Smaller corpus callosum subregions containing motor fibers in schizophrenia

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Abstract

Neuropsychological and neurophysiological studies provide evidence for abnormal interhemispheric communication in schizophrenia. These abnormalities may have a substrate in structural irregularities of the corpus callosum.

This study investigated schizophrenia patients (n=27) and healthy comparison subjects (n=31). Global and regional measurements of the corpus callosum were acquired from one midsagittal SPGR slice. Eight subregions were approximately matched to fiber pathways from cortical regions.

Overall effects of diagnosis [Wilks’ Lambda $F(8,46)=2.45$, $p=0.03$] and diagnosis by age interaction [Wilks’ Lambda $F(8,46)=2.58$, $p=0.02$] were found in a MANCOVA of the eight functionally specific subregions. Specifically, chronic schizophrenia was associated with a smaller rostral body [lower by 6.9%, $F(1,53)=9.70$, $p=0.003$] and anterior midbody [lower by 9.7%, $F(1,53)=4.89$, $p=0.03$] subregions.

The rostral body and anterior midbody subregions of the corpus callosum primarily have premotor, supplementary motor, and motor cortical fibers transversing through them. Functional abnormalities of the associated cortical regions are reported in schizophrenia. These novel findings suggest that structural abnormalities of the corpus callosum exist in schizophrenia, with perhaps the motor-specific subregions affected more than others. Structural differences in the corpus callosum may be a substrate for interhemispheric functional dysconnectivity in schizophrenia.

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1. Introduction

Schizophrenia might be associated with impaired interhemispheric communication (Coger and Serafetinides, 1990). Structural differences in the corpus
callosum may be a substrate for interhemispheric dysconnectivity in schizophrenia. Neuropsychological and functional studies of the corpus callosum have found associations between function and structure in both schizophrenia and healthy comparison subjects (Colombo et al., 1993; Höppner et al., 2001; Woodruff et al., 1997).

The corpus callosum was one of the first white matter structures to be studied in schizophrenia with postmortem techniques and magnetic resonance imaging (MRI). The postmortem studies examining fiber counts of the corpus callosum have generally found no differences between schizophrenia and healthy comparison subjects (Casanova et al., 1989; Machiyama et al., 1987; Nasrallah et al., 1983) with one newer study finding minute gender-related differences (Highley et al., 1999).

The advent of MRI made it possible to analyze the corpus callosum in vivo and avoid potential complications associated with postmortem studies, such as small sample sizes, differential causes of death, and postmortem changes in brain tissue (Woodruff et al., 1995). The many MRI studies that analyzed the corpus callosum yielded conflicting results regarding structural differences, which may be a consequence of possible confounds including age, handedness, gender, and brain size interactions, as well as differences in midsagittal slice selection and slice thickness. This makes comparison across studies difficult. The 1995 meta-analysis of 11 published studies found that the corpus callosum was significantly smaller in schizophrenia patients (Woodruff et al., 1995) (For a more detailed discussion of recent corpus callosum studies, refer to Shenton et al., 2001; Innocenti et al., 2003. For a review of older studies refer to Raine et al., 1990).

Postmortem and imaging studies provide a way to corroborate other evidence that suggest the corpus callosum might be implicated in schizophrenia. Aboitiz et al. (1992) reports approximately $1.6 \times 10^8$ total axons in the healthy corpus callosum and demonstrates larger callosal size is representative of a larger number of fibers. As well, the corpus callosum continues to increase in size up to the mid-20s age range (Pujol et al., 1993). This is especially relevant, since although early brain developmental disturbances may predispose an individual to schizophrenia, the illness itself manifests in adolescence and early adulthood. Corpus callosum development occurs intimately alongside other midline structures, some of which may be associated with the pathophysiology of schizophrenia, such as the fornix, hippocampal commissure, hippocampal formation, septum pellucidum, and cingulate cortex (Swayze et al., 1990). As well, although rare, the occurrence of callosal agenesis is more frequent among schizophrenia patients than among the clinical population (Swayze et al., 1990).

