SEX DIFFERENCES IN THE CORPUS CALLOSUM IN SCHIZOPHRENIA: A COMBINED MRI AND DTI STUDY

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Abstract

Past research has identified abnormalities in the corpus callosum (CC), a structure that serves as the primary pathway for interhemispheric communication, in patients with schizophrenia, but the existence of sex differences in the CC remains contentious. This thesis is an investigation of CC size and microstructural abnormalities and the presence of sex differences in the structure in people with schizophrenia.

Using Magnetic Resonance Imaging (MRI) techniques including volumetric and diffusion tensor methods, the area, volume and fractional anisotropy (FA) of the CC and its 5 constituent segments were measured in a large group of schizophrenia patients ($N = 120$), consisting of both first-episode and chronic cases, and a control group of age and sex matched healthy individuals ($N = 75$).

Results indicated that the size (both area and volume) of the CC was significantly reduced in patients relative to controls, with chronic patients demonstrating the smallest volumes, followed by first-episode patients and healthy controls. There were no significant differences in CC size between the sexes, nor was the interaction between sex and diagnosis significant. At the same time, CC FAs did not differ significantly between the sexes or between schizophrenia patients and controls.

The results suggest that the CC is neither sexually dimorphic in healthy individuals nor in schizophrenia patients. The neurodegenerative hypothesis of schizophrenia is supported as findings suggest that structural abnormalities worsen with illness progression.

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1. What is Schizophrenia?

Schizophrenia is a disorder characterized by distortions of reality that profoundly affects an individual's social, cognitive and emotional functioning. It is estimated that countries spend close to 3 percent of their health care budget in treating patients with schizophrenia (Knapp, Mangalore, & Simon, 2004), as more than half of the patients who have been hospitalized for an acute episode eventually end up being hospitalized again (Eaton, Moortonsenk, Herrman, & Freeman, 1992). The risk of developing schizophrenia is estimated to be approximately 0.7% (Saha, Chant, Welham, & McGrath, 2005), with males facing a higher risk of developing the disorder than females (McGrath et al., 2004).

According to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association [*DSM-IV-TR*], 2000), the diagnosis of schizophrenia is made by a clinician when patients exhibit at least 2 of the following symptoms for a minimum of 1 month: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviours, or negative symptoms (such as avolition, alogia, and flat affect), and show a decline in social and occupational functioning since the onset of the disorder. In addition, the signs of disturbance must have been present for at least 6 months before a diagnosis of schizophrenia can be given (American Psychiatric Association [*DSM-IV-TR*], 2000). *DSM-IV-TR* also categorizes schizophrenia into 5 subtypes based on the symptoms observed from the patients, namely: paranoid, disorganized, catatonic, undifferentiated and residual schizophrenias (see Table 1).

Table 1

Diagnostic criteria for schizophrenia subtypes in the DSM-IV-TR

Subtype	Criteria
Paranoid	Presence of prominent delusions or auditory hallucinations; absence of prominent disorganized speech, catatonic behaviour, flat or inappropriate affect.
Disorganized	Presence of prominent disorganized speech, disorganized behaviour and inappropriate or flat affect; criteria for catatonic type not met.
Catatonic	Clinical picture dominated by at least 2 of the following: motoric immobility; excessive motor activity; extreme negativism; peculiarities of voluntary movement; echolalia or echopraxia.
Undifferentiated	Criteria for schizophrenia met, but criteria for paranoid, disorganized or catatonic subtypes not met.
Residual	Prominent delusions, hallucinations, disorganized speech, and catatonic behaviour currently absent; continuing evidence of disturbance present, as indicated by negative symptoms or positive symptoms in an attenuated form.

At present, the exact cause of schizophrenia remains unknown, although a variety of factors that increase the risk of developing the disorder have been identified. A genetic basis for schizophrenia had long been proposed (Kallman, 1946), and in line with that concept, Kety et al. (1994) reported that the disorder was 10 times more likely to strike biological relatives of adoptees who had schizophrenia than biological relatives of adoptees who were normal. Furthermore, non-biological relatives of the adopted schizophrenia patients were not at increased risks for developing schizophrenia (Kety et al., 1994). Nevertheless, being genetically predisposed does not mean that individuals will certainly get a diagnosis of Schizophrenia sometime in their lives. Tandon,

Keshavan and Nasrallah (2008) reviewed studies that have explored the genetic associations for schizophrenia and derived the following conclusions:

(i) Heritability is high and genetic factors contribute about 80% of the liability for the illness.

(ii) There is no 'major' gene locus that could explain a substantial portion of the heritability and a large number of candidate susceptibility genes may contribute to the liability for the illness.

(ii) No gene appears to be either sufficient or necessary for the development of schizophrenia.

(iv) Although there are many "findings" of genetic variations being linked to differential risk for developing the illness, inconsistent replication prevents the consideration of any single allelic variant as a gene for schizophrenia with absolute certainty at this time.

Other environmental factors have also been implicated in the onset of the disorder. For instance, maternal influenza had been frequently linked to higher rates of schizophrenia in their offspring (Cannon et al., 2003; Mednick et al., 1988), especially when the viral infection occurred during the second trimester of their pregnancies (Mednick et al., 1988). Being born in winter has also been shown to increase an individual's risk of developing schizophrenia (Davies, Welham, Chant, Torrey, & McGrath, 2003). In addition, childhood traumatic experiences (David & Prince, 2005), being the victim of inappropriate childrearing practices (Bateson, Jackson, Haley, & Weakland, 1956), being an immigrant (Cantor-Graae, & Selten, 2005), and the use of cannabis during teenage years (Moore et al., 2007) have all been highlighted as risk factors for schizophrenia. In sum, although there is general consensus that a combination of

genetic and environmental factors can lead to schizophrenia, the "threshold" and the exact mechanism that will trigger an onset has not been identified as yet.

1.1. Brain abnormalities in Schizophrenia

Studies have revealed significant widespread differences between a normal healthy brain and that of a schizophrenia patient, with the most replicated finding being the enlargement of the lateral and third ventricles (Raz & Raz, 1990) suggesting atrophy of surrounding brain tissue. An overall loss of brain tissue often accompanies the ventricular enlargement (Lawrie & Abukmeil, 1998), and these abnormalities are present early in the course of illness. In addition, first-episode schizophrenia patients were found to have significantly smaller total grey matter volumes, larger lateral ventricles, and greater amounts of cerebrospinal fluid than healthy age-matched individuals (Zipursky, Lambe, Kapur, & Mikulis, 1998). Similar abnormalities have also been observed in children diagnosed with schizophrenia (Frazier et al., 1996). Whether these abnormalities increase in severity as the illness progresses is still controversial however; while some longitudinal studies suggest that most structural changes occur in the early stages of schizophrenia and stabilize thereafter (e.g. Vita, Dieci, Giobbio, Tenconi & Invernizzi, 1997), others note that the brain degeneration is progressive (e.g. Nair et al., 1997).

The prefrontal cortex has also been implicated in schizophrenia, as imaging studies have detected significant loss of grey matter in the region (Buchanan, Vladar, Barta, & Pearlson, 1998). Barch, Csernansky, Conturo, and Snyder (2002) have also detected abnormal activations in the dorsolateral prefrontal cortex in schizophrenia patients during the performance of a working

memory task, further confirming suspicions of disturbed prefrontal regions schizophrenia. Other brain regions have also showed signs of abnormalities in schizophrenia; A review undertaken by Shenton, Dickey, Frumin, and McCarley (2001) pointed out that the majority of studies evaluating the size of the temporal lobe found it to be significantly smaller in schizophrenia patients. The authors further highlighted that 9 out of 15 studies reported abnormalities in the parietal lobe, and close to 70% of the studies reviewed found abnormalities in the basal ganglia structures. Summarized, these studies present convincing evidence that schizophrenia is a biological condition, warranting more research on the extent of damage in the brain and how it impacts daily functioning.

2. The Corpus Callosum (CC)

The corpus callosum (CC), as depicted in figure 1, is another structure where abnormalities have been detected in schizophrenia patients. The CC is the largest bundle of fibres that connects the left and right cerebral hemispheres of the human brain. It consists around 200 million axons (Tomasch, 1954), which provide the necessary connections that allow information to be integrated or inhibited across the hemispheres (Bloom & Hynd, 2005). The CC is hence the main pathway for communication between homologous cortical areas (Hellige, 1993). Callosal fibres are topographically organized (deLacoste, Kirkpatrick, & Ross, 1985), such that fibres in the anterior portions of the CC generally project into the prefrontal cortices, while those at the posterior regions of the CC lead into the occipital lobes (Aboitiz, Ide, & Olivarez, 1999). In perhaps the most widely used CC segmentation method (Witelson, 1989), the CC can be divided into seven regions, namely: (i) rostrum, (ii) genu, (iii) rostral body, (iv) anterior midbody, (v) posterior midbody, (vi) isthmus, and (vii) splenium, where fibres in each subdivision are thought to project into the (i) caudal prefrontal and inferior premotor, (ii) prefrontal, (iii) premotor and supplementary motor, (iv) motor, (v) somaesthetic and posterior parietal, (vi) superior temporal and posterior parietal, and (vii) occipital and inferior temporal cortical regions respectively[1].

[1] Figure 2 shows the Witelson's (1989) CC parcellation scheme. Further discussion on the CC subdivisions can also be found in section 3.2.

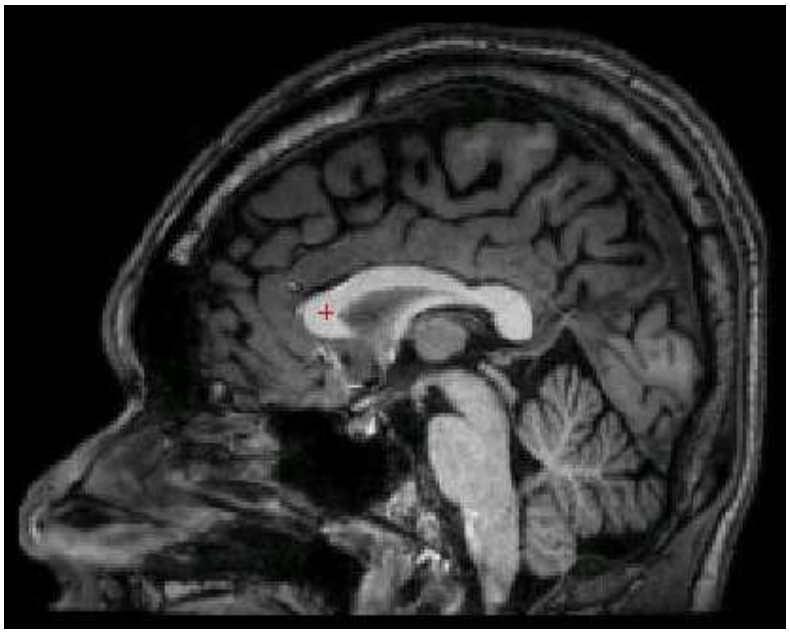

Figure 1. MRI of the human corpus callosum. The CC is indicated with a red cross.

