosis

There were significant effects of Diagnosis for the top and bottom callosal surface meshes (most superior points) [F(1,48) = 7.34, P < 0.001 and F(1,48) = 6.25, P = 0.016 respectively], and for the rostrum of the corpus callosum [F(1,48) = 8.84, P < 0.033] with callosal location displaced in the vertical axis (y-domain) in three-dimensional space in patients versus controls for all three measures. Diagnosis × Sex interactions were apparent for the curvature of top [F(1,49) = 19.49, P < 0.001] and bottom [F(1,49) = 9.30, P < 0.004] callosal surface meshes. The superior boundaries of bottom and top callosal surfaces showed Diagnosis × Sex interactions even after covariate correction [F(1,48) = 7.69, P < 0.008 and F(1,48) = 8.85, P = 0.005 respectively]. In all cases male patients had higher means reflecting callosal displacement in midbody regions. Finally, in univariate tests assessing the assumption of equality for the effect of the covariate on the four groups, there was a significant Diagnosis × Sex × Slope interaction for the superior extent of the bottom callosal surface. This measure was reanalyzed without the covariate, but again produced a significant Diagnosis × Sex interaction [F(1,49) = 4.00, P < 0.05].

Figure 6. Parametric mesh construction. Digital points representing boundaries of the corpus callosum are redigitized to render each respective set of callosal points uniform. An algorithm generates a parametric grid by creating a rectangular mesh over the uniform points from each callosal surface. Points from each two-dimensional surface mesh are pulled into correspondence to represent an average callosal surface and retain intragroup variability profiles.

Figure 7. Corpus callosum partitioning protocol. Many partitioning protocols have been applied to generate comprehensive analyses of callosal area. The partitioning scheme employed in this study divided midsagittal callosal area into anterior third, anterior midbody, posterior midbody, isthmus and splenium (adapted from Wotelson et al., 1989; Clarke et al., 1994). Measures of maximal callosal width were obtained for each subdivision.

Figure 8. Brain volume and segmentation of the ventricles. To acquire brain volumes and volumes of the lateral and third ventricles, raw image data was processed in a number of steps. Different tissue types were classified according to signal intensity values and brain volumes were calculated. Volumes of the lateral and third ventricles were obtained by filling in the regions of interest in native space according to neuroanatomical landmarks and CSF boundaries.

Figure 9. Color shape averages. Different shape profiles of the corpus callosum are seen in male Alzheimer’s patients (AD; green), male schizophrenic patients (SZ; blue) and male adult controls (INC; red). The callosal renderings are taken from variability maps that represent the mean shape profiles within each group after AC–PC distance normalization in stereotaxic space. The following composite was aimed at demonstrating that Alzheimer’s patients possess a mean shape profile of the corpus callosum (Thompson et al., 1998) that is different from that of schizophrenic patients in spite of ventricular enlargement.
Diagnosis × Sex Interactions

Finally, of measures that revealed significant Diagnosis × Sex interactions, post hoc tests of simple effects showed differences in shape parameters between male patients and controls only. In male groups there were significant differences in curvature for bottom and top callosal surfaces \( F(1,28) = 50.862 \) and 13.959 respectively, \( P < 0.001 \) with surface curvature substantially increased in male patients. Significant differences in superior points of top and bottom callosal surfaces \( F(1,27) = 26.72, P < 0.001 \) and \( F(1,27) = 19.351, P < 0.001 \) also reflected vertical displacement of the callosum in three-dimensional space in male patients.

