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A longitudinal study of the corpus callosum in chronic schizophrenia

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Abstract

Background—Decreased callosal size and anisotropy have been described in schizophrenia patients but their longitudinal progression remains poorly understood.

Methods—We performed diffusion-tensor and structural magnetic resonance imaging at baseline and at follow-up four years later in 49 chronic schizophrenia patients and 16 healthy comparison subjects. Schizophrenia patients were subdivided into good-outcome (n=23) and poor-outcome (n=26) groups. Baseline-to-follow-up changes in size, shape, position and fractional anisotropy of the corpus callosum, divided into five sagittal sections and five rostral-caudal segments, were assessed.

Results—At baseline scan and in comparison to healthy subjects, schizophrenia patients displayed 1) smaller callosal size, 2) lower average anisotropy in all sagittal sections except the midline, 3) more dorsal average coordinate position. During the four years after the baseline scan, patients with schizophrenia exhibited a more pronounced decline in absolute size of the corpus callosum than healthy comparison subjects. As compared with the good-outcome group, the corpus callosum in poor-outcome patients at baseline was of smaller size and lower average anisotropy, more elongated and posteriorly positioned. During the follow-up interval, poor-outcome patients displayed a more pronounced decline in size but less pronounced decline in anisotropy of the corpus callosum than patients with good outcomes.

Conclusions—Differences in callosal size between schizophrenia patients and healthy subjects seen at baseline continue to widen in the chronic phase of the illness, especially in patients with poor functional outcome. Baseline differences in callosal anisotropy among patients with different outcomes, however, diminish over time.

Keywords

Corpus callosum; MRI; Kraepelinian schizophrenia; poor outcome; longitudinal course; follow-up

1. Introduction

Prominent theoretical models have accorded the corpus callosum with a pivotal role in the pathophysiology of schizophrenia (David 1994; Cogger and Serafetinides, 2006; Crow et al, 1998, 2007). Indeed, many morphological and neuroimaging studies have detected abnormalities in callosal shape (DeQuadro et al, 1999; Downhill et al, 2000; Narr et al, 2000; Frumin et al, 2002), size (Arnone et al, 2008; Rotarska-Jagiela et al, 2008), density (Hulshoff-Pol et al, 2004; Seok et al, 2007; Wolf et al, 2008), structure (Flynn et al, 2003; Diwadkar et al, 2004; Kubicki et al, 2005) and function (Innocenti et al, 2003). In contrast to the pioneering postmortem work of Rosenthal and Bigelow (1972), who found dorsoventral dimension of the callosal body increased in schizophrenia patients, most of the following studies using variety of methodologies have found the smaller rather than larger absolute callosal size (see their meta-analyses in Arnone et al, 2008 and Woodruff et al, 1995; and reviews in Innocenti et al, 2003 and Shenton et al, 2001), with few exceptions (Nasrallah et al, 1986; Uematsu and Kaiya, 1988; John et al, 2008). Several of the reports have also found increased curvature of the whole corpus callosum and/or its subdivisions (Downhill et al, 2000; Narr et al, 2000; Frumin et al, 2002), but no differences in full callosal length or its size relative to the whole-brain volume (Woodruff et al, 1995). The bulk of this literature has especially expanded in the last decade since the development of diffusion-tensor imaging and its first application to the study of schizophrenia (Buchsbaum et al, 1998). Almost invariably, diffusion-tensor imaging studies described decreased anisotropy in callosal subregions, including the genu (Brambilla et al, 2005; Kanaan et al, 2006; Buchsbaum et al, 2006a; Price et al, 2007; Mitelman et al, 2007; Miyata et al, 2007; Kubicki et al, 2008; Rotarska-Jagiela et al, 2008), body (Ardekani et al, 2003; Hubl et al, 2004; Kubicki et al, 2005; Brambilla et al, 2005; Buchsbaum et al, 2006a) and splenium (Foong et al, 2000; Agartz et al, 2001; Ardekani et al, 2003; Kumra et al, 2004; Brambilla et al, 2005; Price et al, 2007; Cheung et al, 2008; Gasparotti et al, 2009).