The functional importance of the CC can be highlighted by the various cognitive impairments observed in individuals with significant CC damage. For instance, a patient with combined lesions in the right occipital lobe and the splenium of the CC was reported to show severe left hemispatial visual neglect, even though patients with isolated occipital lesions were spared from visual neglect (Park et al., 2005). Cognitive deficits have also been associated with CC lesions in patients with benign multiple sclerosis (Mesaros et al., 2008). Gait impairment in the elderly has likewise been linked to the integrity of the anterior CC (Bhadelia et al., 2009).

Acallosal patients (individuals without the CC altogether) have also been shown to fare worse than their healthy counterparts in the Tactual Performance Test, which involves an interhemispheric transfer of spatial information (e.g. Ferriss & Dorsen, 1975; Sauerwein, Nolin, & Lassonde, 1994). Delayed recall of the Rey-Osterrieth figure is also worse in these individuals (Temple & Ilsley,

1994), suggesting that normal visuospatial memory cannot be sustained without an intact CC. Children with callosal agenesis also show difficulties in understanding the precise meaning of literal and nonliteral expressions when compared to healthy, same-age peers (Brown et al., 2005).

Last but not least, studies on split-brain patients who had their CCs surgically severed in an attempt to treat epileptic seizures have also yielded insights into the roles of the interhemispheric 'bridge'. The performance of patient L.B. (who had undergone a complete commissurotomy but suffered minimal damage outside the CC) on a lexical decision task differed sharply from healthy individuals, as presenting words to both visual fields simultaneously did not result in improvements in performance (Mohr, Pulvermüller, Rayman, & Zaidel, 1994). As the CC is essential for the integration of information across hemispheres, split-brain patients are also unable to compare different stimuli presented to the distinct hemifields (Intriligator, Henaff, & Michel, 2000). The implication of these findings is that without the CC serving as the critical communication link between the hemispheres, the behaviour of each hemisphere appears to be independent of each other.

Clearly, structural damage to the CC has adverse consequences on an individual's cognition, behaviour and daily experiences. So important is the CC that Gazzaniga (2000) wrote: "it becomes reasonable to suppose that the corpus callosum has enabled the development of the many specialized systems by allowing the reworking of existing cortical areas while preserving existing functions".

2.1. The CC in Schizophrenia

Interest in the CC in the schizophrenia population increased rapidly as a direct result of Rosenthal and Bigelow's (1972) postmortem study, which concluded that schizophrenia patients had thicker CCs than healthy controls. Subsequently, Bigelow, Nasrallah and Rauscher (1983) also reported an increased CC thickness in schizophrenia patients, in line with reports of increased CC: brain ratio in the schizophrenia group (Matthew et al., 1985). An early MRI study also showed that the anterior CC was enlarged in schizophrenia patients compared to controls (Uematsu & Kaiya, 1988). In contrast, Stratta et al. (1989) found a significantly reduced CC: brain ratio in schizophrenia patients than in controls. There is also some evidence that the CC rostral body and anterior midbody were smaller in chronic schizophrenia patients (Goghari, Lang, Flynn, MacKay, & Honer, 2005). Adding to the inconsistencies, Frumin et al. (2002) noted no significant differences between schizophrenia patients and controls in CC area, though it was highlighted that CC shape differences exist between the groups. The conflicting findings across studies simply highlight the need for more research to elucidate the relationship between CC size or integrity and schizophrenia symptoms.

Given that fibres in the CC are mapped topographically (Aboitiz et al., 1999; deLacoste et al., 1985) and that abnormalities exist in the surrounding cortical regions, researchers were also motivated to look for damage in specific CC regions that are connected to affected cortical regions. For instance, researchers can look for abnormalities in the anterior splenium of the CC as it connects the bilateral temporal lobes, often compromised in schizophrenia patients. As it turns out, some studies have reported size reductions in the

splenium region of the CC (Bersani et al., 2010; Keshavan et al., 2002), when previous research had already shown that grey matter volumes were reduced in the superior temporal gyrus (Okugawa, Tamagaki, & Agartz, 2007; Shenton et al., 1992) and the amygdala/hippocampal complex of schizophrenia patients (Anderson et al., 2002). Similarly, alterations of the genu have been reported, together with impairments of the bilateral frontal lobes that are connected by the genu (Foong et al., 2001). These findings inevitably lead to more studies on the specific roles of the different CC sub-regions, and how they might be impaired in schizophrenia.

The fact that schizophrenia patients often perform poorly on neuropsychological tasks that require the interhemispheric transfer of information also suggests that certain cognitive impairments seen in patients might have originated from the CC. Researchers have, for instance, found that schizophrenia patients face difficulties in visuo-spatial matching (Beaumont & Dimond, 1973), a task which involves the CC. While normal individuals showed a right visual field advantage (reflecting the left-hemisphere's language dominance) and a bilateral advantage in processing words presented to both visual fields, schizophrenia patients only exhibited the former, suggesting interhemispheric transfer deficits in schizophrenia (Mohr, Pulvermüller, Cohen, & Rockstroh, 2000). Schizophrenia patients also perform worse than healthy controls on the Crossed Finger Localisation Test (CFLT) (Rushe, O'Neill, & Mulholland, 2007), a task designed to assess interhemispheric transfer of somatosensory information. The presence of abnormalities in the CC in schizophrenia was further highlighted when a recent study in a group of recent-onset psychosis patients showed a positive relationship

between CFLT scores and CC volume (Chaim et al., 2010) - the CC appeared to be the smallest in subjects with the lowest scores.

At the same time, schizophrenia-like symptoms such as delusions and hallucinations have been frequently observed in patients with CC agenesis, to the extent that many patients with CC agenesis ended up having a diagnosis of schizophrenia as well. David, Wacharasindhu and Lishman (1993) noted that out of 7 patients with CC abnormalities, 3 suffered from clear delusions and hallucinations, a central feature of schizophrenia. Others either presented with odd speech, behavioural or social problems that more or less resembled schizophrenic symptoms. One other example was the reported case of a woman with a partial agenesis of the CC, who also presented with alien hand syndrome and received a diagnosis of schizophrenia (Simon, Walterfang, Petralli and Velakoulis, 2008). Hallak et al. (2007) also reported another young patient diagnosed with childhood-onset schizophrenia eventually found to have a missing CC. In fact, many similar reports have surfaced over the years (e.g. Lewis, Reveley, David, & Ron, 1988; Motomura, Satani, & Inaba, 2002; Taylor & David, 1998), suggesting that the CC is somewhat involved in the manifestation of schizophrenia-like symptoms, if not the direct cause of it.

Subsequent studies have certainly reinforced the idea of a compromised CC in patients diagnosed with schizophrenia. For example, a recent meta-analysis which included 28 separate studies have found that CC areas were significantly reduced in schizophrenia patients, though the effect was larger in first-episode patients than chronic patients (Arnone et al., 2008). Progressive reductions in the size of the CC have also been documented in a follow-up study of first-episode patients, where the rate of change in the area of the isthmus significantly differed

between patients and healthy controls (DeLisi et al., 1997). This was in line with the findings from a longitudinal study of chronic schizophrenia patients, in which the absolute size of the CC was smaller in patients with poor functional outcomes than those with better outcomes, 4 years after the initial baseline scan (Mitelman, et al., 2009). There is also some metabolic evidence that the CC is abnormal in people who are at a higher risk for developing the disorder later on in life (Aydin et al., 2008).

2.2. Sex differences in brain morphology in Schizophrenia

Investigations of sex differences in the CC in the schizophrenia population were inevitable, as sex differences were already well documented in the clinical presentation and course of the disorder. With regards to the epidemiology of schizophrenia, males are considered to be at a higher risk of developing schizophrenia than females in a meta-analysis (Aleman, Kahn, & Selten, 2003), and studies have established that schizophrenia women usually have later ages of onset (DeLisi, Dauphinais & Hauser, 1989; Forrest & Hay, 1971). Loranger (1984) reported that approximately 17% of women but just 2% of men had an age of onset of 35 years and above. Hafner and Heiden (1997) also noted that women tend to develop the disorder 3 to 4 years later than men, with a second peak onset around menopause.

In terms of prognosis, women with schizophrenia generally exhibit better functioning than schizophrenia men, requiring fewer hospitalizations across the lifespan (Grossman, Harrow, Rosen, & Faull, 2006). During the course of the illness, schizophrenia men seem to be afflicted by more negative symptoms (such as blunted affect) than women (Choi, Chon, Kang, Jung, & Kwon, 2009; Maric,

Krabbendam, Volleberg, de Graff, & van Os, 2003). A team of Japanese researchers also found that schizophrenia women were less likely to suffer from auditory hallucinations than men with schizophrenia (Kitamura, Fujihara, Yuzuriha, & Nakagawa, 1993). Since the bulk of the evidence suggested that schizophrenia affects males and females differently, it is important to understand schizophrenia from two overlapping yet distinct perspectives.

The study of sex differences in brain morphology is likely to contribute to the understanding of the different subtypes of schizophrenia that may be affecting the sexes. Understandably, sex differences in brain morphology have been studied extensively and were frequently reported in the schizophrenia population. For one, the volume reduction in the amygdala in schizophrenia was shown to be bilateral in male patients but restricted to the right hemisphere in female patients (Niu et al., 2004). In addition, the sex differences in brain torque were found to be 7 times larger in schizophrenia patients than in healthy individuals (Guerguerian & Lewine, 1998). In other studies, sex differences present in the normal healthy population appear to be diminished in the schizophrenia population. For example, Takahashi and colleagues (2003) investigated grey and white matter volumes of the perigenual cingulate gyrus, a structure known to be involved in affect. Their results revealed a significant sex difference in the total grey and white matter volumes of the structure in control subjects, but failed to find a similar difference in the schizophrenia sample. Further analyses also showed that the volume of the perigenual cingulate gyrus was reduced in female patients compared to in female controls, but there was no significant difference between male patients and male controls. These findings suggest that the disruption of normal processes in schizophrenia is unequal between the sexes, and given the associations between

CC abnormalities and schizophrenia symptoms, the findings certainly provide a reason to study sex differences in the CC in depth.

3. Studying the CC with Postmortem methods and Magnetic Resonance Imaging (MRI)

3.1. Introduction to postmortem methods and MRI technology

Prior to the advent of in-vivo imaging technology, the study of the CC or any brain region was severely restricted as researchers could only gain access to the brains after an individual's death. The various problems associated with postmortem research studies were summed up by Nasrallah et al. (1986):

> There are many confounding variables of postmortem brain measurements, including unreliable retrospective diagnoses, changes in brain tissue in the death-to-autopsy period, mechanical distortion following autopsy, changes secondary to preservation or inadequate preservation, neurological effects of the medical cause of death, and methodological problems of measurement of postmortem brain tissue.

Researchers had to find a way to overcome all these factors, and the arrival of MRI technology provided them with a much-needed solution.

During an MRI scan, a strong magnet aligns the majority of hydrogen protons in the body to either magnetic North or South. A radio frequency (RF) pulse is then applied to "loose" protons (i.e. protons that were not aligned), allowing them to absorb the energy and spin in a different direction. When the RF pulse is eventually turned off, these "loose" protons spin back to their initial alignment within the magnetic field, releasing energy in the process. This produces a signal that can be detected and forwarded to a computer system for

further analysis. A 2-dimensional image or 3-dimensional model can then be created and interpreted (Gould, Todd, & Edmonds, 2010). The entire process is non-invasive and safe for the subject, as long as metal objects are kept away from the scanning room. Essentially, this provides researchers with a tool for neuroscience research that does not come with the various caveats associated with postmortem methods.

