

The Disrupted Connection Between Cerebral Hemispheres in Schizophrenia Patients: A Diffusion Tensor Imaging Study



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SUMMARY

Aim: In schizophrenia, the disruption of the communication between two brain hemispheres has not been shown clearly in the anatomical aspect despite other studies with different modalities suggested so. In this study, the structural integrity and the variables affecting the structural integrity of the corpus callosum, which is the main connection between two hemispheres, was investigated via diffusion tensor imaging (DTI).

Methods: The participants were evaluated by SCID-I and symptoms of the patients were assessed with PANSS. DT images of 25 schizophrenia patients and 17 healthy volunteers were acquired via 1.5 T MR. Fractioned Anisotropy (FA) values of two groups, measured on the DT images, were compared.

Results: It was found that fractioned anisotropy (FA) values were lower in the genu of the patients than the healthy controls; however, there was no difference between the FA values of the patients and the controls in the splenium. Moreover, a significant negative correlation between the splenium FA values and the antipsychotic medication doses; and a trend level negative correlation of splenium FA and PANSS scores were found.

Conclusion: Corpus callosum is the most important structure that connects two frontal lobes. The hypothesis that posits the fundamental role of the disconnection of frontal lobes in schizophrenia is supported by the findings of this study.

Key words: schizophrenia, corpus callosum, diffusion tensor imaging, connectivity, positive and negative symptoms scale (PANSS)

INTRODUCTION

It has been suggested that abnormal brain development in schizophrenia leads to disruption in the connection of different brain regions, which may be demonstrated by the examination of white matter (Peters et al 2008). In fact the idea of 'disconnection' is not new, being put forward by both Wernicke and Kraepelin at the beginning of previous century (Kubicki et al 2005). The largest connection between the brain regions is corpus callosum (CC), which connects the two hemispheres of the brain, and there are many studies detecting abnormality in the CC of schizophrenia patients, corroborating the predictions of Wernicke and Kraepelin (Foong et al 2000, Ardekani et al 2003, Kubicki et al 2005, Kanaan

et al 2005, Caan et al 2006, Price et al 2007, Rotarska-Jagiela et al 2008, Friedman et al 2008, Kubicki et al 2008, Cheung et al 2008, Camchong et al 2009, Rotarska-Jagiela et al 2009, Gasparotti et al 2009, Davenport et al 2010, Pomarol-Clotet et al 2010, Davenport et al 2010, Whitford et al 2010). However, there are also studies indicating that CC of schizophrenia patients is not different from that of healthy controls (Price et al 2005, Kanaan et al 2006, Peters et al 2008, Mandl et al 2010).

As corpus callosum consists of white matter, conventional magnetic resonance imaging (MRI) techniques remain inadequate in the analysis of this structure. In the examination of the integrity and density of the connections, a new MRI tech-

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nique diffusion tensor imaging (DTI) yields better results. One of the data obtained by DTI, is fractional anisotropy (FA), which provides information on the diffusion pattern of water molecules. Water molecules are expected to move along axon parallel to myelin sheath. In case where there is a disruption in the axon membrane, microtubule structure or myelin sheath, parallel movement of water molecules is impaired. The higher the number of water molecules moving in the same direction in a certain region, the higher the FA value. FA is scored between 0 and 1 and if all water molecules diffuse in the same direction, the value is 1. In case water molecules do not diffuse in the same direction, the value of FA approaches 0 (Kyriakopoulos et al 2008).