Another question that corpus callosum studies attempt to answer is whether the differences in the corpus callosum are global or regional. Subregional analysis of the corpus callosum is made possible by evidence from monkey and human studies indicating that callosal fibers connect homotopically positioned cortical regions, with prefrontal, premotor, and motor fibers crossing through the rostral half and parietal, temporal, and occipital lobe fibers crossing through the caudal half of the corpus callosum (de Lacoste et al., 1985; Pandya and Rosene, 1985; Pandya and Seltzer, 1986). The type of fiber differs according to the cortical regions connected, larger diameter fibers connect sensory and motor areas, compared with those connecting association and prefrontal areas (Aboitiz, 1992).

A wide range of methods were implemented to subdivide the corpus callosum, thereby complicating the picture of inconsistent regional findings (Tibbo et al., 1998). Witelson (1989) devised an approach to define subregions according to their anatomical connectivity. The same or similar methodology has been used in variety of mental disorders studies assessing the corpus callosum. Piven et al. (1997) found a smaller body and posterior corpus callosum in autism and Lyoo et al. (2002) found a smaller genu and posterior midbody in minor depression. To our knowledge, only one other study has adapted the Witelson technique and applied it to a schizophrenia population (Keshavan et al., 2002). Keshavan et al. (2002) reported a smaller corpus callosum, anterior genu, anterior body, isthmus, and anterior splenium in schizophrenia.

With this background, we performed a study that was restricted to males to eliminate gender as a possible confound, as the corpus callosum may be sexually dimorphic (Clarke et al., 1989; Steinmetz et al., 1995; Witelson, 1989). For regional analysis, the well-respected methodology developed by Witelson...
(1989) was adopted. The hypotheses were that the total corpus callosum area would be smaller in schizophrenia, the functionally specific subregions of the corpus callosum when assessed in combination would show an effect of diagnosis, and the individual functionally specific subregions would be differentially affected. We did not have more precise hypotheses about which specific subregions would be affected due to the variability in corpus callosum findings.

2. Methods

2.1. Participants

Demographic and clinical information appear in Table 1. Included in this study were 27 males who fulfilled the DSM-IV criteria for schizophrenia and 31 healthy male comparison subjects. Chronic schizophrenia patients were recruited from in-patient units at general hospitals and a psychiatric hospital. Medications included: clozapine (n=10), olanzapine (n=8), risperidone (n=5), fluphenazine (n=1), flupenthixol (n=1), loxapine (n=2), pipotiazine (n=1), and quetiapine (n=1). Some patients were taking more than one antipsychotic and data were missing for two patients. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Healthy comparison subjects were recruited from the hospital staff and lay public with the aim of matching the patient group for age and parental education. All but five subjects (two schizophrenia patients, three healthy comparison subjects) stated right-hand dominance. An objective handedness rating scale was not used. Subjects were excluded if they had a recent history of substance abuse, history of significant head trauma, or a neurological disorder. Healthy comparison subjects with any history of a psychiatric disorder were also excluded. All subjects participated voluntarily and provided written informed consent. The University of British Columbia Clinical Research Ethics Committee approved the protocol.

2.2. Corpus callosum regions of interest

SPGR scans were acquired in the axial plane using a General Electric Signa 1.5 T MR scanner (1.5 mm thickness, 124 slices). Scans were reconfigured into the sagittal plane (1.02 mm thickness). The full sagittal series was reviewed and on the consensus of three raters (VMG, DJL, SWF) a slice was selected based on stringent internal midsagittal landmark criteria: a distinguishable cerebral aqueduct and either a distinct anterior commissure or the presence of the interhemispheric falx of dura. All regions of interest were manually selected three times using the imaging software NIH Image (Rasband, 1997) by one rater (VMG), blind to diagnosis. The mean of the three measurements was used for analyses.

The total area and the maximum anterior to posterior length of the corpus callosum were acquired. The corpus callosum was subdivided into seven subregions in accordance with the methodology developed by Witelson (1989) (see Fig. 1 and Table 2). The genu was further divided into a superior and inferior portion as a study by Downhill et al. (2000) found that only a portion of the genu was smaller in schizophrenia. The genu was subdivided by the maximum anterior to posterior length of the corpus callosum. A similar protocol was used by Highley et al. (1999) to subdivide the genu. Total intracranial volumes were ascertained to use as a covariate by the same rater (VMG). Inter-rater and intra-rater reliability of the corpus callosum protocol were assessed using the intra-class correlation coefficient (ICC) (0.81–0.98 for inter-rater reliability
and 0.92–0.99 for intra-rater reliability). Previous assessment of inter-rater reliability for the total intracranial volume protocol yielded an ICC value of 0.99 (Lang et al., 2001).