3.2. CC area segmentation

At present, the most commonly used measures for comparisons of the CC in both postmortem and MRI studies, are the area of the CC as a whole, and the areas of various CC sub-regions. Different CC parcellation schemes have been introduced and employed over the years, as it is impossible to identify clear midsagittal anatomical landmarks that can delineate the callosal subdivisions at present.

One of the most widely used parcellation scheme is the Witelson's approach (Witelson, 1989), which involves segmenting the CC into 7 subdivisions proportionally: researchers first identify the extreme ends of the CC and draws 2 perpendicular lines at those points, before subdividing the CC into halves, thirds and fifths. As illustrated in Figure 2, the end result is a CC with 7 partitions, each corresponding roughly to different cortical regions, although significant overlaps may exist (Witelson, 1989).

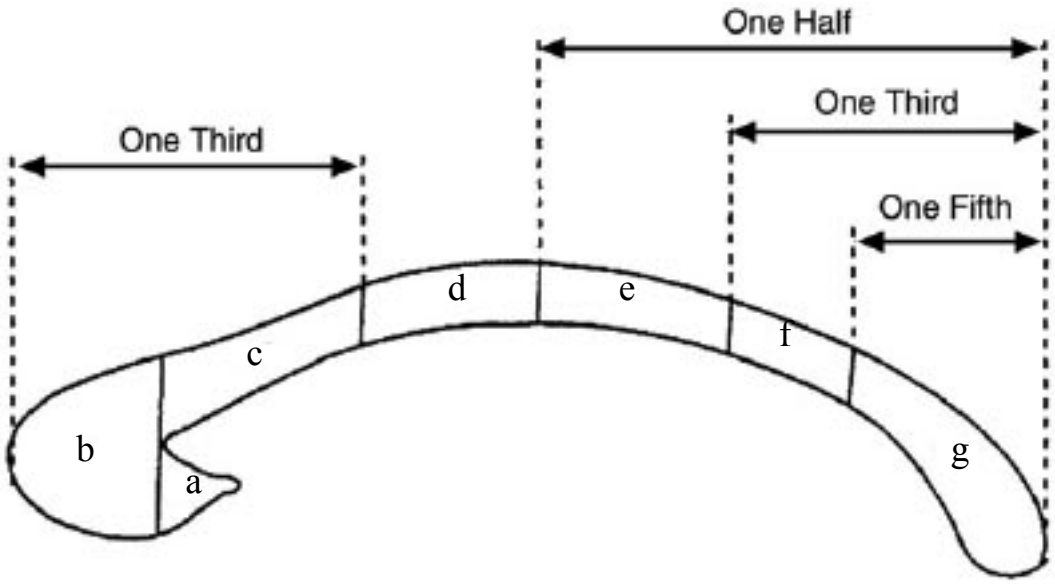

Figure 2. Witelson's subdivisions of the corpus callosum: (a) rostrum, (b) genu, (c) rostral body, (d) anterior midbody, (e) posterior midbody, (f) isthmus, (g) splenium. Adapted from Witelson (1989).

Despite its popularity (e.g. Chura et al., 2010; Keller et al., 2003; Tuncer, Hatipoglu, & Özates, 2005), others have criticized the Witelson's (1989) 7-subdivisions approach as inaccurate "at the cellular level" (Hofer & Frahm, 2006). Besides, the cadaver brains that Witelson (1989) studied originally came from people who died from metastatic disease. Even though subjects were assessed and noted to be free from neurological symptoms at the time of recruitment, the sample was hardly representative of the normal population. Alternative segmentation methods have been employed and they include dividing the CC into 3 equal thirds as depicted in Figure 3 (e.g. Westerhausen et al., 2004), 5 equal segments (e.g. Bachmann et al., 2003), or 5 "radial" divisions (e.g. John, Shakeel, & Jain, 2008), though these parcellation methods were no more 'accurate' than Witelson's (1989) approach at reflecting actual callosal subdivisions. More recently, researchers are starting to employ Diffusion Tensor Imaging (DTI)

tractography to understand the fibre pathways in the CC, before partitioning the CC according to the fibre boundaries (e.g. Miyata et al., 2007).

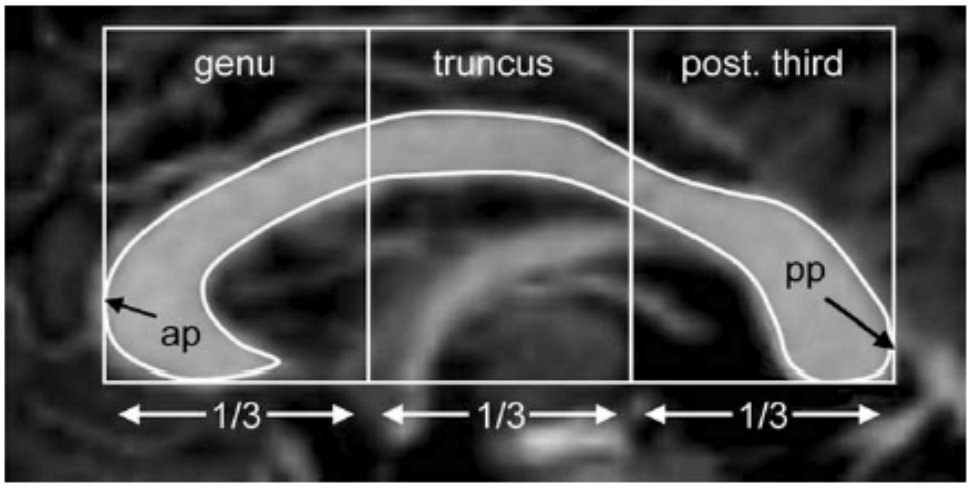

Figure 3. Westerhausen et al.'s 3-part CC segmentation method. Reprinted from "Effects of handedness and gender on macro- and microstructure of the corpus callosum and its sub-regions: a combined high-resolution and diffusion-tensor MRI study," by Westerhausen et al., 2004, *Cognitive Brain Research, 21,* p. 420. Copyright 2004 by Elsevier B. V. Adapted with permission.

Apart from these area measurements, other CC parameters that have been investigated in MRI and postmortem studies include CC length (e.g. Woodruff, Pearlson, Geer, Barta, & Chilcoat, 1993), CC width (e.g. Downhill et al., 2000), CC thickness (e.g. Raine et al., 1990), and CC shape (e.g. Narr et al., 2000). These measures are, however, even less reliable than area measurements, as small differences in the CC outline could alter readings significantly (Woodruff et al., 1993).

3.3. Methodological issues with MRI studies

Parcellation issues aside, MRI studies also differ on their imaging methodologies. Slice thickness, for one, varies significantly across studies,

ranging from 3.0 mm in recent studies (e.g. Miyata et al., 2007) to 12.0 mm in earlier studies (e.g. Smith et al., 1984). While some earlier studies reported an inter-slice gap of 2 mm (Hoff, Neal, Kushner, & DeLisi, 1993), improvements in technology now allow the acquisition of contiguous slices (e.g. Walterfang et al., 2008). The comparison of results across studies hence becomes complicated, as differences in findings may well be due to differences in imaging protocols.

The fact that the derivation of the midsagittal slice was different across studies also makes studies difficult to replicate. For instance, while many authors obtained CC area measurements on a single midsagittal slice, Narr et al. (2002) chose to average CC areas from 3 medial slices. In some studies, the definition of the midsagittal slice was not clearly described to begin with. In Woodruff et al. (1993), it was clearly described that the midsagittal slice should fulfill all the following criteria: "(1) a distinct outline of the corpus callosum; (2) an easily identified cerebral aqueduct; (3) clear visibility of cortical gyral crests both anteriorly and posteriorly to the corpus callosum; and (4) absence of visible intrusion into grey and white matter." In Lewine et al. (1990) however, it was only vaguely stated that: "corpus callosum analyses were based on the midsagittal slice yielding the clearest view of the corpus callosum".

In the first instance, the measurement of CC area from the midsagittal slice is far from ideal because the area of a single midsagittal slice may not be representative of the whole CC volume. Researchers should in fact measure and compare CC volumes instead of CC midsagittal areas, as it entirely eliminates the problems associated with midsagittal slice selection.

3.4. Postmortem and MRI studies of sex differences in the CC in the normal population

In the general healthy population, a majority of MRI studies have reported larger CCs in women than in men (e.g. Allen et al., 2003; DeLacoste-Utamsing & Holloway, 1982; Steinmetz, Staiger, Gottfried, Huang, & Jancke, 1995), although studies with conflicting results do emerge from time to time. Much of the inconsistencies may have stemmed from methodological differences across studies. Sullivan, Rosenbloom, Desmond and Pfefferbaum (2001) for instance, concluded that healthy men have larger CCs than their female counterparts, even after taking the overall brain size into account. In contrast, neither Constant and Ruther (1996) nor Weis, Weber, Wenger and Kimbacher (1989) found any significant sex differences in the area of the CC. Nevertheless, it has been shown in a meta-analysis that while men appeared to have larger CCs, CC area was actually larger in women than in men after correcting for total brain size (Driesen & Raz, 1995).

3.5. Postmortem and MRI studies of sex differences in the CC in schizophrenia

Despite the large body of literature in brain imaging in the schizophrenia population, the number of studies that have specifically examined sex differences in the size of the CC is relatively small. A PubMed search with the keywords "corpus callosum and schizophrenia" yielded 338 entries up to March 2011, yet only 19 of these studies were MRI studies that have investigated sex differences in the size of the CC by comparing a group of schizophrenia patients to healthy controls. Furthermore, the investigation of sex differences was often not the

primary goal these studies; for instance, Jacobsen et al. (1997) were mainly interested in the size of the CC in childhood onset schizophrenia patients, while Keshavan et al. (2002) were primarily motivated in comparing the size of the CC between treatment-naïve patients, non-schizophrenia, psychotic patients and controls. As for postmortem studies, only Highley et al. (1999) studied the size of the CC with respect to gender in a schizophrenia population.

So far, the majority of the studies have reported a significant effect of diagnosis on the size of the CC, though some have failed to find any significant difference between schizophrenia patients and controls (refer to Table 2). Amongst the studies reporting an effect of diagnosis, a larger proportion concluded that CC sizes were compromised in schizophrenia patients relative to healthy controls. For example, Woodruff et al. (1993) noted that patients had significantly smaller mid-CC areas than healthy controls that cannot be explained solely by overall brain shrinkage. Along the same lines, Keshavan et al. (2002) observed a significant reduction in the size of the anterior genu, anterior body, isthmus, and anterior splenium in schizophrenia patients but not in healthy subjects. A recent meta-analysis involving 28 studies confirmed that CC area was indeed reduced in schizophrenia patients, and the effect was found to be more prominent at the early stages of the illness (Arnone, McIntosh, Tan, & Ebmeier, 2008).

