Published in final edited form as:
Schizophr Res. 2011 August ; 130(0): 78–85. doi:10.1016/j.schres.2011.04.016.

Diffusion Tensor Imaging of Anterior Commissural Fibers in Patients with Schizophrenia

Hongyoon Choi[1,2], **Marek Kubicki**[1,3], **Thomas Whitford**[1,4], **Jorge L. Alvarado**[1], **Douglas P. Terry**[1], **Margaret Niznikiewicz**[3], **Robert W. McCarley**[3], **Jun Soo Kwon**[5,6], and **Martha E. Shenton**[1,3,7]

[1]Department of Psychiatry, Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Seoul National University College of Medicine, Seoul, Republic of Korea

[3]Clinical Neuroscience Division, Laboratory of Neuroscience, VA Boston Healthcare System, Brockton, Massachusetts, USA

[4]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, and Melbourne Health, Melbourne, Australia

[5]Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea

[6]Department of Brain & Cognitive Sciences-WCU program, College of Natural Sciences, Seoul National University, Seoul, Republic of Korea

[7]Surgical Planning Laboratory, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Introduction—Alterations in white matter connections in schizophrenia have been investigated using diffusion tensor imaging (DTI). There is also evidence from post-mortem studies as well as from magnetic resonance imaging morphometry studies that the anterior commissure (AC) might be implicated in schizophrenia, but no studies, to date, have investigated the AC using DTI or tractography.

Method—DTI scans were analyzed from 25 patients and 23 controls. Mean fractional anisotropy (FA) and trace were measured from the AC tracts. SANS and SAPS were used to evaluate clinical symptoms, and the Iowa Gambling Task, related to decision making, was also examined.

Results—Results revealed a significant decrease in mean FA and a significant increase in mean trace of AC tracts in patients compared with controls. In addition, patients, but not controls, showed a negative correlation between age and AC integrity. Statistically significant positive correlations were also found between AC FA and total positive symptom score. Decision making was negatively correlated with FA in patients on the Iowa Gambling Task, but not in controls.

Corresponding Author: Martha Shenton, Ph.D., Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston Street, Boston, MA, 02215; Shenton@bwh.harvard.edu.

Conflict of interest: All authors declare that they have no competing financial interests.

Contributors: Hongyoon Choi, Marek Kubicki, Thomas Whitford, and Martha E. Shenton designed the study and wrote the protocol. Hongyoon Choi also wrote the first draft of the manuscript. Jorge L. Alvarado and Douglas P. Terry collected some data and undertook the statistical analysis. Margaret Niznikiewicz and Robert W. McCarley managed the recruitment and collected clinical information of participants. Martha E. Shenton, Marek Kubicki, Thomas Whitford, and Jun Soo Kwon supervised the statistical analyses and edited multiple iterations of the manuscript. All authors contributed to and have improved the final manuscript.

Conclusion—This study provides quantitative evidence for a reduction of interhemispheric connectivity in schizophrenia within the AC. Negative correlation between age and AC FA in the patients is consistent with the idea that schizophrenia may be a disorder of white-matter maturation. Positive correlation between FA and positive symptom is discussed in the context of white-matter's established role in modulating neural conduction velocity.

Keywords

Schizophrenia; diffusion tensor imaging; anterior commissure; white matter tractography; fractional anisotropy; trace

1. Introduction

The idea that connections between brain regions are disrupted in schizophrenia goes back at least as far as Kraepelin (1911/1917), who speculated that schizophrenia was caused by a disruption of connectivity between the frontal and temporal lobes. The tools to investigate such connections, however, had to await new imaging techniques such as Diffusion tensor imaging (DTI), which is a relatively new magnetic resonance method used to investigate water diffusion within living tissue (Basser et al., 1994). This method also provides an opportunity to investigate white matter (WM) integrity in the brain. More specifically, fiber tracts restrict the motion of water, especially in directions that are perpendicular to the tract, so that water diffusion is anisotropic in WM while more isotropic in cerebral spinal fluid or gray matter. Accordingly, quantitative indices of water diffusivity and diffusion anisotropy have been introduced based on the properties of biological tissues. Trace (Tr), which characterizes the overall displacement of the water molecules, and fractional anisotropy (FA), which characterizes the degree of directionality of anisotropic water diffusion, are the most commonly used indices to evaluate WM integrity (Basser, 1995).