The majority of DTI studies investigating the CC structure of schizophrenia patients found the FA values of the patients to be lower than those of controls. However, differences in patient groups between the studies lead to some controversies on whether these results are generalizable (Kyriakopoulos et al 2008). In addition, since the anterior part of CC (genu) and posterior part of CC (splenium) are derived from neurodevelopmentally different structures and mature at different developmental stages (Mihirshahi 2006); it would not be an appropriate approach to consider CC as a whole. Moreover, tracts passing from the genu and splenium regions connect different areas of the brain (Whitford et al 2010). In many studies the CC was divided into subregions and the subregions were investigated separately (Foong et al 2000, Ardekani et al 2003, Price et al 2005, Caan et al 2006, Price et al 2007, Cheung et al 2008, Rotarska-Jagiela et al 2008, Friedman et al 2008, Kubicki et al 2008, Gasparotti et al 2009, Cheung et al 2008, Peters et al 2008, Kubicki et al 2008, Camchong et al 2009, Gasparottiet al 2009, Davenport et al 2010, Pomarol-Clotet et al 2010, Mandl et al 2010, Whitford et al 2010).

The measurement method is also important in addition to the patient sample and chosen investigation region. Measurements based upon the manual drawings of an experienced investigator using a computer program is termed as region of interest (ROI) analysis and yields the most reliable information on the chosen region. In the voxel based analysis (VBA) method carried out using statistical modeling, the entire brain is examined without choosing any special region. VBA yields more reliable information in pathological investigations since it evaluates whole brain, but due to resolution and modeling problems, its reliability is lower (Kanaan et al 2005).

When the relation between medication use and the severity of disease and the DTI data is evaluated, it does not seem possible to reach definitive conclusions based upon the data of the studies. Indeed, there are very few studies investigating the relation between objective evaluations such as PANSS and the DTI data regarding CC (Rotarska-Jagiela et al 2008, 2009, Michaels et al 2008, Whitford et al 2010).

Although CC abnormalities have been found in the majority of studies comparing FA values obtained from DTI images of schizophrenia patients with healthy controls (Kyriakopoulos et al. 2008), the results of studies considering different subregions of CC are far from being consistent. If we take the development of the CC and the direction of tracts passing from the CC into account, elucidating the integrity of genu and splenium will provide important data in understanding the pathophysiology of schizophrenia. In the present study, the subregions of the CC are considered separately by ROI analysis and based upon the measurement of FA values, we aimed to compare the structure of CC between schizophrenia patients and healthy individuals and to determine the clinical variables which may influence FA values in the patient group.

METHOD

Sample

This study was carried out with 25 schizophrenia patients (11 female, 14 male) who received outpatient treatment in the Psychiatry Department of Ege University, Faculty of Medicine, and who were referred there from various centers in the district. Volunteers were evaluated in two stages: first, volunteers underwent psychiatric examination by an experienced psychiatrist and then a different psychiatrist administered a structured clinical interview (SCID-I) according to diagnostic criteria of DSM-IV (American Psychiatry Association 1994). SCID-I is a semi-structured interview that allows the experienced clinician to tailor questions to fit the patient's understanding; to ask additional questions that clarify ambiguities; to challenge inconsistencies; and to make clinical judgments about the seriousness of symptoms. The information collected from the family members of the patients was also included in the process to increase reliability (First et al 1997, Çorapçıoğlu et al 1999). The patient group comprised volunteers that did not receive any diagnosis except schizophrenia after the aforementioned two stages and who were able to be given informed consent. Those who had a systemic or neurological disease, according to physical examination, out of normal range laboratory findings or those who experienced head trauma resulting in loss of consciousness were excluded from the study. In addition, all schizophrenia patients were followed up for type II diabetes and no patient was diagnosed with any metabolic disorder. In the event that a tumor was detected in the MR image of a patient diagnosed with schizophrenia during the study, that patient was excluded from the study. Control groups consisted of hospital staff working in non-medical procedures and their relatives and healthy individuals that could be reached by local means. The Ethics committee of Ege University School of Medicine, approved the study and all volunteers gave written informed consent.