Reports on differential callosal pathology at various stages of illness progression, however, have been few and not nearly as consistent. Cross-sectional comparison of first-onset with chronic schizophrenia patients reported mainly genu width reductions in the recent onset patients and more widespread reductions, involving also the isthmus, in the chronic schizophrenia group, thus suggesting posterior callosal involvement with longer duration of illness and dynamic anteroposterior spread of white matter decline over time (Walterfang et al, 2008a). Attempts to correlate callosal size with illness duration proved inconclusive, with an inverse relationship noted in one study (Downhill et al, 2000), no such relationship in another (Meisenzahl et al, 1999) and a direct relationship with callosal length in a third one (Colombo et al, 1994). Supportive of the relationship with illness duration, one study reported decreased anisotropy in the splenium (and not the genu) of the chronic but not first-episode schizophrenia patients (Friedman et al, 2008), yet another revealed no between-group differences (Schneiderman et al, 2009). Other cross-sectional studies have found a relationship between the decline in callosal anisotropy and longer duration of illness (Mori et al, 2005), suggesting that early observable deficits are progressive and tract-specific as no such correlations were found in the pyramidal tracts (Carpenter et al, 2008), but these findings have not been universal either (Foong et al, 2000; Miyata et al, 2007; Rotarska-Jagiela et al, 2008). The only longitudinal volumetric study to date, involving patients with childhood-onset schizophrenia, documented a greater splenial shrinkage over time in the schizophrenia group (Keller et al, 2003). Yet, in dissonance, a recent meta-analysis of callosal morphometry concluded that reductions in size are more pronounced in first-episode than chronic patients (Arnone et al, 2008) and a diffusion-tensor imaging study reported a lesser anisotropy decline with aging in both the genu and splenium in schizophrenia patients than healthy subjects (Friedman et al, 2008).

Several studies probed a relationship of callosal deficits with illness severity. Reductions in posterior callosal anisotropy (unlike decreases in the genu) have been associated with poor functional outcome in patients with chronic schizophrenia (Mitelman et al, 2007), as have been more widespread reductions in callosal density (Hulshoff-Pol et al, 2004) and increased callosal length (Uematsu and Kaiya, 1988; Colombo et al, 1994). Greater severity of positive, negative and general psychopathology symptoms has been associated with lower anisotropy values throughout the corpus callosum (Brambilla et al, 2005; Mitelman et al, 2007; Kubicki et al, 2008), as well as with diminished magnetization transfer ratio (Foong et al, 2001) and with variously measured reduced callosal size (Günther et al, 1991; Woodruff et al, 1997; Tibbo et al, 1998; Downhill et al, 2000).

It appears that callosal abnormalities are already present close to illness onset (DeQuadro et al, 1999; Keshavan et al, 2002; Bachmann et al, 2003; Price et al, 2007; Arnone et al, 2008; Cheung et al, 2008; Gasparotti et al, 2009) and perhaps even premorbidly (Walterfang et al, 2008b). Their longitudinal course and its relation to outcome, however, can only be properly ascertained using a follow-up design. In this study, we utilized diffusion-tensor and structural magnetic resonance imaging to investigate longitudinal progression of morphometric and structural deficits in the corpus callosum of patients with chronic schizophrenia on average two decades after the first psychotic outbreak. We evaluated the relation of longitudinal changes to the functional outcome of the illness, having hypothesized that progressive course will be most evident in those with a more severe symptomatology. To our knowledge, no longitudinal neuroimaging studies of the corpus callosum in adult patients with schizophrenia have previously been published.

2. Methods

2.1. Subjects

The follow-up cohort comprised 49 patients with schizophrenia (age at baseline scan 42.69 ± 12.29 years; illness duration at baseline 18.67 ± 12.05 years; 7 women; 2 left-handed) and 16 healthy subjects (age at baseline 41.63 ± 12.23 years, $t_{63}=0.30$, $p=\text{ns}$; 7 women; no left-handed), scanned approximately 4 years apart (4.10 ± 0.54 years for schizophrenia patients and 4.22 ± 0.52 years for healthy subjects, $t_{63}=0.76$, $p=\text{ns}$; see full sample description in Mitelman et al, 2009). Schizophrenia patients had significantly lower baseline Mini-Mental State Examination (MMSE) scores than healthy subjects (26.47 ± 3.15 vs. 30.00 ± 0.00 , $t_{63}=4.17$, $p=0.0001$). PANSS subscale scores were 19.04 ± 6.80 (positive), 19.00 ± 7.25 (negative), and 40.53 ± 13.23 (general). Based on the prevailing pattern of antipsychotic treatment over the three-year period preceding the baseline scan (available for 37 participants), schizophrenia patients were divided into those treated with predominantly typical antipsychotics (30%), atypical antipsychotics (24%), no antipsychotics (30%), and a mixture of both antipsychotic types (16%). These 65 participants underwent morphometric analyses, while a smaller sample of 49 participants (15 healthy subjects and 34 schizophrenia patients, of which 17 with good outcomes and 17 with poor outcomes) was available for the diffusion-tensor imaging analyses. All subjects signed informed consent for their participation in the study.