Width

Measures of callosal thickness were obtained by taking the maximum vertical width from each callosal subdivision used in the area analysis (Fig. 7). The MANCOVA again confirmed the significance of the AC–PC covariate \( F(1,48) = 51.96, P < 0.001 \). A significant multivariate Diagnosis × Sex interaction was found \( F(1,48) = 9.20, P < 0.004 \). The multivariate effect of Diagnosis differed for the dependent measures \( F(4,192) = 3.47, P < 0.009 \). Univariate ANOVAs revealed a significant difference across Diagnosis for the width of the anterior callosal segment \( F(1,48) = 8.17, P < 0.006 \), with the width increased in schizophrenic patients even after covarying for AC–PC distance. The Sex × Diagnosis interaction was significant for the splenial and anterior callosal regions \( F(1,48) = 4.58 \) and 6.19, \( P < 0.05 \) and \( P < 0.016 \) respectively. A univariate F-test of simple effects in male patients and controls showed significant group differences for the anterior callosal segment, posterior midbody and splenium \( F(1,27) = 4.5, 8.78 \) and 14.44, \( P < 0.05, 0.006 \) and 0.001 respectively. In these regions male patients exhibited an increase in callosal thickness compared to controls. There were no significant differences in callosal widths between female groups.

Ventricular Volumes

In a 2 (Sex) × 2 (Diagnosis) MANCOVA using brain volume as a covariate and raw lateral and third ventricle volumes as dependent variables there was a trend towards an effect of Diagnosis \( F(1,48) = 3.29, P < 0.08 \), but a significant Diagnosis × Sex interaction \( F(1,48) = 4.07, P < 0.01 \) that also interacted significantly with the dependent variables \( F(1,48) = 5.91, P < 0.02 \). There was significant effect of the covariate, but again this differed for the dependent variables \( F(1,48) = 4.06, P < 0.05 \). Univariate analyses showed brain volume interacted with lateral ventricle volume \( F(1,48) = 4.09, P < 0.05 \), but not with third ventricle volume. There remained, however, a significant Sex × Diagnosis interaction for third ventricle volume without the covariate \( F(1,48) = 4.86, P < 0.03 \); covarying for brain volume, this Sex × Diagnosis interaction was present for lateral ventricle volumes \( F(1,28) = 6.80, P < 0.01 \). Tests of simple effects revealed male patients had larger lateral ventricle volumes \( F(1,27) = 10.43, P < 0.001 \) and third ventricle volumes \( F(1,27) = 6.80, P < 0.01 \) than male controls.

Correlations

Correlations were performed between callosal shape parameters (including curvature and vertical extents of the superior and inferior callosal surfaces), and the volume of the lateral and third ventricles. Significant two-tailed probability values were found for correlations between lateral ventricle volumes and callosal parameters, reflecting displacement from the above analyses (top and bottom curvature and superior limits, \( P < 0.01, r = 0.36, 0.52, 0.64, 0.70 \) respectively). Ventricular volume increases are therefore related to increases in callosal surface curvature and displacement. To ensure that significant correlations between the shape measures and lateral ventricle volume were not due to effects of AC–PC scaling or brain volume, partial correlations between each measure, controlling separately for the effect of AC–PC distance and for brain volume, were carried out. In all cases the correlations remained significant upon removal of variance associated with either AC–PC distance or brain volume. There were no significant correlations between third ventricle volumes and the callosal shape parameters.

Conclusion

Clear differences in patterns of variation and callosal shape were observed in this morphometric analysis of the corpus callosum between patients and controls (Figs 1–5). These differences were clearly modulated by sex, suggesting different structural patterns in male and female patients. Statistical tests confirmed group differences in callosal shape parameters in three-dimensional stereotaxic space, especially between male patients and controls. Significant correlations reflecting a relationship between ventricular enlargement and callosal displacement were evident.

Area and Width

Studies assessing standard callosal parameters in schizophrenia have produced mixed results. MR studies report smaller (Rossi et al., 1989; Woodruff et al., 1993), larger (Nasrallah et al., 1986; Jacobsen et al., 1997), or no differences in callosal areas in patients (Uematsu and Kaiya, 1988; Casanova et al., 1990; Raine et al., 1990; Gunther et al., 1991; Woodruff et al., 1997). Studies measuring callosal thickness have similarly reported increases (Nasrallah et al., 1986), decreases (DeQuardo et al., 1996) and no difference in callosal width across groups. Since the corpus callosum connects functionally related regions, efforts have been made to divide this structure into different areas to isolate malformation of specific callosal channels (Thompson et al., 1999a). Roughly equivalent estimates of the anterior corpus callosum have been reported as thicker or larger in area (Nasrallah et al., 1986) in patients, a finding compatible with ours where maximum anterior callosal widths were greater in patients compared to controls although not different in area.