Tools

In order to evaluate the severity of the disease concurrent with DTI images in patients who gave informed consent, the positive and negative symptom scale (PANSS) was administered to the patients. PANSS includes subscales of 16 items evaluating general psychopathology and seven items each evaluating the presence and severity of positive and negative symptoms. Information on the evaluation of the patients can be obtained both from him/herself and the family members and relatives (Kay et al 1987, Kostakoğlu et al 1999). MRI examinations were made with 1,5 Tesla MR system (Siemens Symphony, Vision to Symphony Upgrade, Erlangen, Germany). DTI sequence characteristics and parameters are as follows: Spin-echo single shot echoplanar sequence, size of voxels: 2x2x2.2 mm, FOV: 256x256, Matrix: 128x128, TR/TE: 10070/103 ms, b: 0, 700 s/mm², number of directions: 60. Two experienced radiologists blind to the diagnosis of the patients evaluated MR images taken during study.

Determination of region of interest and measurements

DT images transferred to a different workstation (Leonardo Workstation) were analyzed by DTI Task Card software (MGH, Boston, USA). Using this software, FA and ADC (apparent diffusion coefficient) maps were formed from source DT images. For FA measurement, the ROI was chosen on the images at the sagittal axis. In the determination of anatomic segments, Witelson (1989) classification, modified by Hofer et al (2006) according to fiber tractography findings were used. Mean FA values were taken from genu (segment I) and splenium (segment V) segments of the CC. FA measurements were made using ADC maps, which feature

significantly improved anatomic details than others, (Figure 1) using the manually ROI method.

Statistics

In the statistical evaluation, a t test was used to analyze the differences between groups. When the confounding effect of the volume of the region evaluated was added to the model, univariate variance analysis was made. In this analysis, as age and sex did not have any relation with FA values, they were not considered as confounding factors. The relation between clinical variables and FA was investigated using Pearson correlation analysis. Because the PANSS scores and antipsychotic medication doses were not normally distributed, these data were transformed with logarithmic transformation procedure to log 10 base for the correlation analysis.

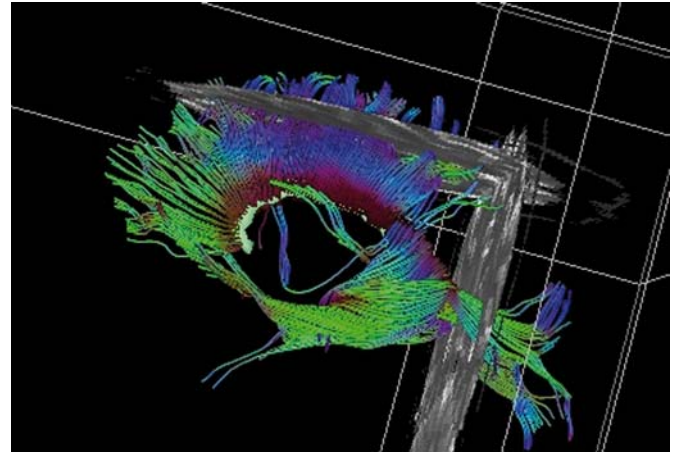


FIGURE 1. ADC map of FA measurements. Claret red area corresponds to corpus callosum.

TABLE 1. The comparison between age, sex and DTI data of healthy volunteers and patients