Patients with schizophrenia were classified into the good-outcome ($n=23$) and poor-outcome ($n=26$) subgroups based on the criteria by Keefe et al (1987). In brief, these required that poor-outcome patients met the following criteria for at least five years prior to study contact: 1) continuous hospitalization or complete dependence on others for food, clothing, and shelter; 2) no useful employment; and 3) no evidence of symptom remission. All other schizophrenia patients were considered good-outcome. Patients classified as poor-outcome (age 47.35 ± 11.9 years; 1 woman) were significantly older at baseline scan than patients with good outcomes (37.44 ± 10.68 years, $t_{47}=3.05$, $p=0.004$; 6 women), but did not differ in length of between-scan interval (3.98 ± 0.4 years vs. 4.24 ± 0.65 years, respectively, $t_{47}=1.76$, $p=0.09$). PANSS

assessments at baseline showed that patients with poor outcome, as compared to those with good outcome, had significantly more severe positive (22.4 ± 6.64 vs. 15.39 ± 4.92 , $t_{47}=4.12$, $p=0.0002$), negative (22.36 ± 7.40 vs. 15.35 ± 5.08 , $t_{47}=3.79$, $p=0.0004$), and general psychopathology scores (45.12 ± 10.05 vs. 35.32 ± 14.63 , $t_{47}=2.7$, $p=0.01$), as well as a longer duration of illness (24.77 ± 11.71 vs. 12.29 ± 8.78 years, $t_{41}=3.94$, $p=0.0003$), but did not differ significantly in MMSE scores (25.79 ± 3.56 vs. 27.32 ± 2.36 , $t_{47}=1.6$, $p=0.12$).

2.2. Image acquisition and processing

T₁-weighted MR images were acquired using a 1.5T Signa 5× scanner (GE Medical Systems) with a 3D-SPGR sequence (TR=24msec, TE=5msec, flip angle=40°, matrix size 256×256, field of view 23cm, NEX=1, slice thickness 1.2mm, total slices 128). The diffusion tensor sequence acquired fourteen 7.5-mm-thick slices (TR=10s, TE=99ms, TI=2.2s, b=750s/mm², $\delta=31$ ms, $\Delta=73$ ms, NEX=5, voxel size 1.8×1.8×7.5 mm, FOV=230, no gaps). In order to solve for the components of the diffusion tensor, seven diffusion EPI images were obtained: six with different non-collinear gradient weightings and one with no diffusion gradient applied. The diffusion tensor for every voxel in a slice was then computed by solving the seven simultaneous signal equations relating the measured signal intensity to the diffusion tensor. Anatomical SPGR MR images were resectioned to standard Talairach-Tournoux position using the algorithm of Woods et al (1993), a 6-parameter rigid-body transformation, and the standard MNI brain. The anisotropy images from each subject were then aligned to subject's own standard-position anatomical images using the 12-parameter transformation.

2.3. Callosal regions of interest

The corpus callosum was manually outlined on 5 sections in the sagittal plane, followed by co-registration with the matching anisotropy images. To this end, the midsagittal section was first identified by the x-coordinate in the center of the axial cerebral cross-section with the most visible splenium. We then used our standard Sobel gradient filter to enhance the contrast, place the outlining points and spline the full extent of the corpus callosum on the midsagittal and two adjacent slices in each hemisphere yielding 5 contiguous 1.2-mm-thick region-of-interest edges. The slices were labeled 1 to 5 from the right hemisphere (peripheral-most slice 1, more central slice 2) through the midline (slice 3) to the left hemisphere (more central slice 4 and peripheral-most slice 5). Each edge was then divided into 5 equal rostro-caudal segments by cutting a perpendicular line through the medial axis of the outline generated by a skeletonization algorithm (Fig. 1). These segments, starting anteriorly, were anatomically approximated as the rostrum and genu (segment 1), anterior body (segment 2), midbody (segment 3), posterior body (segment 4) and splenium (segment 5). Previous 5-segment parcellations of the corpus callosum in schizophrenia have not shown consensus over the isthmus identification (Venkatasubramanian et al, 2003), variously ascribing it to segment 4 (Bachmann et al, 2003) or 5 (John et al, 2008). We therefore chose to refer to segment 4 as the posterior body and to segment 5 as the splenium. In each traced sagittal slice we obtained:

1. Areas of full slice and each rostro-caudal segment in mm².
2. y and z coordinates of centroids of each rostro-caudal segment. We identified the midline and dorsoventral center of the anterior commissure visually on the axial MRI slice with its greatest prominence. The y and z position of each callosal segment was then expressed in mm relative to the y and z position of the anterior commissure.
3. Length of full slice and of each rostro-caudal segment – as distance between the extreme points in each outline.
4. Radii of full callosal curvature and of callosal body (comprising only truncal segments 2, 3, and 4), and radii of each rostro-caudal segment.

5. Mean fractional anisotropy (across all pixels) in each rostro-caudal segment. In order to control for changes in the DTI acquisition environment over the follow-up period (averaging for 5 NEX was done in the Matlab routine for the first participants and using the GE software for the later subjects), these values were expressed relative to mean whole-brain white matter anisotropy, as we have previously done (Mitelman et al, 2006 and 2007; Buchsbaum et al, 2006b; Schneiderman et al, 2007 and 2009). The whole-brain measures were obtained from the traced and segmented coronal images, as described in Mitelman et al, 2009. This FA normalization is quite analogous to correcting BOLD or FDG PET values to whole-brain activity levels as is widely done to control unwanted drift effects over time.

