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Schizophrenia Research 42 (2000) 193–208

SCHIZOPHRENIA RESEARCH

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Shape and size of the corpus callosum in schizophrenia and schizotypal personality disorder

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Received 15 January 1999; accepted 23 June 1999

Abstract

The size and shape of the corpus callosum were assessed on sagittal section magnetic resonance images in 27 patients with schizophrenia, 13 patients with schizotypal personality disorder (SPD), and 30 healthy volunteers. High-resolution 1.2 mm axial SPGR images were acquired and resectioned so that the sagittal plane passed through the anterior and posterior commissures and was parallel to the interhemispheric fissure. The corpus callosum and the whole brain were traced on midsagittal section slices of each brain, and the callosum was divided into 30 anteroposterior sectors. Pixel-by-pixel chi-square and thin-plate spline analyses were used to assess between-group shape differences. Size of the corpus callosum was smaller anteriorly in the genu of the corpus callosum and posteriorly in the splenium in schizophrenic patients than in normal controls. The genu of the corpus callosum was larger in SPD patients than in schizophrenic patients or normal controls. The posterior corpus callosum was largest in normal controls, smaller in SPD patients, and smallest in schizophrenic patients. Shape analysis was consistent with these size comparisons, and suggested a downward bowing of the corpus callosum in schizophrenic and SPD patients. SPD patients also had a region of the callosum just posterior to the genu that was narrower than in the other two groups. The decreases in corpus callosal size in schizophrenia varied directly with length of illness, perhaps indicative of a progressive process. The patient–control differences in callosal size and shape are consistent with a hypothesis of decreased connectivity between the left and the right hemispheres in schizophrenia and SPD. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Cerebral circuitry; Laterality; Magnetic resonance imaging; White matter

1. Introduction

The corpus callosum, the largest white-matter fiber tract in the brain, provides the majority of axonal transmissions between the two cerebral hemispheres and subserves interhemispheric information transfer. Since there is substantial evidence that schizophrenic patients have difficulties with cognitive tasks that require interhemispheric transfer of information (see review in David, 1994), studies of the corpus callosum might reveal the anatomical correlates of these deficits. Although previous studies (reviewed below) have shown abnormalities in the size of the callosum in schizophrenia, it has not been studied in schizotypal personality disorder (SPD), which is related to

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PII: S0920-9964(99)00123-1

schizophrenia in its phenomenology, genetics, biology, outcome and treatment response (Siever et al., 1993). SPD patients have been reported to show cognitive impairments in tests sensitive to frontal-lobe function, with their scores generally being intermediate between those of schizophrenic patients and normal controls (Trestman et al., 1995). A single photon emission computed tomography study during the performance of the Wisconsin Card Sorting Test (WCST) also found SPD patients to be characterized by a pattern of frontal activity intermediate between that in normal subjects and schizophrenic patients (Buchsbaum et al., 1997a), providing further evidence for a relationship between SPD and schizophrenia. While the corpus callosum has been studied relatively little in SPD patients, they have been reported to show midline abnormalities including cavum septum pellucidum (Kwon et al., 1998). The incidence of this abnormality in SPD patients seemed to be intermediate between that in schizophrenic patients and their normal controls, suggesting a severity continuum. The septum, which lies just below the corpus callosum in the midsagittal plane, might be partly formed by the same mechanisms that modulate callosal development as suggested by Kwon et al. (1998). (For cavum septum pellucidum findings in schizophrenia, see DeLisi et al., 1993; Scott et al., 1993; Nopoulos et al., 1996, 1997; for review, see Coppola et al., 1995.)

Interhemispheric transfer problems in schizophrenia have been demonstrated in a variety of sensory and perceptual paradigms, and their anatomical relation to the corpus callosum, as well as their centrality to schizophrenia, has been widely studied (e.g., Crow, 1998). Green (1978), Dimond et al. (1979), Carr (1980), Schrift et al. (1986) and Craft et al. (1987) all reported that schizophrenic patients had problems with tactile information transfer compared with normal controls. Patients made more errors when transferring localization of touch from side to side, had difficulty in identifying objects with the non-dominant hand, and were impaired compared with controls on the Tactual Performance Test. Tasks requiring comparisons across visual fields of digits, letters, abstract shapes, letter-matching and color-naming present particular problems for schizophrenic patients (Beaumont and Dimond, 1973; Eaton et al., 1979; David, 1987; for review, see Coger and Serafetinides, 1990).

The anterior and posterior portions of the corpus callosum are topographically organized to carry connections from the anterior (frontal) and posterior (temporal, parietal and occipital) cortex (Pandya and Seltzer, 1986). As part of his work performing callosalectomies in human patients with intractable epilepsy, Sperry studied the functional implications of surgically interrupting the callosal connections of presumably normal cortical regions (Gordon et al., 1971). Based on the results of neuropsychological testing of patients with partial and complete commisurectomies of the corpus callosum, Sperry (1974) posited primary responsibility for the transfer of information for cognitive processes to anterior regions, and responsibility for cross-hemispheric transfer of sensory information to posterior regions. Anterior callosal deficits may thus be related to the widely reported poor performance of schizophrenic patients on measures of perseveration (number and percent of perseverative errors) in the WCST. Perseveration is seen by many investigators to be a sensitive indicator of frontal lobe dysfunction, with more perseverative errors reflecting difficulty in changing task strategy (Kolb and Whishaw, 1983; van der Does et al., 1993). Another task that poses difficulty for schizophrenic patients is the Stroop Color–Word Interference Test, which is believed to involve posterior callosal function (David, 1992, 1994). Correlations between posterior callosal area and Stroop performance have been reported in both normal volunteers and schizophrenic patients (Woodruff et al., 1997).