Table 2

Study characteristics of previous MRI studies that investigated sex differences in the size of the CC in schizophrenia

Study	Sample size		Mean age of patients (yrs)	Age at onset (yrs)	Effects of diagnosis	Effects of sex	Interaction effects
	Patients	Controls					
Venkatasubramanian et al. (2010)	40M, 26F	32M, 14F	28.6	26.4	Genu and body of CC sig. smaller in patients	*ns*	not specified
John et al. (2008)	10M, 13F	10M, 13F	30.13	29	Anterior parts of CC sig. bigger in patients	Females had sig. larger CCs	*ns*
Rotarska-Jagiela et al. (2008)	12M, 12F	12M, 12F	39	26.2	Total CC and posterior genu volume sig. smaller in patients after bonferroni corrections	Females had sig. smaller total CC, posterior genu and anterior midbody volumes before bonferroni corrections	*ns*
Walterfang et al. (2008)	chronic: 73M, 13F; 1st-episode: 56M, 20F	34M, 21F	chronic: 34.6; 1st-episode: 21.2	chronic: 22.1; 1st-episode: 21.1	*ns*	Trend: females had larger CCs	Females had larger CCs than males in the control group only.
Miyata et al. (2007)	20M, 20F	18M, 18F	37.4	25.2	*ns*	*ns*	*ns*

Study	Sample size		Mean age of patients (yrs)	Age at onset (yrs)	Effects of diagnosis	Effects of sex	Interaction effects
	Patients	Controls					
Bachmann et al. (2003)	14M, 17F	6M, 6F	26.4	not specified, but all patients had less than 2 weeks of neuroleptic medication	All CC subdivisions were sig. smaller in patients	Females had sig. larger total CC and anterior CC areas	*ns*
Keller et al. (2003)	33M, 22F	34M, 24F	14.8	10.3	*ns*	Males had sig. larger CCs before correcting for total cerebral volume	*ns*
Panizzon et al. (2003)	52M, 19F	49M, 18F	M: 35.9, F: 39.8	M: 16.7, F: 20.3	*ns*	*ns*	Trend: Male patients had sig. smaller total CC areas than male controls, while female patients had larger CC areas than female controls
Keshavan et al. (2002)	Schiz: 20M, 11F; non-schiz: 6M, 6F	20M, 20F	Schiz: 24.2	25.1	Schiz patients had sig. smaller total CC, anterior genu, anterior body and splenium areas	*ns*	not specified
Chua et al. (2000)	17M, 10F	^20M, 15F	37.1	20	*ns*	not specified	*ns*

Study	Sample size		Mean age of patients (yrs)	Age at onset (yrs)	Effects of diagnosis	Effects of sex	Interaction effects
	Patients	Controls					
Downhill et al. (2000)	Schiz: 20M, 7F; SPD: 12M, 1F	23M, 8F	Schiz: 38.3	23	The genu and splenium were sig. smaller in schiz patients than in controls	Females had sig. smaller CCs than males	*ns*
Jacobsen et al. (1997)	13M, 12F	31M, 24F	13.9	9.9	*ns*	Females had sig. smaller areas in the rostral body, anterior midbody, posterior midbody, and isthmus	Trend: The posterior midbody and the isthmus were larger in male patients than in female patients and controls
Hoff et al. (1994)	39M, 23F	20M, 15F	26.5	26.4	not specified	Males had sig. larger CCs than females	Male patients and male controls did not differ in CC size, but female patients had sig. smaller CCs than female controls, male controls and male patients
Colombo et al. (1994)	13M, 6F	9M, 6F	25.9	21.6	*ns*	*ns*	*ns*

Study	Sample size: Patients	Sample size: Controls	Mean age of patients (yrs)	Age at onset (yrs)	Effects of diagnosis	Effects of sex	Interaction effects
Woodruff et al. (1993)	15M, 8F	34M, 10F	30.0	22.4	CC area was sig. smaller in patients	Males had sig. larger CC areas only before controlling for overall brain size	Male patients had sig. smaller CC areas than male controls, but female patients did not differ from female controls
Casanova et al. (1990)	not specified	°MZ twin discordant for schiz	32.6	not specified	*ns*	*ns*	*ns*
Lewine et al. (1990)	Schiz: 27M, 4F; non-schiz: 16M, 12F	not specified	Schiz: M: 31.1, F: 31.5	Schiz: M: 21.1, F: 27.3	Trend: CC areas were smaller in schiz patients than non-schiz patients and normal controls	Trend: Males had larger CC areas	ns
Raine et al. (1990)	Schiz: 9M, 6F; non-schiz: 9M, 4F	9M, 9F	Schiz: 34.0	26.1	*ns*	*ns*	*ns*
Hauser et al. (1989)	Schiz: 11M, 13F; non-schiz: 13M, 9F	14M, 11F	Schiz: 33.0	not specified	*ns*	Male had larger CC areas	*ns*

Note. Schiz refers to schizophrenia patients, non-schiz refers to other non-schizophrenia patient groups, and SPD refers to schizotypal PD. ˆNumber of normal controls only. Study also compared schizophrenia patients with their relatives. °12 pairs of monozygotic twins discordant for schizophrenia were studied.

In contrast, Nasrallah et al. (1986) reported no CC area differences between right-handed male schizophrenia patients and right-handed male controls. In addition, callosal area was actually found to be smaller in male patients than in male controls when only left-handed subjects were included in the analysis. There were also no differences in CC area between female schizophrenia patients and female controls. Interestingly, when the entire sample was combined, the authors detected a significantly larger CC area in schizophrenia patients than in controls. Together with reports of significantly increased thickness in the anterior and middle CC in female schizophrenia patients than in female controls, and a lack of similar differences in male patients versus controls, Nasrallah et al. (1986) suggested that callosal dimensions were affected by handedness and gender. Nevertheless, some studies have tested the link between handedness and callosal size, but have failed to confirm the presence of the relationship (e.g. Preuss et al., 2002; Steinmetz et al., 1992).

Similarly, the effects of sex on CC size have not been consistently reported. Regardless of handedness, Tuncer et al. (2005) identified greater areas in the rostrum and posterior midbody in all male subjects than in female subjects. In sharp contrast, CC area was found to be larger in all female subjects, irrespective of diagnosis in John et al. (2008). At the same time, there is an even greater volume of literature suggesting the lack of sex differences in CC size (e.g. Miyata et al., 2007; Panizzon et al., 2003; Woodruff et al., 1993). Many studies have also failed to find significant interactions between sex and diagnosis with respect to CC size (e.g. Chua, Sharma, Takei, Murray, & Woodruff, 2000; Keller et al., 2003).

Results obtained from these studies have been inconclusive so far, largely because the characteristics and methodologies of the 19 published MRI studies were far from consistent. As summarized in Table 2, out of the 19 MRI studies, only Rotarska-Jagiela et al. (2008) reported CC size in terms of volume; the remaining studies reported CC areas instead. Some studies also looked into other CC parameters such as width (e.g. Hauser et al., 1989), thickness (e.g. Casanova et al., 1990; Nasrallah et al., 1986; Walterfang et al., 2008), and shape (e.g. Casanova et al., 1990; Downhill et al., 2000) in addition to CC size. Furthermore, studies varied in their choice of variables to control for. While the majority of studies used intracranial volume as a covariate (e.g. Bachmann et al., 2003; Keshavan et al., 2002), a few studies saw age as a factor to control for (e.g. Panizzon et al., 2003; Venkatasubramanian et al., 2010), while some did not control for any potentially confounding variables at all (e.g. Hauser et al., 1989; Westerhausen et al., 2004). In addition, sample sizes were generally small; there were only 4 studies with data from more than 50 schizophrenia patients and 50 healthy controls (Panizzon et al., 2003; Keller et al., 2003; Venkatasubramanian et al., 2010; and Walterfang et al., 2008). While Walterfang et al. (2008) included 162 schizophrenia patients (consisting of 76 first episode patients and 86 chronic patients) and 55 healthy control subjects in their study, Casanova et al. (1990) only obtained scans from 12 individuals, which was understandable as it was definitely more difficult to recruit monozygotic twins who are discordant for schizophrenia.

4. Studying the CC with Diffusion Tensor Imaging (DTI)

A lack of significant findings when comparing the overall size of the CC between schizophrenia patients and controls, or males and females in general, does not provide definite proof that the structure has not been compromised in any way however. To examine whether the microstructural integrity of the CC has been altered in a certain population, researchers turn to diffusion tensor imaging (DTI) for better answers. DTI involves the introduction of additional magnetic field gradients in a conventional MRI scanner to determine the diffusion properties of water molecules in the brain (Kanaan et al., 2005). The diffusion is highly anisotropic (directionally dependent) in oriented structures, and isotropic where diffusion is homogeneous in all directions. The extent of diffusion is then represented by the measure Fractional anisotropy (FA), which ranges from 0 to 1, where a larger value implies greater anisotropy (Basser & Pierpaoli, 1996). Any reduction in FA can reflect alterations in axonal density, myelination or the organization of fibres (Kubicki et al., 2005; Walterfang et al., 2006).

4.1. DTI studies of sex differences in the CC in the normal population

It has been reported that FA values differ from one CC region to another in a normal population, with the highest FA being observed in the splenium, while the lowest being noted in the genu (Chepuri et al., 2002). According to the same authors, the regional FA differences remained significant even after stratification by age and by sex (Chepuri et al., 2003). In a study of corpus callosum developmental changes across the lifespan involving 99 healthy children and adults, the FA values in the whole CC did

not differ across the sexes, indicating "non-significant sex effects" (Hasan et al., 2009). In spite of that, other studies have suggested that microstructural sex differences exist within the CC. For instance, a recent DTI study from Germany detected lower levels of FA in females than in males in the thalamus, cingulum and the CC (Menzler et al., 2011). Similarly, Liu, Vidarsson, Winter, Tran and Kassner (2010) reported significantly reduced FA values in the genu of the CC in healthy females as compared to males, and concluded that their results "demonstrate a regional dependence of sex differences in the microstructural composition and organization of fibre tracts within the CC". The small subject numbers in that study (11 males and 11 females) however implied that their findings must be replicated before they can be generalized to the entire healthy population.

4.2. DTI studies of sex differences in the CC in schizophrenia

Cumulative evidence points to the presence of lower mean FAs in the CC in schizophrenia patients, though the degree of reduction varies across CC sub-regions. In a group of first-contact schizophrenia patients who were never medicated, FA was significantly reduced in the splenium but not in the genu, as compared to healthy controls (Gasparotti et al., 2008). Gasparotti and colleagues' (2008) finding replicated those of Cheung et al.'s study in 2007, as the latter reported significantly lowered FA values that are confined to the splenium in drug-naïve schizophrenia patients. Together, the findings suggest that aberrant connections in the CC are present at the onset of the disorder and are not the effects of antipsychotic medications. Gasparotti and colleagues (2008) further noted that the FA reduction "tended to be more evident in

males", though statistical significance was not achieved. This was consistent with the results of another DTI study on chronic schizophrenia patients (Foong et al., 2000), where FA was reduced in the splenium but not in the genu of patients, and no sex differences were observed in both the patient and the control groups.

Nevertheless, the FA reductions in the CC in schizophrenia patients were not always demonstrated. Contrary to Foong et al. (2000) and Gasparotti et al. (2008), Price, Bagary, Cercignani, Altmann and Ron (2005) revealed that FA in the splenium and the genu did not differ significantly between first-episode schizophrenia patients and healthy controls. Additionally, while the two former studies presented insufficient evidence for a sex difference, Price et al. (2005) showed that women had significantly lower FAs than men, regardless of diagnosis, similar to Rametti et al. (2009). Rotarska-Jagiela and her colleagues (2008) likewise reported lower FAs in women than in men, though contrary to Price et al. (2005), schizophrenia patients were found to have significantly reduced FAs in both the genu and the splenium of the CC in comparison to healthy controls.