2.4. Statistical analysis

In order to put the longitudinal data in proper perspective, we analyzed baseline between-group differences in size, shape (length, radii of curvature), position (y and z coordinates) and anisotropy first. For these analyses, we entered all regional values into a multiway ANCOVA (subjects' age as covariate) with independent diagnostic groups (schizophrenia patients and healthy subjects or good-outcome and poor-outcome patients) and repeated measures for sagittal slices (1 to 5) and rostro-caudal segments nested within each slice (1 to 5). Main effects of diagnostic group membership and group interactions with measured regional values were documented.

For longitudinal analyses, all of the obtained regional measures were entered into a similar nested multiway ANCOVA (age at baseline as covariate) with two independent factors (schizophrenia patients and healthy subjects or good-outcome patients and poor-outcome patients) and within-group factors (baseline and follow-up scans, 5 sagittal slices, and 5 rostro-caudal segments). Significant diagnostic group $\times$ time and higher-order (group $\times$ time $\times$ slice, group $\times$ time $\times$ segment and group $\times$ time $\times$ slice $\times$ segment) interactions were documented, each significant interaction was subjected to the Huynh-Feldt procedure for degree-of-freedom inflation correction and graphs were examined for any discernable patterns of differential longitudinal changes, — all described in the results section (Huynh-Feldt corrected p values are provided only when different from the original p values). In order to estimate the impact of illness duration on observed differences among schizophrenia patients with good and poor outcomes, we ran a separate ANCOVA adding illness duration (years between first neuroleptic treatment and baseline scan) as the second covariate (note that illness duration was not available for 5 patients); it is reported when disparate results were obtained. In addition to the analyses of the absolute callosal size, we also normalized the absolute measures by adding total brain volume as a covariate to cross-sectional ANCOVAs (as recommended by Constant et al, 1996) and a baseline minus follow-up difference in total cerebral volume as a covariate in longitudinal ANCOVAs; we report these relative to brain size results following the presentation of the absolute data. Adding gender as an independent factor in the ANCOVAs did not produce significant interactions by sex and is not separately reported.

3. Results

3.1. Schizophrenia patients and healthy subjects

3.1.1. Callosal size at baseline—Overall callosal size (mean area of 5 sagittal slices) was smaller in schizophrenia patients than in healthy subjects (main effect of diagnostic group at a trend level, $F_{1, 62}=3.87$, $p=0.054$) and this tended to be most evident in the right hemisphere and interhemispheric midline slices (diagnostic group $\times$ slice interaction, $F_{4, 248}=2.81$, $p=0.026$, Huynh-Feldt corrected $p=0.08$, Table 1). Significant diagnostic group $\times$ segment interaction ($F_{4, 248}=2.94$, $p=0.02$, Huynh-Feldt corrected $p=0.03$) indicated smaller areas in patients than in healthy subjects for every rostro-caudal segment except posterior body (segment 4).

Controlling for variation in brain size by adding total brain volume as covariate yielded a significant main effect of diagnostic group ($F_{1, 61}=4.79$, $p=0.03$), indicating smaller relative callosal volumes (ratios) in patients than in healthy subjects.

3.1.2. Longitudinal changes in callosal size—During the time to follow-up, patients with schizophrenia showed decline in the overall callosal size (mean area of 5 callosal slices) whereas it remained steady (or slightly increased) in healthy subjects (diagnostic group $\times$ time interaction, $F_{1, 62}=4.63$, $p=0.035$, Fig. 2). This interaction was not significant when baseline-to-follow-up change in total cerebral volume was added as a covariate.

3.1.3. Callosal shape and position—Patients with schizophrenia displayed greater callosal length than healthy subjects in peripheral-most slices 1 and 5, but were somewhat shorter in the more central slices 2, 3, and 4 (diagnostic group $\times$ slice interaction, $F_{4, 248}=3.64$, $p=0.0066$, Huynh-Feldt corrected $p=0.01$). There were no significant between-group differences in the radii of callosal curvature or y coordinates of rostro-caudal segments (Table 2). The z coordinates of segmental centroids tended to be overall higher (i.e. situated more dorsally) in schizophrenia patients than in healthy subjects (main effect of diagnostic group, $F_{1, 56}=3.39$, $p=0.07$) and this pattern was seen in every callosal segment except the splenium (diagnostic group $\times$ segment interaction, $F_{4, 224}=2.86$, $p=0.02$, Huynh-Feldt corrected $p=0.065$).

There were no between-group differences in progression of the callosal length, radius of its curvature, or y and z coordinates of segmental centroids over time.

3.1.4. Callosal Anisotropy—At baseline, average fractional anisotropy in patients with schizophrenia tended to be lower than in healthy subjects in peripheral hemispheric slices (1, 2, 4, 5), with no differences in the midline slice (diagnostic group $\times$ slice interaction, $F_{4, 232}=2.43$, $p=0.048$, Huynh-Feldt corrected $p=0.09$).

There were no between-group differences in the progression of callosal anisotropy over the time to follow-up.