A number of studies have investigated differences in shape and size of the corpus callosum in schizophrenia (for review, see Jacobsen et al., 1997; Tibbo et al., 1998). The most frequently measured parameter has been total area of the sagittal section, either as an absolute measure or in relation to brain area or volume. In addition, width or thickness and length (in one dimension) have been measured. Rosenthal and Bigelow (1972), in a post-mortem planimetric study, found that the corpus callosum in schizophrenia was thicker than

in control brains. Jones and Miller (1981), using similar techniques, also reported increased thickness. A later finding of increased cross-sectional thickness in early-onset (Bigelow et al., 1983) and decreased thickness in late-onset schizophrenia compared with controls suggests a neurodegenerative course. Increased callosal size was also found in a magnetic resonance imaging (MRI) study of childhood-onset schizophrenia (Jacobsen et al., 1997); another study, however, found reduced callosal size in children with mixed diagnoses of schizophrenia and schizotypal disorder (Hendren et al., 1995). Two studies found a callosal size increase only in schizophrenic females (Nasrallah et al., 1986; Raine et al., 1990), while a third study (Woodruff et al., 1993) found that the mid-portion of the corpus callosum was significantly smaller only in schizophrenic males compared with controls. Another study (Hoff et al., 1994), however, found first-episode schizophrenic females to have a smaller corpus callosum. Still other studies found no statistically significant differences in callosal size in schizophrenia (for review, see Jacobsen et al., 1997; Woodruff et al., 1997).

The meta-analysis by Woodruff et al. (1995) confirmed smaller callosal area in schizophrenia, but no significant differences in length of the corpus callosum or ratio of corpus callosal/sagittal brain. The meta-analysis did not include examination of anteroposterior position within the callosum, a key feature in the consideration of frontal vs. temporal/occipital information transfer deficits.

Most of the anatomical studies of the corpus callosum in schizophrenia that have been reported to date were done using older MRI scanners, with slice thickness of 5–10 mm. Earlier studies also tended not to use resectioning techniques based on internal brain landmarks to obtain a precise mid-sagittal placement. This is a potential source of error, because callosal area increases greatly as the plane of the section moves laterally. The edge of the corpus callosum also becomes less clearly defined, and angulation error can result in increased sagittal area anteriorly or posteriorly (Coppola et al., 1995). Since errors of this type tend to be largely random, they would increase variability and tend to obscure potential group differences.

Seven MRI studies of schizophrenia have approached the issue of corpus callosal *shape* by dividing the structure into three or more anterior/posterior segments (Uematsu and Kaiya, 1988; Hauser et al., 1989; Casanova et al., 1990b; Colombo et al., 1993; Hoff et al., 1994; Woodruff et al., 1993, 1997). Three of the seven studies found the anterior segment smaller in schizophrenia than in controls (Woodruff et al., 1993, 1997; Colombo et al., 1993), although the difference was statistically significant in only one study (Woodruff et al., 1993). However, only Hoff et al. (1994) evaluated the interaction of segment position with diagnostic group (but with a non-significant effect). Relatively small regions of the corpus callosum may be involved in the schizophrenia–control shape differences and could have been missed in analyses that used a small number of callosum divisions. More refined analyses to address the *shape* of the corpus callosum may enhance our understanding of the frequently studied *size* variations. For example, a thin-plate spline shape analysis (DeQuardo et al., 1996) showed a thinner, more arched corpus callosum in schizophrenia, a result similar to the increased curvature measured by Casanova et al. (1990a,b) and interpreted as reflecting ventricular enlargement. However, a very recent study with a large sample of schizophrenic patients and high-resolution MRI revealed only a general reduction in corpus callosal size and failed to confirm shape differences (Tibbo et al., 1998).

The aims of the current study were threefold:

1. Because most of the previous studies were confined to chronic neuroleptic-treated schizophrenic patients, we wanted to extend our studies to include SPD patients as well as schizophrenic and control subjects.
2. We wanted to address the sagittal angulation problem by using thin 1.2 mm slices and post-acquisition resectioning to re-align each brain on the anterior commissure–posterior commissure (AC–PC) line with the interhemispheric fissure oriented vertically to insure reliable sagittal alignment.
3. Finally, we wanted to examine relationships between callosal shape differences and results of neuropsychological testing and clinical vari-

ables such as symptomatology, age of onset, duration of illness, and number of hospitalizations.

2. Methods

2.1. Subjects

Subjects were recruited from the outpatient and inpatient programs of the Mount Sinai Hospital, the Bronx Veterans Administration Hospital, and Elmhurst Hospital. The 70 subjects comprised 13 SPD patients [1 female, 12 males; mean age = 43.3 years, SD = 13.6, mean Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) score = 37.5, SD = 6.2], 27 schizophrenic patients (7 females, 20 males; mean age = 38.3 years, SD = 14.3, mean BPRS score = 53.2, SD = 10.7, mean age of onset = 23, SD = 5.1, mean number of hospitalizations = 5.8, SD = 5.5, mean duration of illness = 15 years, SD = 12.7) and 30 healthy volunteers (8 females, 23 males; mean age = 41.1 years, SD = 12.7). SPD patients were assessed for lifetime Axis II personality disorder diagnoses using the Structured Interview for DSM-III-R Personality Disorders (SIDP-R; Pfohl et al., 1989). Whenever possible, a person close to the patient was interviewed as well to provide additional information. Diagnostic consensus was achieved when all information gathered was presented to an expert diagnostician ($\kappa = 0.73$ for SPD). Patients with schizophrenia were evaluated with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Both SPD and schizophrenic patients met DSM-III-R diagnostic criteria (American Psychiatric Association, 1987) for their respective disorders. Normal control subjects, who were recruited by advertisement and by word-of-mouth, were screened with the CASH to exclude psychiatric disorder in themselves or their first-degree relatives. Both patients and controls had a physical examination and laboratory tests. Subjects with substance abuse/dependence, neurological disorders, and head trauma were excluded. All subjects provided informed consent.

Data on ventricular volume and asymmetry in a subsample of the subjects described here were reported previously (Buchsbaum et al., 1997b).

2.2. Neuropsychological data

Patients received a battery of neuropsychological tests, including the WCST (Grant and Berg, 1948; Heaton, 1981), the California Verbal Learning Test (CVLT; Delis et al., 1987), the Line Orientation Test (Benton et al., 1983), and a test of verbal fluency (generation of as many 'animal' names as possible in a 60 s period). Testing procedures are described in detail in Trestman et al. (1995).

2.3. MRI procedures

MRI scans were acquired using a GE Signa 5× system with an SPGR sequence (repetition time: 24 ms, echo time: 5 ms, flip angle: 40°) yielding 124 contiguous 1.2 mm slices. (For details, see Buchsbaum et al., 1997b.)