	Healthy volunteers (N=17)	Patients (N=26)	Statistical results
Age	33.4 (SD= ±10.4)	38.1 (±12.0)	t=1.32; df=40; p>0.05 ⁽¹⁾
Gender (male/female)	9 / 8	14 / 11	X ² = 0.04;p>0.05 ⁽²⁾
FA Genu	0.84 (SD= ±0.04)	0.80 (SD= ±0.04)	t= 2.38; df= 40; p= 0.02 ⁽¹⁾
Genu volume (mm ³)	18.0 (SD= ±4.5)	17.5 (SD= ±4.1)	t= 4.1; df= 40; p> 0.05 ⁽¹⁾
Adjusted FA Genu	0.837 (SD= ±0.008)	0.804 (SD= ±0.007)	F= 9.5; df= 1.42; p= 0.004 ^{(3)**}
FA Splenium	0.84(SD= ±0.05)	0.83 (SD= ±0.03)	t= 0.37; df= 40; p>0.05 ⁽¹⁾
Splenium volume (mm ³)	10.8 (SD= ± 2.3)	9.6 (SD= ± 2.3)	t= 1.09; df=40; p>0.05 ⁽¹⁾
Adjusted FA Splenium	0.83 (SD= ±0.01)	0.83 (SD= ±0.008)	F= 0; df= 1.42; p> 0.05 ⁽³⁾
PANSS positive subscale scores		12.8 (SD= ± 5.7)	
PANSS negative subscale scores		21.0 (SD= ± 10.2)	
PANSS general psychopathology subscale scores		35.8 (SD= ± 9.0)	
PANSS overall scores		70.1 (SD= ± 20.2)	
Chlorpromazine equivalent drug dose(mg)		437.30 (SD= ± 400.30)	

* ROI volume was taken as confounding factor

** Statistically significant difference was found

⁽¹⁾ t-test was used

⁽²⁾ Chi-square test was used

⁽³⁾ ANOVA was used

RESULTS

Demographic data of the sample and their relation with FA values

No significant difference was found between patient (mean age $\pm$ SD=38,1 $\pm$ 12,0) and healthy volunteers (mean age $\pm$ SD=33,4 $\pm$ 10,4) in terms of age and sex. (Patient female/ male=11/ 14; healthy female/male = 8/9) ($t=1,32$; $df=40$; $p>0,05$ and $X^2=0,04$ $p>0,05$; respectively). Mean age of the onset of disease was expressed in years 27,6 ($\pm$ SD= $\pm$ 12,0) and mean duration of disease in months was 125,8 ($\pm$ SD= $\pm$ 85,9).

No significant relation was found between the age of the onset of disease and the duration of disease ($r=-0,31$; $p>0,05$), duration of disease and PANSS scores ($r= 0,07$; $p>0,05$) and the age of onset of disease and PANSS scores. ($r=-0,25$, $p>0,05$).

FA values were distributed normally within the two groups, as was sex (in genu FA values $t= 0,59$; $df= 40$; $p>0,05$ and in splenium FA values $t= -0,43$; $df= 40$; $p>0,05$) and age (in genu FA values $r= -0,10$; $p>0,05$ and in splenium FA values $r= 0,42$; $p> 0,05$) were not found to be related to FA values, in the subsequent analysis these variables were not used as confounding factors.

Comparison of FA between groups according to Corpus Callosum regions

In the genu region of the CC, FA values of schizophrenia patients were found to be lower (mean $\pm$ SD=0,80 $\pm$ 0,04) when compared to healthy control group (mean $\pm$ SD=0,84 $\pm$ 0,04) ($t=2,38$; $df=40$; $p=0,02$). The volume of the ROI did not vary between groups (patient mean value $\pm$ SD=17,5 $\pm$ 4,1 mm³; healthy mean value $\pm$ SD=18,0 $\pm$ 4,5 mm³; $t=4,1$; $df= 40$; $p>0,05$). However, when the size of the ROI was considered as a confounding factor in the univariate analysis, the difference in FA values between two groups became more apparent ($F=9,5$; $df=1,42$; $p=0,004$).

No difference was found between two groups in terms of splenium FA values (Patient mean value FA $\pm$ SD=0,83 $\pm$ 0,03 and healthy mean value FA=0,84 $\pm$ 0,05 and $t= 0,37$; $df= 40$; $p>0,05$). No difference was found between schizophrenia patients and healthy volunteers in terms of the volume of the splenium (patient mean values $\pm$ SD=9,6 $\pm$ 2,3; healthy mean values $\pm$ SD=10,8 $\pm$ 2,3; $t=1,09$; $df=40$; $p>0,05$) and adding the volume of splenium to the statistical model as a confounding factor did not change the results ($F=0$; $df=1,42$; $p>0,05$).