3.2. Good-outcome and poor-outcome patients

3.2.1. Callosal size at baseline—Areas of the sagittal callosal slices 1 and 2 (right hemisphere) were larger while area of slice 4 (left hemisphere) was smaller in poor-outcome patients than in patients with good outcomes (diagnostic group $\times$ slice interaction, $F_{4, 184}=4.18$, $p=0.003$, Huynh-Feldt corrected $p=0.004$ and with total brain volume as covariate $F_{4, 180}=4.16$, $p=0.003$, Huynh-Feldt corrected $p=0.004$). Main effect of diagnostic group did not reach statistical significance.

3.2.2. Longitudinal changes in callosal size—Poor-outcome schizophrenia patients showed a greater decrease in overall callosal size than patients with good outcomes (diagnostic group $\times$ time interaction, $F_{1, 46}=8.41$, $p=0.006$; with illness duration as covariate, $F_{1, 39}=3.97$, $p=0.053$, Fig. 3). This interaction remained significant when baseline-to-follow-up difference in total brain volume was added as a covariate ($F_{1, 45}=6.49$, $p=0.014$, Huynh-Feldt corrected $p=0.02$).

3.2.3. Callosal shape and position—The corpus callosum was more elongated in patients with poor outcomes than in the good-outcome group (main effect of diagnostic group, $F_{1, 46}=4.51$, $p=0.04$). There were no between-group differences in the radii of full callosal or truncal curvature, but radii of the splenial and anterior body curvature tended to be greater and radius of the posterior body curvature lower in the poor-outcome group (diagnostic group $\times$ segment interaction, $F_{4, 184}=2.65$, $p=0.035$, Huynh-Feldt corrected $p=0.065$). The y

coordinates of segmental centroids tended to be lower (situated more caudally) in patients with poor outcomes (main effect of diagnostic group, $F_{1, 41}=3.35$, $p=0.075$), specifically for the splenium and posterior body (group $\times$ segment interaction, $F_{4, 164}=7.72$, $p=0.00001$, Huynh-Feldt corrected $p=0.001$), with no differences in z coordinates.

There were no between-group differences in changes of callosal length, radii of its curvature, or y and z coordinates of segmental centroids.

3.2.4. Callosal anisotropy at baseline—Average fractional anisotropy was significantly lower in patients with poor outcomes than in the good-outcome group (main effect of diagnostic group, $F_{1, 43}=8.55$, $p=0.006$) and this was evident in every sagittal slice (diagnostic group $\times$ slice interaction, $F_{4, 172}=7.50$, $p=0.0001$, Huynh-Feldt corrected $p=0.0005$). Especially marked anisotropy decreases in poor-outcome patients were observed in the splenium, followed by the genu of the corpus callosum (diagnostic group $\times$ segment interaction, $F_{4, 172}=6.56$, $p=0.00006$, Huynh-Feldt corrected $p=0.0002$).

3.2.5. Longitudinal changes in callosal anisotropy—Patients with good outcomes exhibited more pronounced decreases in anisotropy over time than patients with poor outcomes in every sagittal slice, thus diminishing the differences observed at baseline. There was a pattern of most marked between-group differences in the right hemisphere, dwindling with each consecutive slice from right to left (diagnostic group $\times$ time $\times$ slice interaction, $F_{4, 140}=4.55$, $p=0.002$, Huynh-Feldt corrected $p=0.01$, Fig. 4). This pattern was decomposed by a higher-order interaction showing that anisotropy decreased more in the good-outcome group in every segment of the right hemisphere slices 1 and 2, but only in the genu and splenium in the midline and left hemisphere slices 3, 4, and 5 (diagnostic group $\times$ time $\times$ slice $\times$ segment interaction, $F_{16, 560}=1.88$, $p=0.02$, Huynh-Feldt corrected $p=0.058$). This same interaction revealed that anisotropy decreased more in the poor-outcome group in comparison to patients with good outcomes only in callosal midbody in slices 2 and 3 (right hemisphere and midline) and in posterior body in slices 3, 4 and 5 (left hemisphere and midline).

Adding illness duration as covariate diminished these effects (diagnostic group $\times$ time $\times$ slice interaction, $F_{4, 124}=2.39$, $p=0.054$, Huynh-Feldt corrected $p=0.09$), but yielded a diagnostic group $\times$ time $\times$ segment interaction with similar pattern at a trend level of significance ($F_{4, 124}=2.38$, $p=0.056$, Huynh-Feldt corrected $p=0.08$), suggesting that anisotropy decreases in the good-outcome group tended to be most pronounced in the genu, anterior body and splenium of the corpus callosum, i.e. the same segments where the most marked intergroup differences were documented at baseline.