2.3.1. Post-acquisition image data analysis

All analyses of images were performed with MRI Image Processing (MIP) software specifically developed at the Mount Sinai Neuroscience PET Laboratory. To address the problem of obtaining the most anatomically precise and reliable midsagittal slices (Coppola et al., 1995), the MRI scans of the 70 subjects were all placed into the same orientation by first identifying points in the original MRI pixel coordinate system: an anterior commissure (AC) point, a posterior commissure (PC) point, and two points on a coronal slice midway between the AC and PC points: a top point placed in the center of the intercerebral sulcus at the top of the brain and a bottom point placed in the ventral median sulcus of the pons. After identification of the four points, the entire brain MRI was resliced such that the AC and PC points created a horizontal anterior–posterior axis and the top and bottom points were aligned to create the vertical axis. From the resliced brain, a single midsagittal slice was used for all subsequent analyses.

To obtain a midsagittal measurement to express the area of the corpus callosum as a percentage of total slice size for comparison with other studies,

a single slice was created by adding the midsagittal slice and two slices that were set 5 pixels from the interhemispheric fissure on each side. This procedure was necessary, because the 1 mm thick sagittal slice frequently contained large regions of the interhemispheric fissure and did not visualize the cortex. Use of a thicker slice allowed comparability of the whole brain sagittal area measurement with older MRI studies, which also used thicker slices.

2.3.2. Region of interest (ROI) tracing

The edge of the cortex and the contour of the corpus callosum were traced by placing points using a mouse, and a spline curve was fitted to these points (Fig. 1A). Landmark points on the corpus callosum were located at the posterior tip of the genu and the end of the splenium. Next, 29 evenly spaced points on the spline curve were located between these points along the top and bottom edges of the corpus callosum (Fig. 1B). Each of the 29 points on the top of the ROI was connected with its opposite member on the bottom, and the connecting line was then bisected. The resultant points, along with the terminal anchor points, were connected using a computer-generated spline to create an axial line (Fig. 1C), and a new set of 29 evenly spaced points were placed on this line. A line was drawn across the corpus callosum through this point. The angle was chosen by finding the angles of the perpendiculars to this point on the ROI line and the two points on either side and using the average angle of the three. This procedure determined 29 widths and 30 areas in the final image (Figs. 1D and 2). In a few subjects, lines that intersected within the corpus callosum were manually repositioned, such that some intersected on the inner edge of a concavity but none intersected within the outline of the corpus callosum.

The ventricular system was traced as described earlier (Buchsbaum et al., 1997b).

2.4. Statistical analysis

The width, the area, and the ratio of corpus callosal area over sagittal section area were compared by two-way repeated measures analysis of

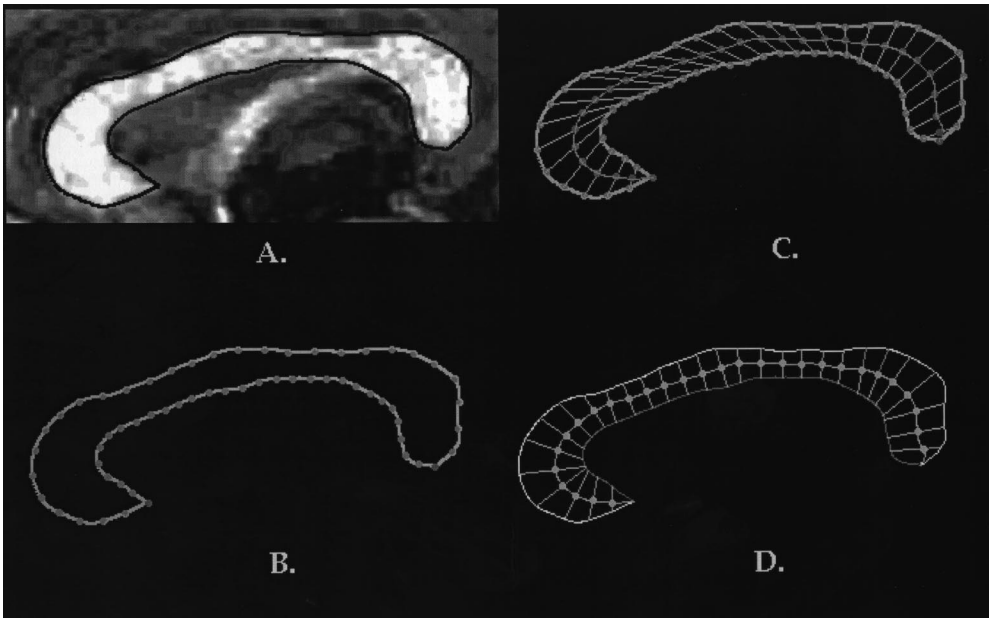

Fig. 1. Method of dividing corpus callosum. (A) Corpus callosum traced on sagittal MRI section. (B) Corpus callosum spline curve fitted and divided into 30 equal segments. (C) Lines drawn connecting each outline division. (D) Thirty areas based on perpendiculars to the midline.