A concern about such DTI studies is that sample sizes have been small so far, as many studies have recruited less than 30 schizophrenia patients (e.g. Gasparotti et al., 2009; Price et al., 2005; Rametti et al., 2009). Researchers were thus prevented from drawing firm conclusions about the presence of abnormal FAs or sex differences in FA in the CC in schizophrenia. Studies should also focus on recruiting schizophrenia patients with varying illness durations instead of focusing on first-episode or chronic patients alone, so that

any progressive changes in the integrity of the CC due to the illness can be captured and that illness duration can be analyzed as a factor.

In short, despite several reports of sex differences in the size of the CC in the normal population, it remains controversial as to whether the same sex differences are present in the schizophrenia population. There is certainly a need to conduct more research with larger sample sizes to verify whether the CC is sexually dimorphic in schizophrenia. After all, it is plausible that sex differences in the CC may have significant contributions to the sex differences observed in the illness itself.

5. Aims of present study

The main aim of the present study is to directly investigate the presence of abnormality in the CC and specifically to determine if sex differences occur in the CC in the schizophrenia population, as findings from previous studies have been inconsistent and thus inconclusive. Based on previous work, it was hypothesized that CC size would be reduced in schizophrenia patients, with chronic patients showing the greatest decrease. Secondly, it was predicted that FA would be significantly reduced in schizophrenia patients. No specific hypotheses on the presence of sex differences in both the size (area and volume) and FA in the CC were set as past studies were generally divided.

6. Method

6.1. Subjects and clinical assessment

The Institute of Mental Health is the sole state psychiatric hospital in Singapore, serving as the main treatment centre for patients with psychotic spectrum disorders. One hundred and twenty patients (85 males and 35 females) who met inclusion and exclusion criteria were recruited from the hospital for the study. Seventy-five healthy controls (49 males and 26 females) were recruited from the community by advertisements. To qualify, participants should not have a history of any major neurological illness (such as head trauma or seizure disorder), or a diagnosis of alcohol or drug abuse based on DSM-IV criteria in the past 3 months. For patients, the treating psychiatrist confirmed the DSM-IV diagnosis of Schizophrenia with information obtained from the clinical history, existing medical records, interviews with significant others, and the administration of the Structured Clinical Interview for DSM-IV disorders – Patient Version (SCID-P) (First et al., 1994). All patients were on a stable dose of antipsychotic medication for at least two weeks, and none of the patients had their medication withdrawn for the purpose of the study. For healthy controls, the SCID-Non-Patient version (SCID-NP) (First et al., 2002) was administered to rule out the presence of an Axis I psychiatric disorder.

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered to all patients to assess symptom severity and psychopathology, and an assessment of psychosocial functioning was performed with the Global Assessment of Functioning (GAF) scale. Handedness was determined in all participants with the administration of the Modified Edinburgh Questionnaire (Schachter et al., 1987).

Written, informed consent was obtained from all participants after a thorough explanation of the study procedures. The Institutional Review Boards of the Institute of Mental Health and the National Neuroscience Institute approved the study protocol.

6.2. Image acquisition

Magnetic resonance imaging was performed with a 3-Tesla whole body MRI scanner (Gyroscan Achieva, Philips Medical Systems, Eindhoven, The Netherlands). A regular quality control procedure ensured the stability of a high signal to noise ratio. Whole brain volumetric scans were then acquired with a high resolution, T1-weighted Turbo Field Echo sequence (TR/TE/TI/flip angle = 8.4 ms/3.8 ms/3000 ms/8^{o}, FOV = 230 mm^{2}, acquisition matrix = 256 x 256) that produced a total of 180 contiguous, 0.9 mm thick axial slices with no gaps.

Diffusion-weighted images were obtained in the same session using a single-shot echo-planar sequence (repetition time, 3725 ms; echo time, 56 ms; flip angle = 90 ^{o}; *b*-factor, 800 s mm^{-2}) in 15 non-parallel directions with the baseline image being acquired without diffusion weighting. Each volume comprised of 42 axial 3.0 mm thick slices with no gap (FOV, 230 mm^{2}; acquisition matrix, 256 x 256 after conversion). A total of 3 volumes were obtained to improve signal-to-noise ratio of the scans. Structural and diffusion tensor images were acquired sequentially in one single scan time with no position change.

6.3. Image processing

Structural MRI images were converted from the original DICOM format into the Analyze format. Free Surfer software package (Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard University, http://surfer.nmr.mgh.harvard.edu/) was used to reformat each brain volume into a 1 mm^3 isovoxels volume, and delineated it into around 200 brain structures[2] (Dale et al 1999, Fischl et al 1999a, 1999b, 2002, 2004a, 2004b). This Free Surfer procedure has been shown to be statistically indistinguishable from manual raters (Fischl et al., 2002). The volume of each brain structure was then calculated by counting the number of voxels within it. The corpus callosum was divided into 5 segments, namely: anterior, mid-anterior, central, mid-posterior and posterior, and the volumes of the various regions were measured separately (see Figure 4). The whole callosal volume was calculated as the sum of the 5 segments. To obtain the CC area measures, the number of pixels in each CC sub-region (as above) was counted on the midsagittal slice, as each pixel is equivalent to 1 mm^2. The total callosal area was computed by adding the areas for all 5 CC segments.

Fractional Anisotropy maps were acquired from the DTI images from the software DTI Studio (Jiang et al., 2006), and were then co-registered automatically to the MP-RAGE images using a mutual information cost function and a 12 parameter affine transformation. Eddy current correction was performed prior to registration. As the DTI images are co-registered to the subjects' structural images, FA images are also automatically delineated into

[2] Free Surfer segmentation of cortical and subcortical structures is based on subject-independent probabilistic atlas and subject-specific measured values. The software assigns each point in space to a given label by finding the segmentation that maximizes the probability of input given the prior probabilities from a training set.

approximately 200 brain structures using the same delineation parameters in the structural images.

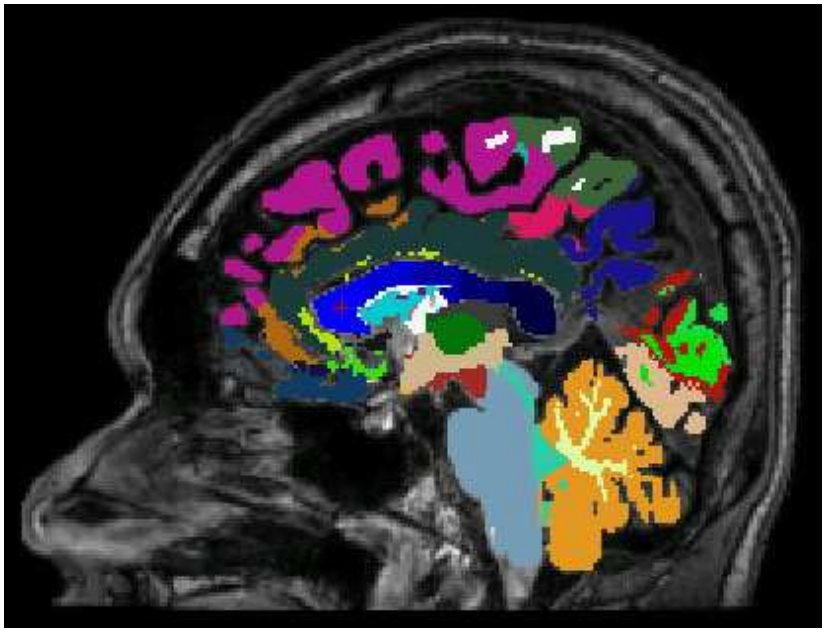

Figure 4. Segmentation of brain structures using Free Surfer. The CC is marked with a red cross and the 5 callosal sub-divisions have been marked in different shades of blue.

6.4. Statistical Analyses

6.4.1. Demographic and Clinical variables

The Predictive Analytics Software (PASW) – PC version 18.0 (SPSS Inc., Chicago, III) was used for data analysis. Group differences on the demographic and clinical variables were investigated with the use of *t*-tests for independent groups. Pearson's correlations were then computed to assess the relationship between the age of onset, duration of untreated psychosis, duration of psychiatric illness and other key variables such as the PANSS and GAF scores. Subsequently, the relationships between the CC volume and FA measures with the demographic and clinical variables were explored with Spearman's correlation analysis. Statistical significance was set a priori at a

conservative alpha level of 0.01 for all comparisons, as 5 CC subregions were studied and analyzed separately.

6.4.2. CC area, CC volume and CC FA

Spearman's rank-ordered one-tailed correlations between the 5 CC areas (as measured from the midsagittal slice) and the corresponding CC volumes were first computed, following which two-tailed Spearman's correlations between the CC areas, CC volumes and CC FAs were calculated. Subsequently, in line with the methodologies from previous studies, separate 2 [diagnosis: patients versus controls] x 2 [sex: males versus females] ANCOVAs (analysis of covariance) were performed, with CC area and volume measures as the dependent variables (whole CC, anterior CC, mid-anterior CC, central CC, mid-posterior CC and posterior CC areas and volumes), and intracranial volume as the covariate to correct for differences in overall brain size[3]. This allows for independent statistical examination of the 5 CC regions. Five ANCOVAs (analysis of variance) were also performed with the CC FA measures as dependent variables and age at brain scan as the covariate. Finally, to further explore the effects of diagnosis and whether results from studies employing first-episode patients were comparable to those using chronic patients, separate ANCOVAs with 3 levels were conducted, with CC areas and volumes as the dependent variables, group category [first-episode patients, chronic patients and controls] as the independent variable, and age at brain scan as the covariate. Post-hoc pairwise comparisons with bonferroni corrections were performed in case of significant effects in the one-

[3] Although area and volume measurements were obtained in stereotaxic space, covarying for ICV was still performed because template registration may not be perfect.

way ANOVAs. Statistical significance was again set a priori at an alpha level of .01.

7. Results

7.1. Subject characteristics

Clinical and demographic details of the participants are listed in Tables 3 and 4. There were 8 left-handed and 1 ambidextrous schizophrenia patients and 7 left-handed control subjects. Out of the 120 schizophrenia patients recruited for the study, 68 were first-episode cases, with a mean duration of psychiatric illness of 2.28 years (SD = 2.42). Chronic schizophrenia patients in the sample had a significantly longer mean duration of psychiatric illness (M = 11.92, SD = 8.39), $t(118) = -9.64$, $p < .001$. The two patient subgroups do not differ significantly on the age of onset and the duration of untreated psychosis.

Combined, schizophrenia patients received significantly less education (M = 11.53, SD = 2.33) than healthy controls (M = 13.87, SD = 2.02), $t(193) = -7.15$, $p < .001$. Further, patients' parents were also less educated than parents of healthy controls, though the difference did not achieve statistical significance after correcting for multiple comparisons (see table 5). The sex difference in PANSS positive, PANSS general psychopathology, PANSS total, and GAF scores in the entire schizophrenia sample showed a non-significant trend, as shown in Table 3. Male patients tend to have more positive and general psychopathology symptoms, and consequently lower functioning than female patients. There were no other significant differences between the groups.