The relation between the clinical variables and FA values

In the evaluation of the variables related to disease, a negative correlation was found in the patient group between FA values

and PANSS results at trend level ($r=-0,37$; $p=0,07$) and antipsychotic medication doses calculated with equivalent doses of chlorpromazine at significance level ($r= -0,47$; $p= 0,03$). No relation was found between the splenium FA values and the age of onset of disease ($r=-0,04$; $p>0,05$) or the duration of disease ($r= -0,04$; $p> 0,05$). In contrast to the splenium, no relation was found between FA values in genu and the variables related to the disease (for PANSS results $r=-0,14$; $p>0,05$; for antipsychotic drug doses $r=-0,32$; $p>0,05$; for the age of onset of disease $r=0,01$; $p>0,05$; for the duration of disease $r=-0,20$).

TABLE 2. The relation between PANSS and antipsychotic drug dose and DTI data

Correlation	Result
FA Genu – PANSS	$r= -0,14$; $p> 0,05$
FA Genu – Antipsychotic drug dose #	$r= -0,32$; $p>0,05$
FA Splenium – PANSS	$r= -0,37$; $p=0,07$
FA Splenium – Antipsychotic drug dose#	$r= -0,47$; $p= 0,03^*$
# Calculated with Chlorpromazine equivalent dose. * $p<0,05$.	

DISCUSSION

In the present study, lower FA values were found in schizophrenia patients in the genu region of CC, which connects the two hemispheres of the brain, as compared to healthy controls. Although FA values in the splenium were not different between patients and healthy controls, an inverse relation was found between FA values in the splenium and PANSS results and antipsychotic medication doses.

Even though the extension of axons and their density and thickness and the cellular architecture within axon influence FA values, it is generally accepted that FA values reflect predominantly axon and myelin sheath integrity with a higher tissue organization (Kubicki et al 2008, Mandl et al 2010, Camchong et al 2009). However, low FA values have different implications for the aforementioned states. If low FA values emanate from the decrease in the number of axons, less information is carried from the CC, which will cause less activity on the ipsilateral side. If it is the impairment in myelination which leads to a decrease in FA values, transmission of information through axons will slow down, bringing about synchronization disorder in the processing of information and the decrease of the ratio of signal/noise (Konrad and Winterer 2008).

In a study carried out by Price et al (2007) comparing schizophrenia patients with healthy controls, it was established that although the volume of the tracts passing from the CC did not decrease in schizophrenia patients, FA values were lower and it was suggested that main pathology was in myelination. Kubicki et al (2005) combined DTI-magnetization transfer ratio (MTR) methods to compare schizophrenia patients with healthy controls. They assumed that as MTR method is one

which gives information on the integrity and thickness of myelin, the combination of DTI and MTR will give more accurate information on the origin of FA value and concluded that the low FA values they found in schizophrenia patients stem from the structure of myelin. One of the most compelling evidence for the presence of an impairment of myelination in schizophrenia is the postmortem study of schizophrenia patients carried out by Hakak et al (2001). They established that the expression of the gene responsible for the production of myelin was decreased in the prefrontal cortex of the patients, which may lead to impairment in the functions of oligodendrocytes.