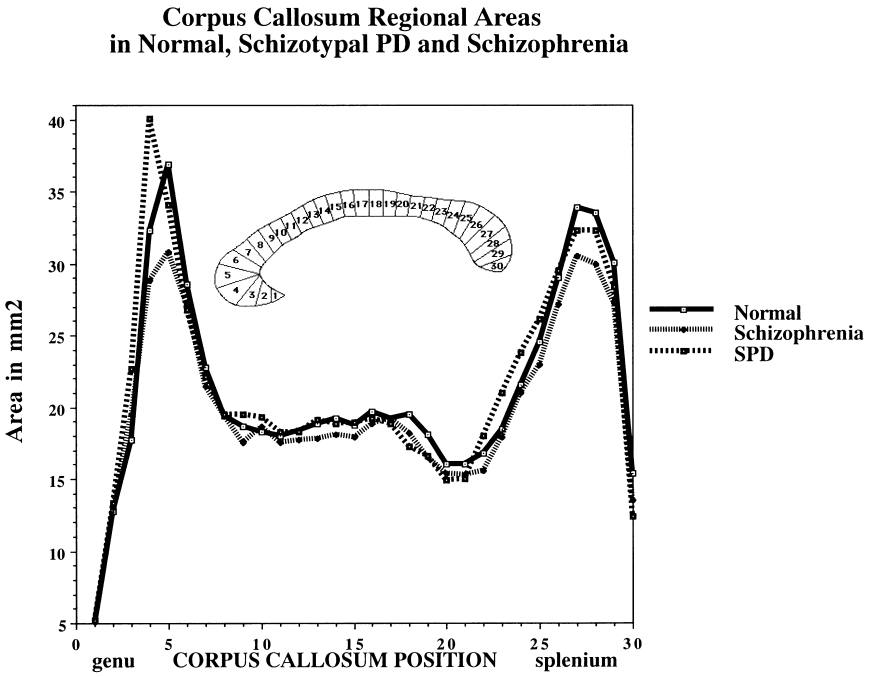

Fig. 2. Corpus callosum areas from anterior to posterior. After the omnibus ANOVA (see text), one-way follow-up ANOVA showed significantly smaller size in schizophrenic patients in area 5 (A5) in the genu ($F=7.236$, df = 1,55, $p=0.094$) and areas A27 ($F=4.81$, df = 1,55, $p=0.0325$), A28 ($F=4.424$, df = 1,55, $p=0.04$) and A29 ($F=5.161$, df = 1,55, $p=0.027$) in the splenium. Size of the corpus callosum in patients with schizotypal personality disorder (SPD) was intermediate, but did not differ to a statistically significant degree from that in either schizophrenic or normal subjects in A5, A27, A28 or A29. Statistically significant between-group differences did emerge in a few other areas: for area A3, size was larger in SPD patients than in normal volunteers ($F=5.001$, df = 1,41, $p=0.0308$); for area A30, size was larger in normal volunteers than in SPD patients ($F=4,258$, df = 1,41, $p=0.0454$); and for A4, size was larger in SPD than in schizophrenic patients ($F=7.815$, df = 1,38, $p=0.0081$).

variance (ANOVA), with the three subject groups as within measures and callosal position as the between measure. Gender and neuropsychological testing measures were included along with diagnosis in subsequent ANOVAs as additional within measurements. Follow-up *t*-tests were used to localize the effects.

2.5. Fisher exact shape analysis

A bounding box on the sagittal section was formed, and each corpus callosum edge was expressed in coordinates relative to the average of all subjects' box heights and widths. Next, corpus callosum ROIs were aligned in this coordinate system by placing the centers of mass of each on the same point. A pixel-by-pixel Fisher exact test analysis was performed by assigning pixels into one of two categories (inside or outside the ROI of the corpus callosum) and comparing each diagnostic group in a paired fashion with the other two. Thus, a two-by-two contrast was formed for every pixel location (Fig. 3).

2.6. Corpus callosum edge shape analysis

The center of mass of each corpus callosum ROI was superimposed and placed within a coordinate system with x and y points separated by 0.898 mm (the same as MRI pixels). A total of 32 points, 16 on the top and 16 on the bottom (every other point of the 29 points on the top and bottom surfaces of the corpus callosum ROI and the two end points as determined in the regional area analysis), were assigned an x and y coordinate based on the point's location within the space.