White matter connections between fronto-temporal regions have been examined in schizophrenia, including the arcuate fasciculus (Burns et al., 2003; Hubl et al., 2004), cingulum bundle (Fujiwara et al., 2007; Kubicki et al., 2003; Mori et al., 2007; Sun et al., 2003), and the corpus callosum (Agartz et al., 2001; Ardekani et al., 2003; Foong et al., 2000; Kanaan et al., 2006; Kubicki et al., 2008; Mori et al., 2007). Findings here have generally supported the idea that there are disruptions in white matter connectivity in schizophrenia although there have also been negative findings (Price et al., 2005; Sun et al., 2003). The anterior commissure (AC) is a white matter fiber tract that connects orbitofrontal cortex with inferior parts of the temporal lobe (Di Virgilio et al., 1999; Peuskens et al., 2004) and which has long been thought to be implicated in schizophrenia (Shenton et al., 2001). This tract, however, has received little attention in schizophrenia, despite the fact that there is evidence to support an association between abnormal connectivity of AC and schizophrenia in post-mortem studies (Highley et al., 1999). Specifically, the number of AC fibers is unchanged, but the fiber density of AC is reduced in schizophrenia (Highley et al., 1999).

Alterations in asymmetry in schizophrenia are also reported in the parahippocampal gyrus and fusiform gyrus (Highley et al., 1998), areas in which AC axons are known to synapse (Demeter et al., 1988; Demeter et al., 1990). Because of an association between brain asymmetry and interhemispheric connectivity (Ringo et al., 1994; Witelson and Goldsmith, 1991), these findings suggest disruptions in the AC in schizophrenia.

Parahippocampal gyrus has been identified as an important brain area in the etiology of delusional symptoms, possibly due to its role in emotion and memory processing (Acioly MA et al., 2010; Casanova MF, 1997). Furthermore, AC interconnects the orbitofrontal

cortices (Di Virgilio et al., 1999; Peuskens et al., 2004) which play an important role in decision making processes (Krawczyk, 2002). There is also neuroimaging evidence of orbitofrontal cortex abnormalities in schizophrenia (Crespo-Facorro et al., 2000; Nakamura et al., 2008; Pantelis et al., 2003). These findings suggest AC could influence the delusional symptoms and decision making impairments that are associated with schizophrenia.

Additionally, the AC contains interhemispheric fibers from the auditory cortex (Bamiou et al., 2007). Planum temporale, in particular, located posterior to the auditory cortex, has been reported as abnormal in schizophrenic patients (e.g., Falkai et al., 1995; Kwon et al., 1999). There is also evidence to suggest an association between planum temporale and AC fibers, where there is an association between hemispheric asymmetry of the anatomical size of the planum temporale and the sectional area of the AC based on a postmortem study (Kopp et al., 1977). It is also well known that one of the most common symptoms of schizophrenia is auditory hallucinations. Findings that suggest alterations in interhemispheric connectivity in schizophrenia, especially in the AC, could, therefore, underlie auditory symptoms in schizophrenia.

To our knowledge, there are no DTI studies of the AC in schizophrenia. Currently, there is only one MRI study evaluating the AC in schizophrenia, where white matter tracts were analyzed using voxel-based morphometry, and a decrease in white matter density was found in the right AC in schizophrenic patients (Hulshoff Pol et al., 2004). A small number of studies have investigated the AC in other disorders, including a finding of AC WM abnormalities using region of interest (ROI) approaches in Chiari II-malformation (Herweh et al., 2009), and in neonatal hypoxic-ischemic encephalopathy (Chan et al., 2009). However, tractography techniques were not employed to measure AC in those studies. In the current study, AC fiber tracts were investigated using novel DTI post-processing techniques to define this WM tract. This study is thus the first to use tractography to investigate and to quantify AC tract integrity. Of further note, fiber tractography has been shown to have higher sensitivity and specificity than ROI approaches or voxel-based analyses (Jones et al., 2006; Kanaan et al., 2006).

The purpose of this study was to identify and to evaluate AC integrity in patients with schizophrenia compared to healthy controls. Since the AC is anatomically related to the orbitofrontal cortex and the temporal lobes (Di Virgilio et al., 1999; Peuskens et al., 2004), we predicted that specific clinical symptoms, including delusions, hallucinations and impairments in executive functioning, would be associated with AC WM integrity anomalies in schizophrenia.

2. Methods

2.1. Subjects

Twenty-six male patients with chronic schizophrenia were recruited from the VA Boston Healthcare System, Brockton, MA campus. Patients were diagnosed on the basis DSM-IV criteria. Twenty-six healthy male controls were recruited through local newspaper advertisements. They were group matched to patients on age, sex, handedness (Oldfield, 1971), parental socioeconomic status (Hollingshead, 1965), and a measure of premorbid WRAT score for IQ (Jastak and Wilkinson, 1993). The study was approved by the IRB at the VA Boston Healthcare System and Brigham and Women's Hospital. All study participants signed an informed consent form.