Table 3

Means of clinical and demographic characteristics of all participants (N = 195)

	Patients		*P*-value	Controls		*P*-value
	Males (N = 85)	Females (N = 35)		Males (N = 49)	Females (N = 26)	
Age (years)	32.16 (8.29)	34.53 (10.17)	.42	30.88 (8.30)	34.38 (12.64)	.15
Years of education	11.36 (2.39)	11.94 (2.17)	.22	14.00 (1.73)	13.62 (2.48)	.44
Mother's level of education (years)	6.82 (3.99)	6.15 (4.16)	.41	8.53 (3.73)	6.92 (4.77)	.11
Father's level of education (years)	7.57 (3.60)	6.89 (3.98)	.36	8.92 (3.67)	7.73 (4.30)	.21
Age of onset (years)	25.00 (6.48)	27.31 (8.48)	.11			
Duration of illness (years)	6.52 (7.58)	6.31 (7.47)	.89			

	Patients		*P*-value	Controls		*P*-value
	Males (N = 85)	Females (N = 35)		Males (N = 49)	Females (N = 26)	
Duration of untreated psychosis (years)	1.32 (1.78)	1.47 (1.69)	.67			
PANSS positive	11.18 (4.17)	9.37 (3.03)	.02			
PANSS negative	9.13 (2.99)	8.66 (3.51)	.46			
PANSS general psychopathology	20.93 (4.20)	19.34 (2.24)	.04			
PANSS total	41.24 (9.36)	37.37 (6.49)	.03			
GAF total	50.66 (16.99)	57.37 (19.98)	.07			

Note. GAF refers to the Global Assessment of Functioning Scale while PANSS refers to the Positive and Negative Syndrome Scale. *SDs* are given in brackets.

Table 4

Means of clinical and demographic characteristics of schizophrenia patients (N = 120)

	First-episode (N = 68)	Chronic (N = 52)	*P*-value
Age of onset (years)	26.27 (7.11)	24.92 (7.25)	.31
Duration of illness (years)	2.28 (2.42)	11.92 (8.39)	<. 001
Duration of untreated psychosis (years)	1.50 (2.06)	1.18 (1.22)	.32
PANSS positive	10.66 (3.93)	10.63 (4.01)	.97
PANSS negative	9.09 (3.16)	8.87 (3.14)	.70
PANSS general psychopathology	20.90 (4.00)	19.90 (3.48)	.16
PANSS total	40.65 (8.79)	39.40 (8.79)	.44

	First-episode (N = 68)	Chronic (N = 52)	*P*-value
GAF total	53.60 (19.30)	51.36 (16.44)	.51

Note. GAF refers to the Global Assessment of Functioning Scale while PANSS refers to the Positive and Negative Syndrome Scale. *SDs* are given in brackets.

Table 5

Mean number of years of education

	All patients		All controls		
	Mean	*SD*	Mean	*SD*	*P*-value
Self	11.53	2.33	13.87	2.02	<. 001
Mother	6.63	4.03	7.97	4.16	0.03
Father	7.37	3.71	8.51	4.03	.04

7.2. MRI

7.2.1. Correlations between CC area and volume

Total midsagittal area of the CC was strongly correlated with whole CC volume in the whole sample, $r(193) = .84$, $p < .001$ (one-tailed). Likewise, midsagittal areas of the anterior CC ($r = .87$), mid-anterior CC ($r = .84$), central CC ($r = .84$), mid-posterior CC ($r = .82$) and posterior CC ($r = .85$) were all strongly significantly correlated with volumes of the respective regions (all $df = 193$, ps $< .001$, one-tailed).

7.2.2. CC midsagittal area comparisons

An ANCOVA performed with diagnosis and sex as independent factors and intracranial volume as covariate revealed a significant main effect of diagnosis in the whole CC area, $F(1, 190) = 6.715$, $p = .01$. Further analyses revealed a trend towards significance in the main effects for diagnosis in the mid-anterior CC, $F(1, 190) = 5.207$, $p = .02$, the central CC, $F(1, 190) = 5.47$, $p = .02$, and the mid-posterior CC, $F(1, 190) = 6.20$, $p = .014$. As shown in Table 6, in all cases, CC midsagittal areas were smaller in patients than in healthy controls. More importantly, the main effect for sex was not significant in any CC region. The lack of significant interactions between sex and diagnosis was also evident in all the CC regions.

The effect of diagnosis on midsagittal CC areas raised the question of whether the reduction in CC areas was more pronounced in patients who have had the disorder for a longer duration, compared to those who recently suffered their first psychotic episodes. To address the issue, six separate one-way ANCOVAs with group category as the independent variable, ICV and

age at brain scan as the covariates and CC area measures as the dependent variables were conducted. Sex was intentionally omitted from the ANCOVAs due to the fact that previous results failed to show any reliable sex differences.

The pattern of results mirrored those of the preceding ANCOVAs, whereby the difference between groups in midsagittal areas was significant in the whole CC, $F(2, 190) = 6.88$, $p < .001$, mid-anterior CC, $F(2, 190) = 5.53$, $p = .005$, central CC, $F(2, 190) = 5.25$, $p = .006$, and mid-posterior CC, $F(2, 190) = 4.32$, $p = .015$. Specifically, post-hoc comparisons revealed significant differences in midsagittal areas between chronic patients and controls in all of these regions. The differences between first episode patients and chronic patients showed a trend towards significance in the whole CC, mid-anterior CC and central CC. The mid-posterior CC was the only region with near-significant differences between first-episode patients and healthy controls. In general, midsagittal areas were smallest in chronic patients and largest in healthy controls in all CC regions measured (refer to Table 7). A brief summary of the results from the post-hoc tests can be found in Table 8.

Table 6

Mean midsagittal CC regional areas in patients and controls (mm^2)

	Patients		Controls	
	Males	Females	Males	Females
Anterior CC	168.47 (31.85)	170.94 (35.00)	180.29 (37.60)	168.58 (22.77)
Mid-anterior CC	108.22 (34.15)	108.71 (46.62)	127.33 (37.10)	118.54 (45.55)
Central CC	109.78 (45.44)	106.34 (44.93)	138.29 (54.86)	113.96 (42.40)
Mid-posterior CC	92.14 (20.78)	91.80 (18.93)	104.65 (25.81)	97.31 (26.71)
Posterior CC	185.07 (29.46)	186.57 (31.90)	196.86 (27.75)	192.65 (27.29)
Whole CC	663.68 (111.56)	664.37 (135.69)	747.41 (133.18)	691.04 (128.87)

*Note. SD*s are given in brackets.

Table 7

Mean midsagittal CC regional areas in first-episode patients, chronic patients and controls (mm^2)

	Subject group category		
CC region	Chronic	First-episode	Controls
Anterior CC	167.71 (32.30)	170.32 (33.15)	176.23 (33.52)
Mid-anterior CC	99.31 (27.39)	115.29 (43.38)	124.28 (40.14)
Central CC	98.54 (36.42)	116.60 (49.65)	129.85 (51.91)
Mid-posterior CC	88.69 (20.15)	94.60 (19.97)	102.11 (26.18)
Posterior CC	187.65 (25.77)	183.87 (33.07)	195.40 (27.48)
Whole CC	641.90 (101.13)	680.69 (128.45)	727.87 (133.59)

*Note. SD*s are given in brackets.

Table 8

P-values in CC midsagittal area post-hoc comparisons

	CC regions					
Group Comparisons	Anterior	Mid-anterior	Central	Mid-posterior	Posterior	Whole
First-episode versus Chronic	n.s.	.045	n.s	n.s.	n.s.	n.s.
First-episode versus Controls	n.s.	n.s.	n.s.	.035	n.s.	n.s.
Chronic versus Controls	n.s.	.001	.002	.008	n.s.	<.001

Note. P-values are only provided for comparisons yielding significant or near-significant results. *N.s.* refers to a non-significant result.

7.2.3. Correlations between CC area and clinical and demographic variables

There were significant positive correlations between whole CC area and (i) the number of years of education received by subjects, $r(193) = .19$, $p = .009$, (ii) the number of years of education received by subjects' father, $r(192) = .19$, $p = .007$, and (iii) the number of years of education received by subjects' mother, $r(191) = .18$, $p = .01$. Generally, a bigger midsagittal CC area was associated with a longer duration of education in subjects themselves and in their parents.

Correlation analyses also revealed that the duration of untreated psychosis was significantly related to the area of the central CC, $r(118) = -.23$, $p = .01$. There was also a trend towards significance in the mid-posterior CC, $r(118) = -.21$, $p = .022$. Finally, the correlations between the duration of psychiatric illness and the area of the mid-anterior CC, $r(118) = -.19$, $p = .037$, and central CC, $r(118) = -.21$, $p = .023$, showed trends to significance.

7.2.4. CC volume comparisons

Out of the six separate ANCOVAs performed on the various CC regional volumes, three reflected significant main effects for diagnosis. These were the whole CC, $F(1, 190) = 8.95$, $p = .003$, mid-anterior CC, $F(1, 190) = 11.83$, $p = .001$, and central CC volumes, $F(1, 190) = 10.84$, $p = .001$. The main effect for diagnosis also trended towards significance in the mid-posterior CC, $F(1, 190) = 6.53$, $p = .011$. These imply that schizophrenia patients generally have smaller CC volumes than healthy controls. As with the ANCOVAs performed on CC area measures, there were no significant

interactions between sex and diagnosis. In addition, the main effect for sex was not statistically significant. The mean CC regional volumes are provided in Table 9.

Subsequently, following the CC area comparisons, one-way ANCOVAs were conducted with sex removed and group category as the sole independent variable. The ANCOVAs were significant in the whole CC, $F(2, 190) = 9.21$, $p < .001$, mid-anterior CC, $F(2, 190) = 9.12$, $p < .001$, central CC, $F(2, 190) = 9.74$, $p < .001$, and mid-posterior CC, $F(2, 190) = 5.64$, $p = .004$. A trend towards significance was demonstrated in the posterior CC ($p = .04$). Post-hoc comparisons showed that volumes were smaller in chronic patients than in healthy controls in these CC regions, and the volume difference between first episode patients and chronic patients trended towards significance in the mid-anterior CC and central CC. A trend towards significance in the comparison between first-episode patients and controls in the central CC was also observed. As expected, the smallest volumes were recorded in the chronic patients, while the largest volumes were found in the healthy individuals. Repeating the analyses with non-right-handers removed did not change the pattern of results. The mean CC regional volumes for the 3 subject groups can be found in Table 10, while results from the post-hoc analyses are summarized in Table 11.

Table 9

Mean CC regional volumes in patients and controls (mm^3)

	Patients		Controls	
	Males	Females	Males	Females
Anterior CC	837.51 (142.30)	834.66 (154.77)	886.63 (156.00)	831.92 (113.81)
Mid-anterior CC	492.12 (118.62)	484.03 (144.90)	583.92 (122.07)	542.65 (179.73)
Central CC	449.58 (101.80)	451.74 (128.52)	533.98 (102.78)	488.08 (121.37)
Mid-posterior CC	438.46 (91.65)	435.06 (89.18)	491.49 (91.54)	457.23 (91.39)
Posterior CC	922.98 (142.35)	928.00 (151.98)	992.22 (141.25)	954.08 (136.96)
Whole CC	3140.64 (447.34)	3133.49 (534.07)	3488.24 (451.91)	3273.96 (506.87)

*Note. SD*s are given in brackets.