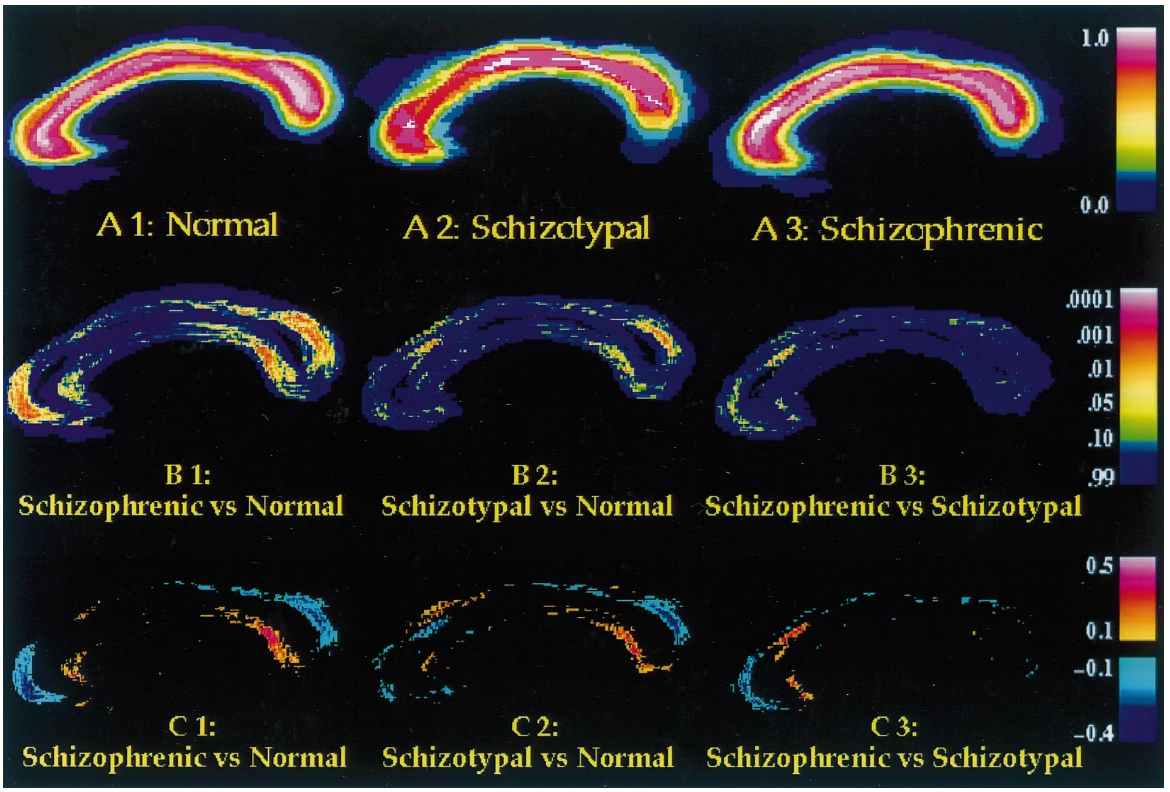

Fig. 3. Tally plot of corpus callosum contour and Fisher exact test analysis. (A) Top row: Tally plot analysis. The pixel colors indicate the proportion of subjects in each group that had points within the outline of the corpus callosum at that particular location in the image. Scale bars are defined as follows: white = 100%, red = 75%, green = 50% and blue = 25%. (B) Middle row: Fisher exact analysis. The analysis image compares each pair of the subject groups and indicates the probability at each pixel location that one group is significantly different from the other from the 2×2 binomial probability analysis (pixel is inside/outside traced outline, subject group 1/subject group 2). The probability associated with each Fisher exact test is indicated by the color scale at the left, which indicates the p-value represented by each color. For example, at a peripheral x, y position in the genu where patients have a smaller corpus callosum, a particular position might be inside their outline for 14 of 27 patients (50%) but inside the outline of 22 of 30 controls (75%). These numbers enter a Fisher exact and the p-value is presented as a colored value. (C) Differences between the number of individuals with a pixel at each location in the first group minus the second. For example, in C1, the light blue areas indicate the positions where more normal volunteers had pixels inside the corpus callosum outline compared with schizophrenic patients, indicating that at that location size is smaller in the patients. The red areas indicate positions where more schizophrenic patients had pixels than normal volunteers. This area is consistent with Fig. 2, sector 5. The color bar shows the proportion difference between the groups; for example, dark blue areas have 0.40 or 40% more normal volunteers than schizophrenic patients having a pixel inside the corpus callosum at that point. The color bar thus expresses the size of the group difference proportion effect.

Next, the location of each point for each subject was compared with the average location of the point for the normal group to yield displacement x and y distances. The data were presented pictorially and analyzed statistically. Fig. 4 shows the average location of the points of the schizophrenic group and the outline of those of the normal group (Fig. 4A), both overlaid on an average image obtained by warping MRIs of individual normal subjects into the same space (Bookstein, 1996a,b). The same methods were applied to the SPD group (Fig. 4B). Vectors were used to indicate the difference in the location of the spline points. Next the x and y displacement coordinates of each point of each subject were compared by repeated measures ANOVA (BMDP 4V; Dixon et al., 1985) with diagnosis as the within factor and the x and y displacements of the 30 points as the between

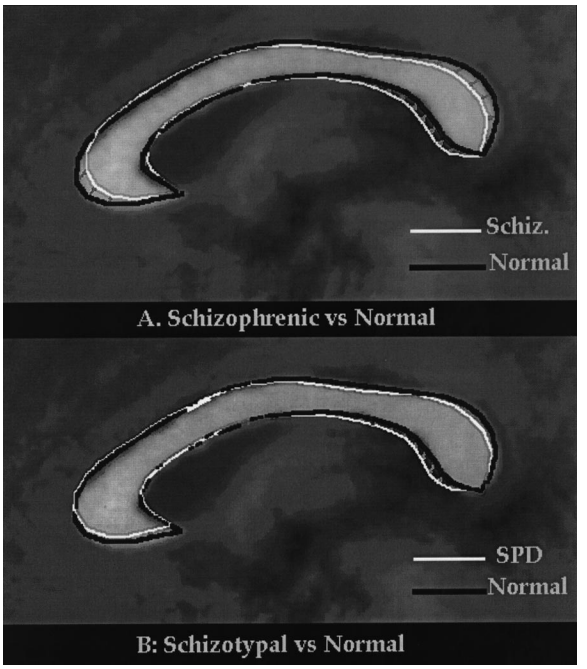

Fig. 4. Landmark-spline images. Positions of 29 equally spaced points on corpus callosum outlines in normal volunteers, patients with schizophrenia, and patients with schizotypal personality disorder (SPD). (A) Schizophrenic patients are shown with white outline compared with normal volunteers with a black line; a greater curvature of corpus callosum and smaller genu size can be seen in schizophrenic patients. (B) SPD patients (white) compared with normal volunteers; a greater curvature of the corpus callosum, but no difference in genu size is observed in SPD patients.

factors, using the Huynh–Feldt correction (Huynh and Feldt, 1976).

3. Results

3.1. Regional width and area analysis of diagnosis and gender

The area of the splenium in SPD patients was intermediate in size between that in schizophrenic patients and controls, but the area of the genu was actually larger in SPD patients than in controls (Fig. 2). Schizophrenic patients had a significantly smaller area (in mm^2) of the genu and the splenium than controls. This effect was confirmed by two-way repeated measures ANOVA of the 30 areas and diagnosis (control, schizophrenia, and SPD), with a diagnosis × position interaction ($F=2.02$, df = 58,1943, Huynh–Feldt adjusted df = 14.8, 495, $p=0.0013$). The mean area of the corpus callosum in normal controls ($638\ mm^2 \pm 94$) was larger than that in schizophrenic patients ($600\ mm^2 \pm 88$), but the difference was not statistically significant in a two-group comparison. The mean area of the corpus callosum in schizophrenic patients was comparable to values in other studies (e.g., Raine et al., 1990; $590\ mm^2 \pm 120$). Next, the 30 areas of the corpus callosum in the three groups were individually compared by diagnosis with a one-factor follow-up ANOVA for post-hoc simple interactions (Fig. 2).

For comparability to other studies, we also performed an ANOVA on relative callosal size scores (sector area/whole slice cortical area). The repeated measures ANOVA comparing the three groups (control, schizophrenia, and SPD) was significant (group × diagnosis interaction: $F=1.88$, Huynh–Feldt adjusted df = 15.1, 507, $p=0.022$). Schizophrenic patients showed similarly located decreases in relative corpus callosum area as in the previous analysis, indicating that the observed changes were independent of brain size. Analyses of between-group width and length differences were not significant. Division into three callosal regions, as done in some earlier studies (Uematsu and Kaiya, 1988; Casanova et al., 1990a,b; Colombo et al., 1993), did not yield significant callosal position × diagnostic group interactions, indicating the advantage of examining smaller callosal regions. Combining the 30 sectors into five groups of six sectors each for post-hoc testing showed a significant size decrease in the posterior-most segment in schizophrenic patients (mean = $187\ mm^2$) compared with controls ($206\ mm^2$; $F=5.23$, df = 1,55, $p=0.026$). The anterior group of sectors was also smaller in size in schizophrenic patients ($154\ mm^2$) than in controls ($165\ mm^2$), but the difference was not significant ($F=2.14$, df = 1,55, $p=0.15$).