Gender Differences

Differences in callosal area and thickness have been found to interact with sex. Hoff et al. (Hoff et al., 1994), for example, reported that first-episode female patients had smaller callosal area than female controls, partially replicating data (Hauser et al., 1989) where chronic female schizophrenic patients were shown to have smaller anterior callosal widths. In contrast, Nasrallah (Nasrallah et al., 1986) found increased thickness of anterior and middle callosal areas in females in some concordance with Raine et al. (Raine et al., 1990) who found anterior and posterior callosal widths smaller in male versus female patients with the opposite effects in controls. A trend towards a reversed sex difference in anterior and posterior callosal size was also reported by Colombo et al. (Colombo et al., 1993). The Diagnosis × Sex interaction in this study revealed significant increases in widths of anterior and posterior callosal regions in male patients, but no difference or reversal in females. These effects appear unrelated to brain size given no effects of diagnosis were evident and sex differences in brain volume did not reflect callosal width differences in female groups.

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Moreover, our analyses show that AC–PC correction sufficiently controls for relative differences in callosal sizes across sex. Interestingly Highley et al. have observed an increase in callosal fiber density in male patients versus controls and the opposite in female groups in all regions but the posterior midbody and splenium (Highley et al., 1999). It is possible that these changes in fiber density could affect callosal thickness, especially for small diameter fibers (Aboitiz et al., 1992). It is more likely, however, that increased widths here reflect bowing of the callosum in male patients as anterior and posterior portions appear more extended in three-dimensional space (Fig. 2). Finally, many studies of callosal morphology have used low-resolution scans that cannot represent true midline, different partitioning protocols, and have sometimes neglected to use head size corrections, all reasons making it difficult to compare results across studies.

**Shape**
Overall, clear vertical displacements of the corpus callosum were observed in the superior–inferior axis of three-dimensional space in male schizophrenic patients, especially in midbody callosal regions (Fig. 5). These results partially replicate one of the few studies measuring callosal shape in addition to standard morphometric parameters in schizophrenia. Specifically, Casanova et al. used a statistical analysis of the coefficients of a Fourier expansion series to demonstrate differences in callosal shape in twins discordant for schizophrenia (Casanova et al., 1990). A bowing of the corpus callosum was reported in the superior–inferior dimension in affected twins compared to unaffected co-twins, thought to reflect enlargement of the midbody of the lateral ventricle superior horns and/or third ventricle enlargement. Furthermore using a two-dimensional skeletonization technique, Frumin et al. report shape differences in the posterior corpus callosum (increased curvature) in chronic schizophrenic patients that was not apparent in bipolar patients or normal controls (Frumin et al., 1998). In our sample, we found significant increases in lateral and third ventricular volumes in male patients with increases in lateral ventricular volume significantly relating to increases in callosal displacement and curvature. It appears that ventricular enlargement results in vertical displacements of the superior horn in male patients that have been shown in stereotaxic space (Moussai et al., 1998). In addition, a study using the same shape analyses in pediatric temporal lobe epilepsy, autism, attention deficit hyperactivity disorder and juvenile onset schizophrenia detected similar displacements and bowing of the corpus callosum in the schizophrenia group only (R. Blanton et al., personal communication) even though ventricular enlargement was not specific. To further establish whether bowing of the corpus callosum is specific to male schizophrenic patients, we compared callosal surface renderings from our male patients and controls with callosal averages from Alzheimer’s patients in the same stereotaxic space. The male Alzheimer’s patients exhibited ventricular enlargement as well as a 24.5% decrease in posterior midbody callosal regions (Thompson et al., 1998) (Fig. 9). While the corpus callosum is bowed in both Alzheimer’s and schizophrenic patients, distinct patterns of shape are found in each group, indicating that the pattern of callosal displacement in schizophrenia may indeed be disease specific.