Table 10

Mean CC regional volumes in first-episode patients, chronic patients and controls (mm^3)

	Subject group category		
CC region	Chronic	First-episode	Controls
Anterior CC	827.27 (133.56)	843.87 (154.42)	867.67 (144.39)
Mid-anterior CC	462.02 (107.57)	510.97 (135.87)	569.61 (144.81)
Central CC	425.08 (96.93)	469.43 (115.58)	518.07 (110.96)
Mid-posterior CC	416.10 (87.83)	453.81 (89.86)	479.61 (92.34)
Posterior CC	928.60 (122.52)	921.26 (160.26)	979.00 (140.05)
Whole CC	3059.06 (413.48)	3199.34 (506.81)	3413.96 (479.38)

*Note. SD*s are given in brackets.

Table 11

P-values in CC volume post-hoc comparisons

	CC regions					
Group Comparisons	Anterior	Mid-anterior	Central	Mid-posterior	Posterior	Whole
First-episode versus Chronic	n.s.	.017	.056	n.s.	n.s.	.028
First-episode versus Controls	n.s.	n.s.	.016	n.s.	n.s.	.044
Chronic versus Controls	n.s.	<.001	<.001	.001	.013	<.001

Note. P-values are only provided for comparisons yielding significant or near-significant results. *N.s.* refers to a non-significant result.

7.2.5. Correlations between CC volume and clinical and demographic variables

Consistent with the results obtained in the CC area analyses, there were significant correlations between the number of years of (i) subjects', $r(193) = .21$, $p = .004$, (ii) subjects' fathers', $r(192) = .21$, $p = .004$, and (iii) subjects' mothers' education, $r(191) = .20$, $p = .006$, and total CC volume.

There were no significant correlations between the duration of untreated psychosis and the CC volume measures. Nevertheless, a trend towards significance was found in the relationship between CC central volume and the duration of psychiatric illness, $r(118) = -.19$, $p = .036$. An increase in the duration of illness appears to be linked to a reduction in CC central volume.

7.3. DTI

7.3.1. Correlations between FA, area and volume

Two-tailed Spearman's correlations were computed to quantify the relationship between (i) FA and area, and (ii) FA and volume measures. A trend towards significance was detected in the mid-anterior CC, $r(193) = -.15$, $p = .03$, when the correlations between FA and area measures were computed in the entire sample. The correlations between FA and volume measures also came close to significance in the mid-anterior CC, $r(193) = -.18$, $p = .012$, central CC, $r(193) = .16$, $p = .02$, and mid-posterior CC, $r(193) = .16$, $p = .02$. Nevertheless, all correlations were small – the biggest R^2 stood at .03.

7.3.2. CC FA comparisons

None of the five ANCOVAs performed detected any significant main effect for sex, diagnosis, or sex and diagnosis interaction in any CC region (see Table 12). In addition, the removal of non-right-handers from the statistical analyses did not alter results.

Table 12

Mean CC FAs in patients and controls

	Patients		Controls	
	Males	Females	Males	Females
Anterior CC	.493 (.096)	.499 (.061)	.521 (.085)	.500 (.063)
Mid-anterior CC	.437 (.079)	.433 (.055)	.436 (.062)	.416 (.050)
Central CC	.501 (.097)	.497 (.058)	.526 (.072)	.510 (.068)
Mid-posterior CC	.534 (.106)	.542 (.069)	.545 (.087)	.521 (.085)
Posterior CC	.650 (.144)	.691 (.049)	.675 (.111)	.668 (.055)

Note. All values rounded off the 3 significant figures. *SD*s are given in brackets.

8. Discussion

To summarize, the results demonstrated that the size of the CC, measured by either area or volume, was reduced in schizophrenia patients as compared to healthy controls. Consistent with predictions, the greatest size reductions were observed in patients with more established illness; The CC was significantly smaller in chronic patients than in first episode patients, while no size differences emerged between first episode patients and healthy controls. However, the second hypothesis that FA would be reduced in schizophrenia patients was not supported. At the same time, there was insufficient evidence to show that sex differences exist in the size or FA of the CC.

To the best of our knowledge, with 120 schizophrenia patients and 75 healthy subjects, this study is one of the largest to date, and also the first to recruit from a non-Caucasian, Asian population. The availability of both first-episode and chronic schizophrenia patients in our sample also allows a direct comparison between groups in order to understand the effects of the duration of illness on CC macro- and micro-structural integrity. In addition, both the midsagittal area and the volume of the whole CC and its subdivisions were studied within the present study, thereby overcoming the problems associated with the selection and use of a single midsagittal slice. Lastly, as DTI FA values were also obtained from the participants, an investigation of the relationships between CC area, volume and FA could be performed.

8.1. Absence of sex differences in the CC

Consistent with the majority of studies comparing sex differences in the CC between a schizophrenia sample and a healthy subject group, the main effect for sex was not significant in any CC region, nor was the interaction between sex and diagnosis significant. The current study is hence in line with Flaum et al.'s (1995) study on brain morphology in schizophrenia showing no significant effect of sex in any other brain region assessed, suggesting that similarities present between the sexes in schizophrenia outweigh the differences (Lewis, 1992). The CC does not seem to reflect the sex differences commonly observed in the etiology of schizophrenia.

Positive findings in several past studies may have stemmed from the lack of statistical corrections for multiple comparisons (e.g. Rotarska-Jagiela et al., 2008), or the failure to take total brain size into account (e.g. Keller et al., 2003; Woodruff et al., 1993), as explained by Jancke, Staiger, Schlaug, Huang, and Steinmetz (1997) that sex differences in CC size "may be better explained by an underlying effect of brain size". The variable selected for comparisons can also affect the resulting conclusions, as significant sex differences in the shape of the CC but not the midsagittal area have been reported in the same healthy population (Allen, Richey, Chai & Gorski, 1991). Furthermore, it must be kept in mind that the developmental patterns of the CC differ between the sexes, with a maturation delay typically observed in males (Luders, Thompson, & Toga, 2010). The age of subjects recruited can hence be a deciding factor as to whether significant differences can be obtained. Studies investigating sex differences in patients with an average age of onset of 16 years may detect the normal developmental gap between males

and females, whereas studies involving patients with a mean onset of 30 years old may report null findings, since CC maturation in both sexes has probably completed and equalized by that age. Conclusions drawn can therefore easily differ between studies.

8.2. CC size reductions in Schizophrenia

The key factor that sets the present study apart from most studies is the use of CC volume for comparisons, instead of relying solely on CC area measurements calculated from the midsagittal slice. As discussed in chapter 3.3, midsagittal slice selection procedures vary considerably from one study to another, making it difficult to replicate results across studies. Although the strong correlations between CC area measures and CC volume measures implied that studies employing the former and the latter can be compared, the results also suggest that the use of two different measures may lead to distinct conclusions. Based on the current study, the main effect for diagnosis was significant only at the whole CC level, and trends towards significance were observed in the mid-anterior, central and mid-posterior CC sub-regions when midsagittal areas were compared. On the other hand, when comparing CC volume measures, the same main effect was significant at the whole CC level, as well as in the mid-anterior and central CC segments, though comparisons still fell short of significance at the mid-posterior CC segment. There is no concrete proof that the extent of size reduction captured in the midsagittal slice is equivalent to the degree of damage outside the selected slice, and as such, abnormalities out of the selected slice may not be reflected accurately when CC midsagittal areas were compared. This could explain why the

volumes of the mid-anterior and central CC were found to be significantly different between patients and controls, despite showing up only as a trend when midsagittal areas were compared.

Generally, the present results indicated that the overall size of the CC was significantly reduced in schizophrenia patients, in line with the majority of studies comparing schizophrenia patients to normal, healthy subjects (e.g. DeQuardo, Bookstein, Green, Brunberg, & Tandon, 1996; Tibbo, Nopoulos, Arndt, & Andreasen, 1998; Downhill et al., 2000; Woodruff et al., 1993). Findings from the present study are also in agreement with Woodruff, Mcmanus, and David's (1995) meta-analysis of 11 published studies on corpus callosum morphology (involving a total of 313 patients and 281 controls), which showed a statistically significant reduction of CC area in schizophrenia patients relative to controls. The size shrinkage observed in the middle segments of the CC bore a resemblance to the results seen in Goghari et al.'s (2005) study, as smaller areas were also detected in the rostral body and the anterior midbody of the CC, in patients with schizophrenia. Keshavan et al. (2002) likewise noted a size reduction in the anterior midbody of the CC in drug-naïve patients diagnosed with either schizophrenia, schizophreniform or schizoaffective disorder. Since these middle sub-regions of the CC are thought to project into the motor cortical areas of the brain (Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindi, 2008; Zarei et al., 2006), the present findings are very much consistent with observations of motor dysfunction in schizophrenia patients.

Motor deficits that were independent of other cognitive impairments had been observed in both first-episode (Bilder et al., 2000) and chronic

schizophrenia patients (Sullivan, Shear, Zipursky, Sagar, and Pfefferbaum, 1994). Several studies have even noted motor abnormalities in children born to schizophrenia patients (Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Marcus, Hans, Mednick, Schulsinger, & Michelsen, 1985). The abnormalities found in the middle segments of the CC in this study possibly contributed significantly to the reported motor deficits, as the fibres in this region are known to project into the bilateral motor cortices in both healthy individuals (Park et al., 2008) and schizophrenia patients (Goghari et al., 2005). These deficits are unlikely to be the sole cause of the impairments however, as alternative pathways may provide compensation in some callosotomy and callosal agenesis patients (Sauerwein & Lassonde, 1994). Even neuroleptics have been known to affect motor functions in patients (Medalia, Gold, & Merriam, 1988).

One important point to note is that the volume differences in the CC were most apparent when comparing chronic patients with healthy controls. Chronic patients appeared to have smaller CCs than first episode patients, though the difference did not reach statistical significance. In contrast to other studies, no significant differences in CC size were seen between controls and the first episode schizophrenia patients (e.g. Bachmann et al., 2003; Keshavan et al., 2002). It is possible that patients recruited for studies with positive findings represent a subgroup on a deteriorating course (Davis et a., 1998), and as such, present more structural abnormalities at illness onset than other schizophrenia patients (Price et al., 2005). The lack of volume differences between first episode patients and healthy controls suggests that even when abnormalities were present before illness onset, they may be too subtle to be

identified accurately. Therefore, structural abnormalities before the first psychotic episode cannot serve as the sole predictor of schizophrenia; instead, functional impairments should also be assessed as they are more observable and easily noticed (Kremen et al., 1994). For instance, future studies may focus on the cause and nature of the motor impairments in schizophrenia subjects more closely, as similar impairments in childhood may predict future risk of developing the disorder (Erlenmeyer-Kimling et al., 2000).