Gender effects were evaluated only in the schizophrenic and normal groups, since there was only one female patient with SPD. The repeated measures ANOVA demonstrated that area of the corpus callosum was significantly smaller in female

subjects than in males (gender effect: $F=2.32$, df = 58, 1943, Huynh–Feldt adjusted df = 8.43, 446.70, $p=0.0168$). However, there was neither a significant gender × diagnosis nor a significant gender × diagnosis × position effect.

3.2. Total callosal area

The total mean areas of the corpus callosum (in mm^2) in normal controls (638 ± 94), SPD patients (641 ± 97), and schizophrenic patients (600 ± 88) did not differ significantly (three-group ANOVA: $F=1.51$, df = 2, 67, $p=0.22$). These means were comparable to those in other studies (e.g., Raine et al., 1990: 590 ± 120).

3.3. Neuropsychological and clinical correlates of callosal area

On an exploratory basis, correlation coefficients were calculated between the WCST score on percent perseverative errors (PPE) and each of the 30 areas of the corpus callosum in the combined group of patients (SPD + schizophrenia). We hypothesized that smaller callosal areas would be associated with poorer performance. Six areas in the posterior callosum showed significant negative correlations (areas 21–24, 26, 28; $p<0.05$, one-tailed). When the corpus callosum was divided into five areas, the posterior-most segment area (sectors 25–30) showed a significant correlation in the expected negative direction ($p<0.05$) with the PPE score. The relationship between callosal size and the PPE score was also examined in high-PPE (poor performance) and low-PPE (better performance) subgroups formed on the basis of the median score (performance group × area interaction: $F=2.36$, Huynh–Feldt adjusted df = 8.0, 377, $p=0.017$). Lastly, a three-group ANOVA comparing control, SPD, and schizophrenic subjects revealed a significant effect of performance group ($F=2.10$, Huynh–Feldt adjusted df = 9.26, 398.06, $p=0.0269$), but the diagnosis × performance group interaction showed only a trend-level effect ($F=1.62$, Huynh–Feldt adjusted df = 18.51, 398.06, $p=0.0509$). No significant correlations were found between the area of the corpus callosum and the animal names test of verbal fluency, line orientation, CVLT total correct scores, or scores of semantic categorization.

Exploratory correlational analyses examined possible relationships between reduced corpus callosum area for the five groups of sectors and clinical variables (BPRS total score, positive and negative symptom groupings, illness duration, and number of hospitalizations). We accepted only correlations consistent with the majority of corpus callosum studies, with reduced size being associated with more severe symptoms. A significant correlation was found in the expected negative direction (bigger corpus callosum associated with less severe symptoms, tested one-tailed) between the anterior-most segment and the BPRS total score for positive symptoms ($r=-0.38$, df = 22, $p<0.05$, one-tailed) and unusual thoughts ($r=0.37$, df = 22, $p<0.05$). The positive symptom subscore of suspiciousness ($r=-0.54$, df = 22, $p<0.005$) was also correlated. No significant correlations in any group were found between the five groups of callosal sectors and negative symptom or total BPRS score. Longer duration of illness was associated with smaller posterior-most sector size ($r=-0.46$, $p<0.02$). It is important to emphasize that no corrections were made for multiple comparisons, so the clinical correlations noted above must be considered purely exploratory.

3.4. Chi-square image analysis

The data are displayed as a two-dimensional pixel-by-pixel frequency distribution image and a pixel-by-pixel chi-square/*p*-value map (Fig. 3). Consistent with the ANOVA, the corpus callosum of the schizophrenic group shows decreased area in the anterior genu and in the splenium. In addition, the splenium and isthmus are rotated downward and inward. In the SPD group, less prominent differences are observed. A region on the superior edge of the callosum just posterior to the genu is narrower in SPD patients than in either controls or schizophrenic patients.

3.5. Corpus callosum edge shape analysis

In the schizophrenic group, the anterior edge of the genu is displaced posteriorly (Fig. 4A) to a

greater extent than the posterior aspect, a finding consistent with a decreased area in this region compared with control values. At the posterior (isthmus and splenium) end, all of the points on the superior and the inferior aspects are displaced inferiorly and anteriorly. However, the inferior aspect is displaced to a slightly lesser extent than the superior aspect, a finding consistent with decreased area in this region and a downward swing of the corpus callosum. In SPD patients (Fig. 4B), the genu portion is essentially the same size as in controls. The posterior region is bowed downward as in the schizophrenic patients, but it does not show the decrease in area noted in the schizophrenic group. These findings are consistent with the results seen in both the regional area and the chi-square analyses. The repeated measures ANOVA examining the displacement shows a statistically significant effect of location × direction (x and y value) × group ($F=2.69$, Huynh–Feldt adjusted df = 8.87, 297.13, $p=0.005$).

3.6. Corpus callosum size, shape and ventricular volume

Since Casanova et al. (1990a,b,c) hypothesized a relationship between bowing of the corpus callosum and ventricular size, we examined the correlation between total ventricular size and callosum surface position. Corpus callosum edge positions were expressed as in Fig. 4 for each patient as the x and y difference between controls and the individual schizophrenic patient. These scores (with adjacent change scores averaged to yield 16 top surface and 16 bottom surface x and y patient displacement scores) were correlated with total relative ventricular size. A series of significant correlations were found with anterior × displacement positions more anterior in schizophrenic patients, and posterior × displacement positions more posterior, consistent with an opening or bowing outward of the corpus callosum in individuals with larger ventricles (on top surface of corpus callosum, from $x1$ at the anteriormost to $x16$ at the posteriormost: for $x4$, $r=-0.44$; $x5$, $r=-0.49$; $x6=-0.50$; $x7$, $r=-0.45$; $x13$, $r=0.37$; $x14$, $r=0.40$; $p<0.05$ for $r>0.32$; $p<0.025$ for $r>0.38$; $p<0.01$ for $r>0.44$). Upward displacement of the center section of the corpus callosum was less striking (no y displacement was significantly correlated with total relative ventricular size or lateral ventricular size). The anterior ventricular volume was associated with downward displacement of the most anterior and most posterior sections of the corpus callosum ($y1$, $r=0.49$; $y2$, $r=0.53$; $y3$, $r=0.56$; $y4$, $r=0.47$; $y5$, $r=0.39$; $y15$, $r=0.41$; $y16$, $r=0.51$) providing some evidence of bowing.