2.3. Analyses

Omnibus analysis of variance (ANOVA) was used to analyze the continuous demographic variables: age, education and parental education, and smoking history. The continuous variables were entered as dependent measures and group (schizophrenia, healthy comparison subject) was entered as the main effect. Analysis of covariance (ANCOVA) tests were used to investigate diagnosis, diagnosis by age interactions, total intracranial volume, and age effects in the total area and maximum anterior to posterior length of the corpus callosum. Multivariate analysis of covariance (MANCOVA) was employed to analyze the eight functionally specific subregions of the corpus callosum in combination as a potentially more powerful test than a simple ANCOVA of the total area. As well, the MANCOVA was utilized to control for multiple comparisons. The eight functionally specific subregions of the corpus callosum were entered as dependent measures and the overall effects of diagnosis, diagnosis by age interactions, total intracranial volume, and age were investigated. Significant findings on the MANCOVA were followed up with individual ANCOVAs of the eight subregions of interest using the same model. Exploratory analysis of relationships between symptom presentation (PANSS total and positive, negative, and general subscores) and corpus callosum areas were investigated using partial correlations covarying for age and total intracranial volume. These analyses were also conducted in the right-handed sample only, as handedness may affect corpus callosum size.

3. Results

3.1. Participants

Subjects were comparable for all demographic information, except educational achievement, with schizophrenia patients having fewer years of formal schooling $[F(1,56)=4.18, p=0.05]$. Education potential as assessed by parental education did not differ between the groups ($p>0.50$), indicating that completion of schooling was likely affected by illness onset (see Table 1).

3.2. Global corpus callosum

No significant differences were found in the simple measure of total corpus callosum area between the groups [schizophrenia 643.48 mm$^2$, S.D.=87.32; healthy 642.76 mm$^2$, S.D.=92.49; $F(1,53)=0.76$, $p=0.39$]. The maximum anterior to posterior corpus callosum length did not differ significantly between the groups [schizophrenia 73.88 mm, S.D.=5.41;
healthy 73.01 mm, S.D.=5.03; $F(1,53)=3.31$, $p=0.07$], however, there was a significant diagnosis by age interaction [$F(1,53)=4.63$, $p=0.04$] (this finding was not significant in the right-handed subjects alone) and a significant effect of total intracranial volume [$F(1,53)=5.52$, $p=0.02$].

3.3. Overall effects on the eight functionally specific subregions

The individual corpus callosum subregion data appears in Fig. 2. A MANCOVA of the eight corpus callosum subregions revealed a significant effect of diagnosis [Wilks’ Lambda, $F(8,46)=2.45$, $p=0.03$], a diagnosis by age interaction [Wilks’ Lambda, $F(8,46)=2.58$, $p=0.02$], and effects of total intracranial volume [Wilks’ Lambda, $F(8,46)=2.35$, $p=0.03$], and age [Wilks’ Lambda, $F(8,46)=4.12$, $p=0.0009$]. All findings remained statistically significant when only right-handed subjects were considered.

3.4. Subregional differences in the corpus callosum structure

Individual ANCOVAs of the eight functionally specific subregions revealed an effect of diagnosis on the rostral body subregion [$F(1,53)=9.70$, $p=0.003$] with schizophrenia patients being 6.9% smaller, a significant diagnosis by age interaction [$F(1,53)=8.61$, $p=0.005$], and a significant effect of total intracranial volume [$F(1,53)=13.78$, $p=0.0005$]. In addition, schizophrenia patients were found to have a 9.7% smaller anterior midbody subregion of the corpus callosum [$F(1,53)=4.89$, $p=0.03$], with a non-significant diagnosis by age interaction [$F(1,53)=3.03$, $p=0.09$]. All findings remained statistically significant when only right-handed subjects were considered.

3.5. Exploratory analyses of corpus callosum subregions and clinical measures

No relationships were found between PANSS total or positive, negative, and general subscores and the rostral body or anterior midbody subregions of the corpus callosum in a partial correlation ($p>0.50$). This remained true when only right-handed subjects were considered.