4. Discussion

4.1. Callosal size

Patients with chronic schizophrenia entered this study with smaller overall callosal size and it continued to decline over the period to follow-up, whereas the size remained steady in healthy comparison subjects. The decline in callosal size was especially marked in schizophrenia patients with poor functional outcomes and this was only partially explained by longer duration of illness in this patient group. While this decline in callosal size may be proportional to the differential decline in total brain volume among schizophrenia patient and healthy subjects, callosal shrinkage in the poor-outcome group was disproportionate to the differences in total brain volume change among patients with different outcomes. Interpretation of the changes in normalized volumes, however, requires caution as the validity of callosal standardization relative to total brain size has been questioned (Constant et al, 1996) and an inverse, if modest, allometric relationship between midsagittal size of the corpus callosum and total brain volume was reported in healthy adults (Jancke et al, 1997). Further, unlike the change in absolute size

of the corpus callosum, decline in the total cerebral volume in the compared subjects groups was not significantly different (Mitelman et al, 2009). Given that we have detected no progressive group differences in length, it appears that callosal shrinkage in patients with schizophrenia, including those with poor outcomes, was driven by its dorsoventral thinning. These findings are consistent with prior reports of more pronounced reductions in callosal size and density in patients with more severe symptomatology (Downhill et al, 2000; Hulshoff-Pol et al, 2004). Our findings also confirm the results from two previous cross-sectional investigations, which reported a more widespread callosal shrinkage in chronic in comparison to first-outbreak schizophrenia patients (Walterfang et al, 2008) and a direct association between callosal shrinkage and duration of illness (Downhill et al, 2000), and do not lend support to the opposite conclusions of a recent meta-analysis (Arnone et al, 2008).

4.2. Callosal shape and position

In shape comparisons with healthy subjects, the corpus callosum in schizophrenia patients was more elongated peripherally and shorter centrally (closer to midline) at study entrance, with these differences proven static. Further, progressive flattening of the trunca curvature was observed in healthy subjects but not in patients with schizophrenia. In line with previous reports (Uematsu and Kaiya, 1988; Colombo et al, 1994), the corpus callosum was more elongated in patients with poor outcome, which was possibly explained by smaller curvature of the anterior body and the splenium in this group of patients in comparison to those with good outcomes.

Finally, the corpus callosum in patients with schizophrenia was positioned more dorsally than in healthy subjects throughout its whole extent and posterior half of the corpus callosum was positioned more caudally in patients with poor outcomes than in the good-outcome group. Given that position occupied by the corpus callosum is mainly determined by tensile forces exerted by surrounding white matter and ultimately by surrounding volumetrics, these topographic differences may be explained by the ventricular enlargement and parietal gray matter loss in schizophrenia patients overall and by the posteriorized pattern of both gray and white matter volume reductions in the poor-outcome patient group (Mitelman et al, 2009). These intergroup differences remained steady throughout the follow-up period.

4.3. Callosal anisotropy

As we have also shown previously (Mitelman et al, 2007), in this study callosal anisotropy was significantly lower in schizophrenia patients with poor outcomes than in the good-outcome group, but these differences narrowed over the time to follow-up and especially in the callosal splenium and genu, - two regions with the starkest differences at baseline. Also consistent with our previous finding of more pronounced right-than-left hemisphere anisotropy reductions in patients with poor outcomes (Mitelman et al, 2006), the narrowing of between-group differences was especially pronounced in the right hemisphere. Although anisotropy tended to be lower in the full sample of schizophrenia patients than in healthy subjects at baseline (Mitelman et al, 2006), we did not find between-group differences in its progressive changes, which is in concert with several cross-sectional studies reporting no association between reductions in callosal anisotropy and illness duration (Foong et al, 2000; Miyata et al, 2007; Rotarska-Jagiela et al, 2008; Friedman et al, 2008). It thus appears that the anisotropy reductions observed in patients with schizophrenia in this and in the vast majority of other investigations take place earlier in the course of the illness, closer to the time of the first psychotic episode and stabilize in its chronic phase. Differential group patterns of progressive changes in callosal anisotropy and volumes among patients with varying outcomes (dwindling differences in anisotropy vis-à-vis widening differences in size), which are in contrast to changes in extrafascicular white matter (dwindling differences in both, see Mitelman et al, 2009), point to separate aging trajectories for these white matter measures in tightly bounded and highly organized white matter bundles.

4.4. Technical considerations

Only approximate generalizability of our callosal parcellation scheme must be emphasized. Although several prior studies have used callosal parcellation into rostro-caudal segments (Uematsu and Kaiya, 1988; Hauser et al, 1989; Casanova et al, 1990; Colombo et al, 1994; Woodruff et al, 1993, 1997; Hoff et al, 1994), their direct comparison can only be approximate. First, the number of segments entered into statistical analyses of size or anisotropy varied across the studies from 3 to 5 equal divisions, with a single 9-segment study (Rotarska-Jagiela et al, 2008) and two 6-segment studies (Keshavan et al, 2002; Goghari et al, 2005) employing unequal anatomical partitioning schemes (Witelson et al, 1989; Highley et al, 1999). Second, few of the analyses based their segmentation on the medial axis of callosal outline (Downhill et al, 2000; Walterfang et al, 2008b), whereas most others used radial (John et al, 2008) or vertical (Bachmann et al, 2003) partitioning. Utilization of the medial axis, however, provides a better estimate of the shape irregularities of the corpus callosum, especially when more sagittal sections are outlined in addition to the midline, which has thus far been seldom done (Bachmann et al, 2003; Rotarska-Jagiela et al, 2008). While area and shape could have been successfully analyzed using deformation-based morphometry, using the traced region of the corpus callosum divided into five rostro-caudal segments adds comparability with a range of published reports with similar or identical parcellation schemes. Further, as compared to voxel-by-voxel mapping both noise and partial volume effects are minimized by studying relatively large ($\sim 80 \text{ mm}^2$) regions.