When DTI studies on schizophrenia patients are evaluated, it can be seen that studies investigating the CC can be divided into three groups. In many studies presenting data on the entire CC, FA values of the patient groups were found to be lower than the control group (Ardekani et al 2003, Kubicki et al 2005, Kanaan et al 2005, Price et al 2007, Kyriakopoulos et al 2008, Rotarska-Jagiela et al 2009). However, there are also studies, albeit few, reporting that FA values of schizophrenia patients were not different from those of healthy controls (Price et al 2005, Peters et al 2008). In the studies examining the genu region, while FA values were found to be lower in patients than in healthy controls in many studies (Caan et al 2006, Price et al 2007, Rotarska-Jagiela et al 2008, Friedman et al 2008, Kubicki et al 2008, Camchong et al 2009, Davenport et al 2010, Pomarol-Clotet et al 2010, and Whitford et al 2010) in some other studies no difference was found between groups (Foong et al 2000, Price et al 2005, Kanaan 2006, Cheung et al 2008, Mandl et al 2010, Friedman et al 2008, Gasparotti et al 2009). Likewise, in the studies on splenium, while FA values were found to be lower in patients than in healthy controls in some studies (Foong et al 2000, Ardekani et al 2003, Cheung et al 2008, Friedman et al 2008, Gasparotti et al 2009, Davenport et al 2010) in others no difference was found between two groups (Price et al 2005, Friedman et al 2008, Peters et al 2008, Kubicki et al 2008, Whitford et al 2010).

It may be suggested that differences in patient selection may account for the discrepancy between study results. Some of the studies finding lower FA values in the genu of patients were carried out with chronic patients (Rotarska-Jagiela et al 2008, Kubicki et al 2008, Pomarol-Clotet et al 2010, Whitford et al 2010). Friedman et al (2008) compared the FA values of first episode schizophrenia patients and chronic ones with healthy controls and found that FA values were lower in the chronic groups both in the genu and splenium. Supported by this finding, it may be stated that the duration of disease and FA values in genu has an inverse relation, whilst there are also investigators proposing that there is no relation between the duration of the disease and FA values (Kyriakopoulos et al 2008, Kanaan et al 2005).

Although there are investigators suggesting that FA is lowered as a consequence of chronic disease, FA values of schizophrenia patients with new onset, at first episode or in adolescence and those of healthy twin siblings of schizophrenia patients were found to be lower than healthy controls (Caan et al 2006, Price et al 2007, Gasparotti et al 2009, Davenport et al 2010, Chamcong et al 2009). Moreover, in a study on chronic schizophrenia patients, no difference was found between patients and healthy controls in terms of FA values (Mandl et al 2010). In conclusion, it seems that FA values are not related to whether the patients have their first episode or they are chronic cases. In the present study, the majority of patients have chronic courses and low values detected in genu region are compatible with the majority of previous studies. Nevertheless, present data are not sufficient to determine whether low FA values found in our patient group are related to the disease process being chronic.

As in many other studies, genu and splenium FA values were different in the present study as well. This difference in FA values may have embryonic, structural and functional causes. The genu and splenium are derived from different embryological structures. While genu region is formed by axons coming from cingulate cortex under the guidance of glia cells, splenium region develops under the guidance of axons passing from hippocampal commissure without any need of the guidance of glia cells (Mihirshahi 2006). The temporal development of genu and splenium is different as well. (Richards et al 2004). In the CC; at first rostrum of genu region and anterior of its body corresponding to fornix develop and then the splenium starts to develop. This sequence of development process is parallel to the rostral-caudal maturation of neocortex (Crow et al 2007).

Axons moving within the white matter of the brain are located in the CC region which is nearest while passing across to the counter side. Axons deriving from frontal regions use the genu region whilst those deriving from parieto-occipital region pass across over the splenium (Richards et al 2004). Due to this, the genu connects frontal regions to each other and mediates healthy operations of executive functions (Rotarska-Jagiela et al 2008, Pomarol-Clotet et al 2010). There is compelling evidence that executive functions, which are of frontal cortex origin, are impaired in schizophrenia and that there are deviations in the number, shape, size and sequence of neurons in frontal region and cellular structure (Rotarska-Jagiela et al 2008). In this respect, it is not surprising that low FA values were found in schizophrenia patients in the genu region connecting frontal regions in the present study. However, no relation was found between FA values in the genu region and PANSS scores.