The fact that CC volumes were smallest in chronic patients, followed by first-episode patients and healthy controls could also be interpreted as support for the view that structural pathologies worsen as the illness progress. In fact, negative correlations were seen between (a) the duration of untreated psychosis and CC size, and (b) the duration of psychiatric illness and CC size, where patients with longer duration of illness appeared to have the smallest CC sizes, despite falling short of significance. This further lends weight to the idea that schizophrenia is in fact a neurodegenerative disorder (Lieberman, 1999). Indeed, Mitelman and colleagues (2009) have reported that the extent of CC size shrinkage was much larger in schizophrenia subjects than in normal controls after comparing baseline MRI scans with subsequent scans done 4 years later. The current findings are also consistent with studies reporting changes in other brain regions with time, such as Gur et al.'s (1998) longitudinal study, which found further frontal lobe reductions in schizophrenia patients at follow-up. Nevertheless, many studies have failed to establish a significant correlation between the duration of illness and CC size (e.g. John et al., 2008; Miyata et al., 2007). It should be noted that the sample sizes for many of these studies were small, and the range of illness durations

amongst their recruited patients may be restricted and hence unable to produce a significant effect. Nonetheless, results from the present study should be interpreted with a degree of caution as the findings are derived from a cross-sectional approach; more longitudinal studies should be conducted to track the degeneration of the CC with illness progression.

8.3. No significant differences in FA between patients and controls

Despite observing a significant decrease in CC size in schizophrenia patients relative to healthy subjects, no significant between-group differences were found in the FA of the CC. This was consistent with Sun et al. (2003), who reported that significant differences between patients and controls in FA only existed in the anterior cingulum, but contrary to Gasparotti et al. (2008), who detected lower mean FAs in the splenium of schizophrenia patients, and Rotarska-Jagiela et al. (2008), who reported reduced FAs in both the genu and splenium of patients. Another DTI study employing the voxel-based approach have also found FA abnormalities in the CC in schizophrenia (Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003).

It has been shown that results can vary considerably depending on the methodologies of the study. The conclusions derived from the use of whole-brain voxel-based analysis differed greatly from the results of a study employing a regions-of-interest approach, even though the same subjects were recruited and scanned (see Foong et al., 2002 and Foong et al., 2000). Alternative factors such as the duration of illness, duration of antipsychotic medications use, and the heterogeneous nature of schizophrenia itself could have also resulted in conflicting findings. Nonetheless, the likelihood remains

that FA disruption is present only in a subgroup of schizophrenia patients, and is not a core feature of the illness. For instance, while schizophrenia patients as a group had lower FAs than controls in several parts of the CC, those patients with auditory hallucinations were found to have higher FAs in the anterior CC than control subjects (Hubl et al., 2004). As noted by Walterfang, Wood, Velakoulis and Pantelis (2006), subtle changes "may be lost when individuals affected to different degrees and by potentially differing underpinning neurobiology are pooled". The reduced CC size accompanied by intact FA found in this study suggests a loss of axons in the CC, as changes in anisotropy do not necessarily follow a reduction in the number of axons (Cercignani & Horsfield, 2001).

8.4. Weak correlations between CC area/volume and FA

In Rotarska-Jagiela et al.'s (2008) study, whole CC volume was found to be significantly correlated with CC FA in both patients and controls. The significant positive correlations were missing in the present study however. Though a trend towards significance was noted in several CC sub-regions, the correlations were weak and not consistent in their directionality. One reason for the weak correlations between CC FA and CC size is that variations in water content in white matter will be reflected only in the FA measure and not area or volume measures (Fjell et al., 2008). In addition, factors such as the presence of fluid bubbles in the myelin sheets (Peters and Sethares, 2002) affect FA and volume measures differently. Hugenschmidt et al. (2008) also suggested that FA reductions are possible without corresponding volume loss.

Further studies are certainly needed to expand our knowledge about the relationship between FA and volume measures.

8.5. Education and Schizophrenia

Even though this study shows that schizophrenia patients and their parents received less education than normal controls, it is impossible to know whether this is the result of the termination of education due to schizophrenia onset, or the consequence of poor academic performance preceding illness onset. Nevertheless, analysis of Primary School Leaving Examination (PSLE) (a standardized national examination that tests primary school leavers in Singapore in 4 subjects: English, Mathematics, Science, Second Language) scores revealed that academic performance of children who later developed schizophrenia spectrum disorders was significantly poorer than healthy children (Chong et al., 2009), suggesting that academic performance can be used as a premorbid marker for schizophrenia (Allen, Frantom, Streauss, & van Kammen, 2005). This was supported by a large study involving 907011 individuals born in Sweden between 1973 and 1983 that found a strong association between poor school performance and the risk of schizophrenia and other psychoses (MacCabe et al., 2007). Lastly, the observation of an association between higher levels of education and larger CC sizes hint that structural brain markers may one day be used to predict cognitive functioning in individuals.

8.6. Study limitations and Future Directions

A limitation of the current study lies in the small number of left-handed subjects, thereby ruling out an investigation of the effects of handedness on CC size and anisotropy. Nevertheless, handedness probably has a minimal impact on CC size or anisotropy in this study, since the removal of all left-handed and ambidextrous subjects from the analyses did not alter results. The inclusion of comparable but small numbers of non-right-handed subjects in studies of the CC has been a common practice (e.g. Keller et al., 2003; Narr et al., 2000; Walterfang et al., 2008), as researchers face difficulties recruiting equal numbers of left- and right-handed participants for their studies. The lack of consensus as to whether handedness affects the CC also makes some researchers omit left-handed participants altogether (e.g. Venkatasubramanian et al. 2010). Future studies should attempt to recruit more left- and mixed-handedness participants, so that the effects of handedness can be thoroughly examined. In addition, the method of assessing handedness (e.g. handedness dominance test, Steingrueber & Lienert, 1971; Annett's hand preference questionnaire, Annett, 1967) should preferably be compared and then standardized across studies.

Also, to facilitate comparisons with previous studies and at the same time remove possible rater's bias, this study used a software to automatically delineate the brain into approximately 200 structures, after which the CC was identified and segmented into 5 sub-regions. The drawback of the approach is that the 5 sub-regions obtained do not correspond exactly with distinct anatomical or functional CC sub-regions in reality, because there are no clear structural landmarks that can aid the segmentation of the CC to begin with

(Hofer & Frahm, 2006). A better approach may be to use diffusion tensor tractography to assist in CC parcellation, as the technique allows the mapping of specific pixels in the CC to connected cortical regions (Huang et al., 2005).

With diffusion tensor tractography, Huang et al. (2005) managed to segment the CC into 6 major subdivisions, and subsequently found that a stroke patient had significant fibre loss in the motor and sensory regions of the CC when compared to healthy controls. Miyata et al. (2007) employed the same procedures and successfully divided the CC into anterior and posterior portions, before demonstrating abnormalities in the anterior regions of the CC in schizophrenia patients, relative to controls. The growth trajectories of the whole CC and its sub-regions have also been studied with diffusion tensor tractography (Hasan et al., 2009). Future research can adapt the CC segmentation scheme proposed by Hofer and Frahm (2006), instead of using the popular, yet controversial Witelson's (1989) scheme (see Figure 5).

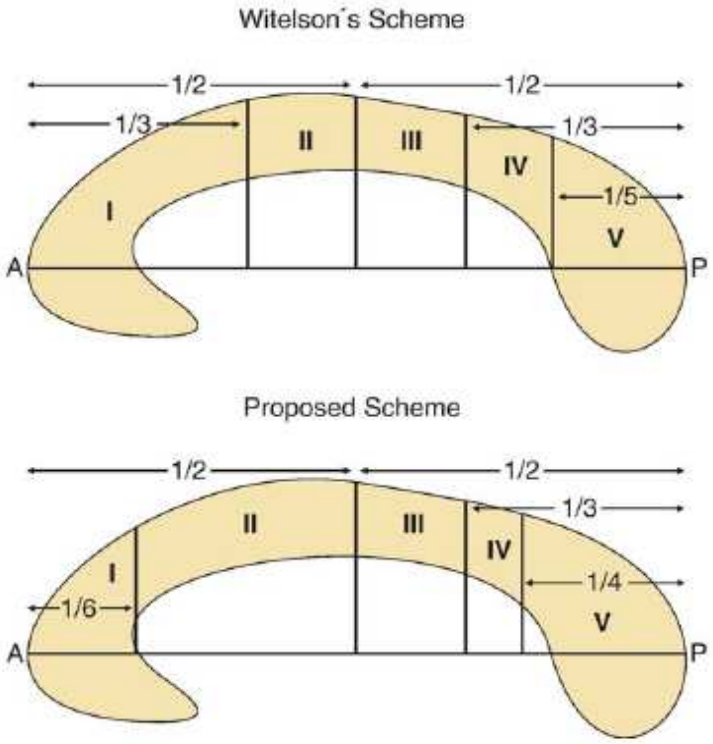

Figure 5. Segmentation of the corpus callosum. The Witelson's scheme (top) and the new proposed scheme by Hofer and Frahm (2006). Top: (I) Anterior third, corresponding to prefrontal, premotor and supplementary motor areas; (II) Anterior midbody, corresponding to motor areas; (III) Posterior midbody, corresponding to somaesthetic and posterior parietal areas; (IV) Isthmus, corresponding to posterior parietal and superior temporal areas; (V) Splenium, corresponding to occipital and inferior temporal areas. Bottom: (I) Corresponds to prefrontal areas; (II) Corresponds to premotor and supplementary motor areas; (III) Corresponds to motor regions; (IV) Corresponds to sensory regions; (V) Corresponds to parietal, temporal and occipital areas. A: Anterior, P: Posterior. Adapted from "Topography of the human corpus callosum revisited – comprehensive fiber tractography using diffusion tensor magnetic resonance imaging," by S. Hofer and J. Frahm, *Neuroimage, 32,* p. 992. Copyright 2006 by Elsevier B. V. Adapted with permission.

Upcoming studies can also look into the use of brain abnormalities as endophenotypes in schizophrenia, as this could potentially lead to the identification of specific genes responsible for the phenotypic manifestations of the illness (Keshavan et al., 2007). As a start, studies can examine the

relationship between CC size or CC FA and behavioral measures, to advance our understanding of the origins of cognitive deficits frequently observed in schizophrenia. In healthy adolescents, the microstructural integrity of the splenium and the body of the CC was found to be related to visuospatial construction abilities, while the integrity of the splenium alone was associated with language and psychomotor functions (Fryer et al., 2008). This suggests that abnormalities in the splenium may underlie psychomotor impairments in schizophrenia, which can be verified by carrying out a similar study in the schizophrenia population. Functional MRI can also be utilized to study the involvement of different callosal regions in specific cognitive tasks in the near future (Gawryluk, D'Arcy, Mazerolle, Brewer, & Beyea, 2011).

8.7. Conclusions

In sum, the present investigation of the area, volume and FA of the CC in a large group of schizophrenia patients and healthy controls did not yield any significant or observable sex differences in the structure. Nevertheless, the study found that the size of the CC was notably reduced in schizophrenia patients relative to healthy controls, such that the smallest CC sizes were recorded in chronic patients, while the largest CC sizes were observed in the healthy controls. Microstructural differences in the CC, as measured by FA, were absent between schizophrenia patients and control subjects however. This shrinkage of the CC in schizophrenia appears to be an important feature of the disorder as it has been replicated across studies, and without any doubt, a key explanation for the various interhemispheric transfer deficits seen in schizophrenia patients.

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