The anteroposterior and dorsoventral shifts of the corpus callosum were assessed relative to the anterior commissure position. While this has the advantage of 1) being the 0,0,0 center of the Talairach-Tournoux coordinate system and 2) avoiding metrical problems associated with a brain bounding box reference such as minor shape changes in the frontal pole and ambiguity of the occipital pole with variations in occipetalia, it may be mechanically and developmentally linked to the corpus callosum position and thus minimize regional position effects. An internal frontal lobe landmark would have been ideal but difficult to define and many reports have actually used the genu of the corpus callosum to define the frontal lobe.

Due to the longitudinal design of the study – begun 8 years ago – some of the methodology (especially pertinent to the diffusion-tensor imaging) inevitably lagged behind the rapid technical advances in the field. Maintaining exact scanner software and hardware over a 4-year period was largely achieved with the exception of the NEX averaging of the diffusion-tensor images. Other undetected or unknown drift in hardware parameters cannot be ruled out, so that the strategy of dividing the regional FA values by mean whole-brain values appeared a conservative data analysis approach as widely used for blood flow, metabolic rate and some other modalities. We selected the strategy of coregistering subjects' baseline and follow-up scan to the same baseline anatomical image to minimize random coregistration variation associated with registration to two different anatomical scans obtained 4 years apart. As we noted elsewhere (Mitelman et al, 2006; Buchsbaum et al, 2006b), the extent of error of coregistration and potential distortion of the diffusion tensor images from less distorted structural MRI was not large. The median difference of the absolute image frame coordinates of the anterior and posterior brain edges between structural and anisotropy images was 0.0 and 1.78 mm respectively and the median difference in brain length was 2.23 mm, just above 1%. The mean absolute value in mm of the differences between the diffusion tensor and MRI locations in the anterior and posterior brain edges was +2.14 and +2.71 mm respectively and means of signed differences were close to zero, indicating a lack of systematic bias. No differences between images collected with the different NEX averaging methods were statistically significant, likewise indicating that bias in coregistration between the two averaging methods was not an important variant in coregistration. Future longitudinal assessments should directly compare larger samples of first-outbreak and chronic

schizophrenia patients, employing newer acquisition techniques and more detailed 3-dimensional shape analyses.

4.5. Conclusions

In summary, the differences in callosal size seen between schizophrenia patients and healthy subjects continued to widen during the chronic phase of the illness, on average two decades after the first psychotic outbreak, with most pronounced decline in callosal size seen in the more severe, poor-outcome patient group. All other baseline differences between schizophrenia patients and healthy subjects, as well as between schizophrenia patients with different outcomes, either remained relatively static (callosal length, curvature and topography) or diminished (callosal anisotropy) over the time to follow-up. Taken together with our prior report of the narrowing intergroup differences in cortical gray and white matter (Mitelman et al, 2009), present study emphasizes the potential uniqueness of continued callosal shrinkage in pertinence to illness progression in the chronic phase of schizophrenia.

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Figure 1.
Segmentation of the corpus callosum. Medial axis of the structure is divided into five equal rostrocaudal segments.

Figure 2.
Differential progression of mean callosal area (mm²) in healthy subjects and schizophrenia patients (diagnostic group by time ANCOVA interaction with age as covariate)

Figure 3.
Differential progression of mean callosal area (mm²) in schizophrenia patients with good and poor outcomes (diagnostic group by time ANCOVA interaction with age as covariate)

Figure 4.

Differential progression of callosal anisotropy¹ across right-to-left sagittal slices² in schizophrenia patients with good and poor outcomes (diagnostic group by time by slice ANCOVA interaction with age as covariate). Note that the most pronounced decreases in good-outcome patients over time occurred in the slices with the most pronounced intergroup differences at baseline.

¹ Note that fractional anisotropy values are standardized as a ratio of the mean regional value to mean whole-brain white matter value ($\times 1000$).

² Slice 1 – right hemisphere, slice 3 – midline, slice 5 – left hemisphere.