The possible adverse effects of antipsychotic drugs on myelination may explain the negative correlation between the splenium FA values and doses of antipsychotic drugs (Segal

et al 2007). However, the probability that high doses of antipsychotics are used for resistant psychotic symptoms suggests that psychopathology is also influential on FA values in the splenium. In fact, the splenium FA values found in the present study tend to display a negative correlation with PANSS scores.

There are very few studies investigating the relation of PANSS scores with FA values directly. In a study carried out by Rotarska et al (2008), a direct relation was found between PANSS scores and genu and splenium body values, but when patient groups were divided into mild and severe symptoms according to PANSS scores, a similar relation was not observed. In another study by Rotarska-Jagiela et al (2009), the entire CC structure was evaluated and a direct correlation was found between FA values and scores in the positive symptom subscale of PANSS. In a more recent study by Whitford et al (2010), a direct proportion was found between positive symptoms and FA values in genu. A study with no control group found negative correlation between splenium FA values and negative symptoms and overall scale scores of PANSS (Michael et al 2008). To the best of our knowledge, our study is the first controlled study demonstrating negative correlation between PANSS and splenium FA values.

It is intriguing that while a direct proportion was found between the splenium FA values and PANSS scores, the same relation could not be found in the genu. Furthermore, considering that low FA values were found in the genu in schizophrenia patients while no difference was found between splenium FA values of patients and controls, one may expect the relation between PANSS and FA seen in splenium to also be seen in genu. The available data are too limited to interpret the relation between FA values and PANSS subscales. Although it does not yet seem possible to predict the relation between FA and PANSS scores in the genu and splenium, in view of the fact that both areas are derived from different structures neurodevelopmentally and mature at different times (Mihirshahi 2006) and have tracts with different projections (Richards et al 2004, Whitford et al 2010), our finding may be important to understand the pathology of the disease.

Whether the cause of low FA values found in the CC of schizophrenia patients is developmental or degenerative still remains to be determined. In animal studies, intrauterine influenza infection induced in the period when the CC development is initiated (second trimester in rats) decreases the expression of genes involved in myelination and impairs the development of the CC, causing a decrease of FA values. (Fatemi et al 2009b). This finding is parallel with the findings of studies of Hakak et al (2001).

It is assumed that the impairment of the communication between the two hemispheres due to the disruption of myelination in the CC leads to the loss of lateralization, which occurs

frequently in schizophrenia (Kubicki et al 2005). Crow et al (2007) pointed out the importance of the loss of lateralization in schizophrenia and suggested that the CC played a key role in this issue. According to this view, disturbance in the development of the CC gives rise to negative symptoms by impairing the reciprocal communication in frontal regions, founding the core of schizophrenia. The fact that the impairment in neuronal migration through the CC under the guidance of glia cells produces such significant effects is consistent with the assumption that glia cells play part in the development of schizophrenia (Cotter et al 2001, Jarskog and Robbins 2005, Kondziella et al 2007).

It is thought that the loss of oligodendrocytes, responsible for myelin production through neurodegenerative process may bring about a decrease in myelin production, hence a fall in FA values. It has long been maintained that in schizophrenia patients, as a consequence of the decrease in the activity of NMDA receptors in the neurons, glutamate release is increased, which in turn leads to glutamate excitotoxicity mediated by AMPA receptors (Segal et al 2007). Not only neurons but also oligodendrocytes have AMPA receptors and are subjected to glutamate excitotoxicity. Dopamine protects oligodendrocytes from the toxic effects of glutamate via D2 and D3 receptors (Rosin et al 2005). Therefore, in patients on long-term antipsychotics, decrease in the number and function of oligodendrocytes is expected, which will affect myelination adversely and lead to a decrease in FA values (Segal et al 2007). In addition, as neurons are expected to contribute to myelination by influencing the functions of oligodendrocytes, it is possible that pathological neuronal functions may impair myelination (Konrad and Winterer 2008).