We also examined the correlation between the lateral ventricle, anterior horn, temporal horn and total ventricular volume to the size of the five segments of the corpus callosum (both expressed in cm^3 and relative to whole brain volume). There were no significant correlations between size (in cm^3) between any part of the ventricular system and the corpus callosum. For structures expressed as relative size, there was one correlation between temporal horn and segment 2 of the corpus callosum, indicating smaller corpus callosum size associated with larger relative ventricular size ($r=-0.351$, $p<0.05$, one-tailed without Bonferroni correction) in patients with schizophrenia. In normal subjects, lateral and total ventricular relative size were correlated with segment 1 of the corpus callosum ($r=-0.422$, -0.402, $p<0.025$, one-tailed). No significant negative correlations were found in SPD patients.

4. Discussion

4.1. Anatomical change

In this study, we found that the genu of the corpus callosum was larger in SPD patients than in normal controls, whereas it was smaller in schizophrenic patients. In contrast, the splenium of the corpus callosum was smaller in SPD patients than controls, but larger in SPD patients than schizophrenic patients. Thus, for the splenium, SPD patients appeared to be on a continuum between schizophrenic and normal subjects. The lesser cognitive impairment in SPD patients could reflect the larger size of the genu, which might serve to compensate for the mild size decrease in the splenium in SPD.

Decreases in area could be related to underlying decreases in fiber number, in fiber diameter, in

non-axonal components resulting in increased fiber density, mechanical pressure on the corpus callosum from expanding ventricular size, or a combination of these variations. In post-mortem samples, Nasrallah et al. (1983) and Casanova et al. (1989) found no difference in the density of corpus callosum fibers (number per unit area) between control and schizophrenic brains. This suggests that the smaller cross-sectional areas found in the genu and splenium of the corpus callosum in the present study derive from fewer total axonal fibers traveling between cortical regions relative to total brain cross-sectional area. Casanova et al. (1989) found no evidence of gliosis or degenerated myelin, perhaps suggesting developmental origins of callosal size differences. While we found no association of a thinner corpus callosum with ventricular enlargement, there was some evidence of a slightly deeper and more flared 'U' shape, not entirely inconsistent with the changes in curvature observed by Casanova et al. (1990a–c), although manifest more in the lowering and opening of the outer thirds rather than a curving of the middle third. Thus, shape may be more affected by ventricular enlargement than actual size.

Pandya and Seltzer (1986) found in rhesus monkeys that the majority of fibers that interconnect prefrontal regions travel through the genu — the area (regions 3–6 in our analyses) that shows the greatest increase in SPD and the greatest decrease in schizophrenia in our study. Fibers that emanate from the medial and ventral surfaces of the frontal lobe pass through the most ventral part of the genu of the corpus callosum, while those that emanate from the arcuate concavity (posterior dorsolateral prefrontal cortex) pass through the most caudal part of the genu. If the same pattern of connectivity found in the rhesus monkey held true in man, then our results could be taken to suggest that the increase in callosal area in SPD patients (greatest difference in sector 3) is associated with enhanced interhemispheric transfer between medial and ventral prefrontal regions, areas often associated with affective function. In contrast, the decreased area in schizophrenic patients falls more posteriorly in callosal sector 5, connecting posterior dorsolateral areas that may be more associated with speech and short-term memory function. We observed our three groups (schizophrenic, SPD, and normal) to be similar in callosal size in the body of the corpus callosum, which conducts fibers from premotor, motor, anterior parietal, and parts of cingulate and insula (our areas 7–19); and the isthmus (our areas 20–25), which connects the posterior parietal lobe and parts of the cingulate and insula. However, temporal lobe connections, along with others, pass through the splenium (our areas 26–30), where we observed decreases in callosal size for schizophrenic and, to a lesser extent, SPD patients. Superior temporal fibers pass through the anterior region of the splenium, overlapping with some fibers from the posterior parietal lobe. Inferior temporal fibers pass through the middle portion of the splenium and the anterior commissure (see Fig. 5).

Several interpretations of the reported size differences must be considered. First, a primary abnormality of related cortical regions could be reflected in secondarily decreased trans-hemispheric inter-cortical connections. Frontal lobe volume decreases (reviewed below) might be associated with corresponding regional corpus callosum change. A cortical defect could result in cells being absent that would normally project axons across the corpus callosum. Alternatively, if there were defects in inter-hemispheric pathway development, fibers leaving their cells of origin, which

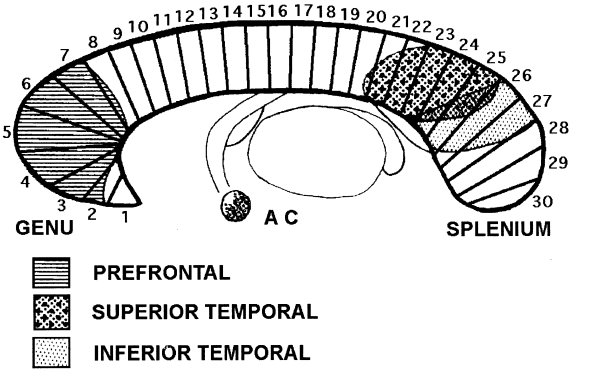

Fig. 5. Locations of fibers in the corpus callosum. Fibers connecting prefrontal and temporal cortical regions as determined in primate studies (adapted from Pandya and Seltzer, 1986) are shown.

would normally transit the corpus callosum, might not reach their intended contralateral cortical targets. Lastly, relatively independent processes, including lack of frontal development or ventricular enlargement, might distort the contours of the corpus callosum leading indirectly to regional size difference. The greater variation in callosal shape seen in Fig. 3 might be explained by such effects.