**Gender**
There has been an ongoing controversy concerning sex differences in callosal morphology with an emphasis on splenial area in normal populations (De Lacoste-Utamsing et al., 1982; Holloway and De Lacoste, 1996; Bishop and Wahlsten, 1997; Davatzikos and Resnick, 1998). Furthermore, callosal size has been shown to correlate with small brain size, but not with large brain size (Rauch and Jinkins, 1994; Jäncke et al., 1997). In either case, gender and/or head size clearly influence normal callosal morphometry, making gender interactions with morphometric abnormalities in schizophrenic populations of considerable interest.

There are a number of reasons why differences in callosal shape may be more apparent in male populations. There appear to be distinct gender differences in schizophrenic populations. For example, negative symptoms are more prominent in male patients and males have an earlier age of onset, a poorer quality of life and a worse course of illness (DeLisi et al., 1989; Waddington, 1993; Gur et al., 1996). Furthermore, not only do clinical features in schizophrenia appear sexually dimorphic but there appear to be relationships between neuroanatomical volumes and specific clinical dimensions across the sexes (Cowell et al., 1996). The curvature of the corpus callosum has also been noted to increase with age in male populations at a higher rate than in females (Rajapakse et al., 1996).

Clinical and psychopathological heterogeneity in schizophrenic patients may also account for inconsistencies in results when assessing structural morphology, including morphology of the callosum (Colombo et al., 1993). For example, patients with negative symptoms show smaller callosal sizes (Gunther et al., 1991; Woodruff et al., 1993), thicker callosa (Coger and Serafetinides, 1990) or no difference relative to other groups. Similarly, early-onset schizophrenic patients have been shown to have larger total, anterior and posterior callosal areas compared to controls (Bigelow et al., 1983; Coger and Serafetinides, 1990; Jacobsen et al., 1997). Clearly more information is needed to establish the relationship of these factors to callosal morphometry in schizophrenia.

**Variability Maps**
Results mentioned above and those from other studies have indicated an enormous range of morphometric findings in the corpus callosum in schizophrenic populations. Different types of head size correction or failure to include these corrections may contribute to discrepancies in results (Jäncke et al., 1997). Failure to replicate findings across studies may also result from patient heterogeneity and differences in callosal structure between the sexes across diagnosis. In our study, variability and displacement maps (Figs 1–5) show clear differences between populations in patterns of callosal variation. Overall, the variability and displacement maps indicate a marked upward shift of the corpus callosum in three-dimensional space in schizophrenic patients that bears a relationship to lateral but not third ventricle enlargement. Many studies have reported no influence of age in their findings of callosal pathology (Thompson et al., 1998), but few have looked at shape across age. Even though the effects of aging and callosal development are still under investigation, these results and those from other studies have controlled for age to some degree. Finally, in our sample, groups were matched for handedness. Handedness appears to be a predictor of neuroanatomical asymmetry and thus bears a relationship to callosal morphology (Clarke and Zaidel, 1994).

In sum, the methods employed in this study revealed unique differences in callosal shape and patterns of variability between schizophrenic patients and normal controls with clear gender differences. Further investigations are in progress, relating
callosal parameters to other neuroanatomical regions shown to possess structural alterations in schizophrenic patients, such as asymmetric perisylvian cortices and prefrontal cortices. Furthermore, structural alterations in surrounding regions such as thalamus and cingulate cortices may also be related to callosal displacements. Finally, it is clear that gender influences callosal morphology in schizophrenia. Larger sample sizes and homogeneous patient populations matched closely with control subjects as well as correlations with symptom complexes are required. This is necessary as it appears callosal morphology in schizophrenic patients is tempered by a number of clinical variables, including symptomatology, disease course and age of onset in addition to sex, handedness and age.

**Notes**

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