Another important factor underlying the different results of previous studies is suggested to be the investigation method that is chosen (Kanaan et al 2005, Kanaan et al 2006, Kyriakopoulos et al 2008). Studies evaluating the CC structure of schizophrenia patients may be divided into two groups. In the first group, there are studies termed region of interest, which make measurements only of the region to be evaluated (Foong et al 2000, Price et al 2005, Friedman et al 2008, Rotarska-Jagiela et al 2008, Gasparotti et al 2009). The other method is based upon the examination of all brain with voxel based analysis (VBA) instead of examining an a priori region and upon the detection of regions exhibiting difference with the assistance of computer programs (Caan et al 2006, Ardekani et al 2003, Price et al 2007, Cheung et al 2008, Rotarska-Jagiela et al 2009, Davenport et al 2010). However, in this method, the number of examined images must be increased compared to ROI studies and due to modeling problems, reliable results can not always be obtained. However, when studies are reviewed, among those using ROI method, there have been studies finding lower FA values in patients (Rotarska-Jagiela et al 2008, Friedman et al 2008,

Kubicki et al 2008, Camchong et al 2009, Whitford et al 2010) as well as studies finding no difference between patient groups and healthy controls (Price et al 2005, Peters et al 2008, Mandl et al 2010).

It has been reported that type 2 diabetes leads to white matter abnormalities due to the microvascular damage it causes (Yau et al 2009, Yau et al 2010). Yau et al (2009) demonstrated that in the comparison of individuals diagnosed with type II diabetes and who do not have psychiatric disorder or large vessel disease with a healthy control group, white matter abnormalities detected in diabetic group by DTI were associated with the disturbance in memory function. The higher rate of diabetes in schizophrenia patients is a long recognized fact (Mukherjee et al 1996). Yet, as far as we know, among DTI studies on schizophrenia patients, there is no study excluding those with metabolic syndrome. Only in the study of Friedman et al (2008), it was stated that patients with severe diabetes and hypertension were not included in the study. As patients with metabolic syndrome were excluded, we may state that the FA difference found in our study does not stem from the microvascular damage caused by diabetes, which is one of the important advantages of our study.

In the present study, the number of patients does not make it possible to investigate female and male patients separately or to compare them. Given the view that cerebral asymmetry is lost or is not present in schizophrenia patients, lack of this data is an important limitation of the study (Crow et al 2007). As in our study, the majority of DTI studies carried out with schizophrenia patients were carried out on patients with chronic disease. In this respect, the question of whether FA differences found developed before disease or in disease process remains unclear in such studies including ours. Another

limitation of our study is that the effect of antipsychotic drugs was not excluded. Although it is assumed that antipsychotic drugs have adverse effect on myelination, recent studies and a meta-analysis showed that antipsychotic drugs exert no effect on the FA values of the CC (Segal et al 2007, Rotarska-Jagiela et al 2008, Kubicki et al 2008, Kyriakopoulos et al 2008). Our study has another limitation common to all DTI studies: the interpretation of the meaning of FA values. Low FA values may imply impairment in axon or myelin structure, while tracts from the same region but which have different extensions may cause low FA values as well. Nevertheless, the probability that low FA values may stem from organization disturbance in the tracts is in keeping with the view of disrupted integrity of connections in schizophrenia.

CONCLUSION

Communication between two hemispheres of the brain has critical importance for both cognitive and sensory-motor functions. The idea that the impairment in the structure of tracts, carrying information between two hemispheres, plays an important part in the pathogenesis of schizophrenia is becoming increasingly common. In the present study, the idea that there is a disturbance in the connection of both hemispheres in the frontal systems of schizophrenia patients is supported, while strong evidence that there is a disturbance of connection between posterior parts of hemispheres could not be found. As further DTI studies on schizophrenia patients are carried out, it will be possible to obtain more evidence on the impairment of white matter providing connection between brain regions and to develop new treatment methods based upon this evidence.

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