4.2. Frontal lobe abnormality

Schizophrenic patients show impairments in frontal lobe functioning as assessed by neuropsychological tests, including shifting sets and impaired executive function (van der Does et al., 1993). Corresponding but milder deficits have been shown in SPD patients (Trestman et al., 1995). In addition to neuropsychological findings, there is anatomical evidence, derived from MRI studies, for decreases in frontal lobe volume (Andreasen et al., 1986; Turetsky et al., 1995). Interestingly, prefrontal area reduction was seen in a nonpatient volunteer sample scoring high on personality measures of schizotypy (Raine et al., 1992). Functional imaging studies have also characterized the prefrontal cortex as having decreased metabolic activity in schizophrenia (for review, see Buchsbaum and Hazlett, 1998) and decreased perfusion during performance on the WCST, a task sensitive to frontal lobe damage (e.g., Weinberger et al., 1986, 1988). SPD patients similarly showed a perfusion pattern that differed from that seen in normal controls during the performance of the WCST (Buchsbaum et al., 1997a). In a ^{31}P-magnetic resonance spectroscopy study, Keshavan et al. (1993) reported a positive correlation between high-energy phosphate in the frontal lobe and corpus callosum genu area in schizophrenia; this finding provides a suggestive link between the reported frontal functional deficit and diminished inter-hemispheric communication in schizophrenia.

The negative correlations between the anterior corpus callosum region and the severity of BPRS positive symptoms suggest that frontal rather than temporal interhemispheric transfer may be more important in the genesis of positive symptomatology. Tibbo et al. (1998) found smaller corpus callosum size associated with more severe negative symptoms as determined by the Scale for the Assessment of Negative Symptoms, but we failed to find a significant correlation with BPRS negative symptoms.

Selemon et al. (1995), in a post-mortem study of the brains of schizophrenic patients, found a significant increase in cell density in frontal area 9 and occipital area 17. Area 9 in the human dorsolateral prefrontal cortex is located in approximately the same portion of the frontal lobe as the possibly homologous principal sulcus region in the rhesus monkey, posited to be essential for working-memory processing (Goldman-Rakic, 1992; Williams and Goldman-Rakic, 1995). Layers III–VI (especially layers IV and V) were the affected areas. Cell size was also found to be decreased, particularly in level III. The finding of decreased cell size was accompanied by a trend-level decrease in overall cortical thickness. There was a 7% decrease in laminar width of layer V, as well as less pronounced decreases in the other layers. Selemon et al. (1995) concluded that there was a decrease in the non-cellular components of the affected layers without a decrease in the actual cell number. A possible implication of these findings is that there is a decrease in afferent fibers and/or a shrinkage of dendritic arbors, which results in the thinning of cell layers. Layers III and V contain the cells of origin of cortico-cortical and cortico-striatal projections. Cells in prefrontal cortex in layer V also have high concentrations of dopamine D_1 and D_2 receptors (Selemon et al., 1995), which may suggest their involvement in schizophrenia. Commissural fibers originating in the isocortex have their cells of origin principally in layer III and terminate in columnar fashion in and around layer IV of the contralateral target zone (Jacobson and Trojanowski, 1974; Pandya and Seltzer, 1986). A failure of cortico-cortical axons to reach their intended contralateral targets might result in a decrease in dendritic arbors and axonal branchings within the lamina, thus leading to a decrease in neuropil such as that seen in layer IV. There may also be a secondary change in metabolic activity in the cortical regions affected, consistent with the findings of functional neuroimaging studies (for review, see Buchsbaum and Hazlett, 1998).

4.3. Temporal lobe abnormalities

Many investigators have found decreases in the volume of the temporal lobes in schizophrenia (for review, see Shenton et al., 1997). Their findings are consistent with our own findings in both schizophrenic and SPD patients of decreased volume in the splenium region of the corpus callosum, which connects inferior temporal and part of superior temporal cortical regions, as well as similar findings in schizophrenia by Woodruff et al. (1993). In a tachistoscopic study, David (1987) reported defects in color naming across visual fields in schizophrenia, an observation that is consistent with a possible posterior corpus callosum dysfunction. Our finding of decreased volume in the splenium, which carries occipital as well as temporal fibers, would be consistent with David's (1987) report.

4.4. Implications of callosal size change for interhemispheric communication

How could defects in interhemispheric communication in schizophrenia result in positive symptoms characterized by delusions and hallucinations, and negative symptoms such as flattened affect, decreased goal-directed activity and cognitive impairment? Nasrallah (1985) hypothesized that activity of the right hemisphere, such as verbal and other thoughts, could be perceived as not part of the self if the right and left hemispheres did not have full communication. Randall (1983) suggested that the activity of the right hemisphere is largely not perceived by the left hemisphere under normal conditions, but that excess connections, possibly resulting from insufficient pruning in development, could result in mistakes about whether voices and thoughts were derived from within or without. Intact communication between the left hemisphere, which is specialized for linear logical relationships, and the right hemisphere, which deals more with pattern recognition, may be a necessary substrate for healthy reality testing. If the right and left hemispheres were not fully connected, it might provide a fertile substrate for mis-analysis of causal and other relationships between perceived events, facts and beliefs — in short, delusions. Increasing bizarreness of delusions could indicate a worsening of hemispheric miscommunication, which could result from too much or too little communication.

The findings in this study, while limited to decreases in specific regions of the corpus callosum, are in accord with a body of literature (see Introduction) suggesting that abnormalities of interhemispheric communication could result in the symptoms and cognitive impairment that characterize schizophrenia. Integrated functioning of linked cortical regions is necessary for normal brain function, and callosal abnormalities such as those reported in the present and earlier reports could disrupt interhemispheric communication.

Acknowledgements

This work was funded in part by a grant from the National Institute of Mental Health (MH R01-40071) and support from the Charles A. Dana Foundation to Dr Buchsbaum; VA Merit Award 7609-20 to Dr Siever; the Mount Sinai Clinical Research Center (5-M01-RR00071) from the National Center of Research Resources, NIH; a grant from the National Institute of Mental Health (MH-56460) and a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression to Dr Hazlett. We thank John Edgar, David Schnur, Jack Hirschowitz, Vivian Mitropoulou, Melissa Nunn, Andrea Solimando, Marja Germans, Melissa Biren Singer, Tina M. Ciaravolo, and Christina Luu-Hsia for assisting in patient recruitment and evaluation; Cheuk Tang for computer systems support; and Lorenna Fuentes for secretarial and administrative aid.

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