4. Discussion

This study found overall diagnosis and diagnosis by age effects in the eight functionally specific corpus callosum subregions, although the total area did not differ. We found that schizophrenia was associated with smaller areas of the rostral body and anterior midbody subregions of the corpus callosum. To our knowledge, this is the first study to find size differences in all regions of the corpus callosum that
contain mainly motor fibers. In support of our findings, a study of first-episode, drug-naive schizophrenia, schizophreniform, and schizoaffective patients reported a significantly smaller anterior body subregion of the corpus callosum, which is similar to our anterior midbody subregion (Keshavan et al., 2002).

Considerable evidence from monkeys and humans suggest that motor, premotor, and supplementary motor fibers generally transverse through the rostral body and anterior midbody subregions of the corpus callosum (Witelson, 1989). These cortical regions may be affected in schizophrenia; as well, they are reciprocally connected to, or functionally associated with, regions of the brain that may be implicated in schizophrenia, such as the anterior cingulate cortex and basal ganglia. It is therefore feasible that these corpus callosum subregions could be selectively impaired in schizophrenia.

The supplementary motor area is reciprocally connected to many cortical and subcortical areas including the motor cortical areas, the basal ganglia, and the cerebellum. Clinical studies of Parkinson’s patients show that when dopaminergic input to the striatum is impaired, so is the activity of the supplementary motor area (Cunnington et al., 1996). Research suggests that sensorimotor cortex and supplementary motor regional activation is diminished, although not always significantly, in schizophrenia (Guenther et al., 1994; Schröder et al., 1995, 1999). The supplementary motor area is thought to have a role in bimanual movements. The basal ganglia may have a role in bimanual movements as well via the supplementary motor cortex. Patients with chronic schizophrenia have been shown to have performance deficits during bimanual coordination, which were likely related to a dysfunction of the corpus callosum and/or the supplementary motor area rather than the basal ganglia (Bellgrove et al., 2001).

Of particular interest, area measurements of the corpus callosum were found to be correlated with cingulate cortex activation during bimanual movements in an fMRI study (Stancic et al., 2003). The anterior truncus region of the corpus callosum (equivalent to our rostral body subregion) was correlated with the cingulate activation in simultaneous and right and left finger-led bimanual movements. The posterior truncus region of the corpus callosum (an amalgamation of our anterior midbody, posterior midbody, and isthmus subregions) was correlated with cingulate activation in left finger-led bimanual movements. The cingulate cortex is thought to be associated with the neuro-pathology of schizophrenia, and anterior corpus callosum size reduction could be a marker for functional disruption.

Several studies have investigated functional impairments in motor conduction in schizophrenia. Single-photon emission computerized tomography has demonstrated activation patterns to be different in schizophrenia patients during a motor task (Günther et al., 1991). Other studies have found differences in transcallosal motor inhibition in schizophrenia (Boroojerdi et al., 1999; Daskalakis et al., 2002; Fitzgerald et al., 2002; Höppner et al., 2001). However, the results of some of the transcallosal motor inhibition studies suggest those deficits may be due to dysfunctional cortical inhibitory mechanisms as opposed to dysfunctional corpus callosum pathways (Daskalakis et al., 2002; Fitzgerald et al., 2002). In the future, studies should attempt to link functional differences to structural abnormalities. A few studies have related function of the corpus callosum to structure (Colombo et al., 1993; Höppner et al., 2001; Rossell et al., 2001; Woodruff et al., 1997), but more studies of such are needed.

This study also found a differential age relationship in healthy comparison subjects compared to chronic schizophrenia patients, which was especially pronounced in the rostral body subregion and the maximum anterior to posterior length of the corpus callosum. In support of our findings, Keshavan et al. (2002) reported differential effects of age on the corpus callosum in drug-naive schizophrenia-related psychosis. Differential effects of age on the corpus callosum have also been found in other studies. In a study of childhood-onset schizophrenia, it was found that the splenium became smaller in patients after the age of 22, consistent with an altered developmental process (Keller et al., 2003). A 4-year follow-up study of first-episode schizophrenia patients found significant decreases in the corpus callosum with time, which was not seen in the comparison subjects. In addition, when the rate of change over the years was examined as a ratio-to-whole brain size, there was a trend for the corpus callosum to get larger in the
healthy comparison subjects but not the patients (DeLisi et al., 1995).