Table 1

Baseline and follow-up morphometry data¹

Slice area (mm ²)		Slice length (mm)		Radius of curvature (mm)		1	Average segment area (mm ²) / fractional anisotropy ⁵		5
Midline	Average ²	Midline	Average ³	Midline	Average ⁴		2	4	
Healthy subjects									
Baseline	655.20±99.94	657.01±97.91	83.60±7.28	35.87±6.18	35.80±4.75	171.18±21.18 1.057±0.20	105.82±22.82 0.812±0.17	103.26±18.97 0.843±0.24	89.98±23.21 0.843±0.24
Follow-up	656.38±124.17	663.46±117.23	83.68±8.10	36.37±4.41	35.93±4.33	173.20±25.34 0.854±0.13	105.62±26.34 0.728±0.14	106.00±23.65 0.725±0.10	90.98±22.01 0.721±0.13
Schizophrenia patients									
Baseline	600.31±83.63	606.87±85.41	84.01±6.85	36.52±5.35	35.20±4.31	156.73±21.16 1.008±0.23	97.11±19.76 0.830±0.20	96.11±16.92 0.848±0.26	87.48±16.31 0.811±0.20
Follow-up	596.90±88.93	595.77±84.56	84.85±7.13	34.69±4.56	34.38±4.06	151.16±21.11 0.871±0.14	96.45±17.25 0.729±0.14	96.11±17.04 0.664±0.17	86.27±16.79 0.664±0.14
Poor-outcome patients									
Baseline	601.30±91.41	610.03±90.51	86.65±6.27	37.72±5.85	36.22±4.57	157.12±20.68 0.915±0.19	98.01±19.29 0.829±0.20	97.07±18.74 0.822±0.25	87.88±18.63 0.789±0.21
Follow-up	585.95±100.36	587.37±95.48	87.54±6.32	36.04±5.08	35.43±4.27	148.13±21.74 0.846±0.17	94.23±17.73 0.739±0.13	96.06±20.36 0.628±0.15	85.59±19.31 0.619±0.11
Good-outcome patients									
Baseline	599.20±75.90	603.30±81.13	81.03±6.33	35.16±4.47	34.04±3.77	156.28±22.16 1.108±0.23	96.10±20.66 0.832±0.21	95.02±14.96 0.877±0.28	87.04±13.62 0.835±0.19
Follow-up	609.29±74.21	605.25±71.15	81.80±6.72	33.15±3.38	33.18±3.53	154.58±20.31 0.895±0.11	98.94±16.73 0.720±0.15	96.17±12.72 0.700±0.18	87.04±13.79 0.668±0.16

¹ All data were derived from the sagittal images

² Slice area averaged across all 5 sagittal slices

³ Slice length averaged across all 5 sagittal slices

⁴ Radius of curvature averaged across all 5 sagittal slices

⁵ Segment area averaged across all 5 sagittal slices (first row) and segment fractional anisotropy averaged across all 5 sagittal slices and expressed relative to the mean whole-brain white matter anisotropy (regional FA/mean whole-brain FA, second row)

Table 2

Segment¹ topography data at baseline and follow-up

	Average centroid coordinates (y, z) ²				
	1	2	3	4	5
Healthy subjects					
Baseline	21.58±1.82, 10.33±1.67	11.63±3.16, 21.19±1.84	-3.94±3.77, 27.37±2.34	-21.39±4.76, 27.33±2.77	-35.71±4.60, 21.80±2.82
Follow-up	21.07±1.63, 10.67±0.97	10.58±2.48, 21.41±1.54	-5.14±2.53, 27.27±2.33	-22.55±3.66, 26.99±2.60	-36.82±3.96, 21.20±1.58
Schizophrenia patients					
Baseline	20.31±2.00, 11.70±2.18	10.44±3.28, 23.00±2.01	-5.10±3.07, 28.61±2.17	-22.33±3.25, 28.01±2.48	-36.33±3.60, 21.39±2.72
Follow-up	19.46±1.78, 11.85±1.32	9.56±2.41, 23.11±1.45	-6.08±2.15, 29.02±2.09	-23.35±2.65, 28.56±2.54	-37.19±3.13, 21.46±2.94
Poor-outcome patients					
Baseline	20.63±1.70, 11.29±1.81	10.31±2.78, 23.04±1.45	-5.69±2.66, 29.02±1.95	-23.59±2.93, 28.63±2.61	-37.99±3.61, 21.55±2.72
Follow-up	19.84±1.72, 11.48±1.35	9.51±2.18, 23.12±1.23	-6.75±1.90, 29.28±1.98	-24.61±2.47, 28.85±2.94	-38.83±3.03, 21.08±3.48
Good-outcome patients					
Baseline	19.97±2.26, 12.14±2.49	10.59±3.79, 22.95±2.49	-4.49±3.40, 28.17±2.34	-21.01±3.09, 27.36±2.22	-34.59±2.71, 21.22±2.77
Follow-up	19.07±1.79, 12.25±1.19	9.62±2.68, 23.10±1.69	-5.37±2.20, 28.74±2.21	-22.03±2.20, 28.25±2.07	-35.46±2.21, 21.85±2.27

¹ Segment 1: genu, segment 2: anterior body, segment 3: midbody, segment 4: posterior body, segment 5: splenium

² y and z coordinates of segmental centroids averaged across all 5 sagittal slices