We found no relationships between the rostral body and anterior midbody subregions and symptoms in schizophrenia. The literature on this issue is equivocal with some studies finding associations between negative symptoms and a smaller corpus callosum size (Tibbo et al., 1998) and negative symptoms and magnetization transfer ratio reductions in the genu of the corpus callosum (Foong et al., 2001) and other studies finding no associations (Foong et al., 2000; Meisenzahl et al., 1999).

Studies that investigated white matter integrity also found abnormalities in the corpus callosum in schizophrenia. Diffusion tensor imaging studies found smaller fractional anisotropy (Agartz et al., 2001; Foong et al., 2000), greater mean diffusivity in the splenium (Foong et al., 2000) and associations between magnetization transfer ratio abnormalities in the genu of the corpus callosum and symptomology (Foong et al., 2001). In our own study utilizing T2 relaxation analysis and MRI to measure myelin water fraction in schizophrenia, we found that the myelin water fraction was reduced in the genu of the corpus callosum, although no difference in the size of genu as measured from a midsagittal SPGR slice was found (Flynn et al., 2003). This suggests that abnormalities of the corpus callosum may be subtler than can be detected by structural analysis and multimodal methods may be required to elucidate the nature of corpus callosum abnormalities in schizophrenia.

The present study has certain limitations. Although all care was taken to ensure the appropriate midsagittal slice was chosen, scans were not realigned and therefore the measurements could be affected by a slight misalignment of heads in the scanner. A further limiting factor was use of regional segmentation as opposed to shape analysis. Shape analysis is a more reliable methodology, and may be more sensitive to differences in corpus callosum morphology. Although several investigators report, although not always significant, abnormalities of corpus callosum shape in schizophrenia (Casanova et al., 1990a,b; DeQuardo et al., 1999; Downhill et al., 2000; Frumin et al., 2002; Gharaibeh et al., 2000; Narr et al., 2002; Narr et al., 2000), this finding is not unchallenged (Tibbo et al., 1998).

The potential effects of psychotropic medications on the corpus callosum morphology should be considered. All the present participants with schizophrenia were chronically ill (mean years of illness was 13 years) and were treated with antipsychotic medication. However, abnormalities in total corpus callosum size and all subregions were also noted in first-episode schizophrenia (Bachmann et al., 2003) and in the total corpus callosum size and selected subregions in drug-naive schizophrenia (Keshavan et al., 2002). Comparison to Bachmann et al. (2003) is difficult as a dissimilar protocol was utilized. However, Keshavan et al. (2002) found a smaller total corpus callosum, anterior genu, anterior body, isthmus, and anterior splenium subregions using a similar protocol. These findings are different from ours and may be attributed to the use of slightly different methodologies between the two studies—the Keshavan et al. (2002) modified the Witelson (1989) technique; the difference in midsagittal slice selection and slice thickness; use of both genders in the Keshavan et al. (2002) study; a smaller sample size in the present study; and differences in patient groups.

A study that utilized both shape analysis and regional segmentation found no differences between corpus callosum areas, but found shape differences between first-episode schizophrenia and healthy comparison subjects (Frumin et al., 2002). Other studies utilizing shape analysis have found differences between first-episode schizophrenia and healthy comparison subjects (DeQuardo et al., 1999), although not always statistically significant (Gharaibeh et al., 2000). Once again, these findings tend to be different from ours and may be due to confounds such as midsagittal slice selection, as well as, the gender, handedness, age of onset, duration of illness, and symptomological profile of the schizophrenia patients sampled. The contribution of medication to corpus callosum morphology, as well as the corpus callosum morphology in first-episode schizophrenia, should be further investigated in longitudinal studies.

A further limitation of this study is that the differential effect of age found on the rostral body and the maximum to anterior to posterior length of the corpus callosum between the groups may have been affected by the medication the chronic schizophrenia patients were prescribed. However, as we note above, differential effects of age between schizophrenia and
healthy comparison group have also been found in a drug-naive sample, suggesting a robust finding.

Despite the limitations, this study has many strengths including using a respected methodology to investigate functionally specific corpus callosum subregional differences in schizophrenia and controlling for many confounds present in previous studies. These findings add to the mounting evidence that corpus callosum abnormalities are present in schizophrenia. Regional analysis of corpus callosum in association with functional studies of basal ganglia and supplementary motor area interactions or transcortical information transfer in schizophrenia may be informative. Presently, many diverse lines of evidence do seem to suggest that corpus callosum is at the very least related to the mechanism of schizophrenia.

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