Inclusion and exclusion criteria for all subjects were : 1) age between 18–55 years; 2) right-handedness; 3) no history of electroconvulsive treatment; 4) no history of neurological illness, including epilepsy; 5) no history of alcohol or drug dependence, nor abuse within the

last year, nor long duration (>1 year) of past abuse (DSM-IV criteria); 6) no present medication for medical disorders that would have deleterious EEG, neurological, or cognitive functioning consequences; 7) verbal IQ above 75; 8) no alcohol use in the 24 hours prior to testing; and 9) English as a first language.

All patients were receiving antipsychotic medication and all medication dosages were converted to chlorpromazine equivalents (Stoll, 2001). Clinical symptoms were measured by the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1981). Additionally, we examined the performance of subjects on the Iowa Gambling Task (Bechara et al., 1994), a decision making task believed to be associated with the orbitofrontal cortex (Bechara et al., 1998). In the Iowa Gambling Task, subjects are asked to select cards from four decks (A, B, C, and D). Each card is associated with either a gain or loss of money. Decks A and B are 'disadvantageous' in that subjects will, in the long run, incur a net loss if they routinely select from them. In contrast, Decks C and D are 'advantageous'. A total of 100 trials were performed without informing subjects the length of the experiment. Net gambling score was measured as the number of advantageous choices minus the number of disadvantageous choices. Total amount won, total amount lost, and total amounted earned (calculated as total amount won minus total amount lost), were also measured to evaluate the decision making process.

2.2. Image acquisition

For the Structural MRI volume measures, images were acquired using a 3T GE scanner at BWH in Boston, MA. The structural MRI acquisition protocol included two MRI pulse sequences. The first resulted in contiguous spoiled gradient-recalled acquisition (fastSPGR) with the following parameters; TR=7.4ms, TE=3ms, TI=600, 10 degree flip angle, 25.6cm2 field of view, matrix=256×256. The voxel dimensions were 1×1×1mm. The second- XETA (eXtended Echo Train Acquisition) produces a series of contiguous T2-weighted images (TR=2500ms, TE=80ms, 25.6 cm2 field of view). Voxel dimensions were 1×1×1 mm. This latter sequence was used as the additional channel of information for brain segmentation. It was also used to measure volume of total intracranial contents, which was then used as an independent factor in a regression procedure to account for the effect of head size.

DTI data were collected on the 3 Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, WI). Scans were acquired using an echoplanar imaging (EPI) DTI Tensor sequence, and a double echo option to reduce eddy-current related distortions. To reduce the impact of EPI spatial distortion, an 8 Channel coil and ASSETT (Array Spatial Sensitivity Encoding techniques, GE) with a SENSE-factor (speed-up) of 2 was used. Eighty-five axial slices parallel to the AC-PC line covering whole brain were acquired, in 51 diffusion directions with b=900. In addition 8 baseline scans with b=0 were also acquired. Scan parameters were as follows: TR17000 ms, TE 78 ms, FOV 24 cm, 144×144 encoding steps, 1.7 mm slice thickness, producing isotropic 1.7×1.7×1.7mm voxels.

2.3. Image processing and analysis

We utilized Slicer 3D software Version 2 (www.slicer.org) to analyze the images and to measure tracts. Tractography from two ROIs was carried out to analyze the AC tracts. We used the fiber assignment by continuous tracking (FACT) method to extract the fiber tract, which made fiber trajectories from seeding points (Mori et al., 1999). This method initiates fiber trajectories from defined ROIs and follows the primary eigenvector, the orientation of the diffusion tensor, from voxel to voxel. After reaching the next voxel, the fiber trajectory moves along the primary eigenvector of the next voxel. Tractography stopping criteria was: FA <0.15 and an angle of curvature >20° per 1 mm (Jones et al., 2006).

To draw the AC, ROIs were manually placed on color-by-orientation maps. Because AC tracts travel from right to left, voxels containing the AC appear red on color-by-orientation maps. The entire AC was therefore drawn using predominantly red voxels in coronal slices. However, since the AC is a very thin tract through the midsagittal slice and is surrounded by other fibers such as the fornix and horizontal portions of the internal capsule, many extraneous fibers were included in this seeding. In order to obtain precise and accurate AC tracts, an additional ROI was drawn in the midsagittal plane that included the medial portion of the AC tracts. Because the AC is one of the commissural bundles, it interconnects both hemispheres, and passes through the midline. Accordingly, we selected for tracts that traveled through the midline ROI (Fig. 1). Only axially-traversing tracts, identified on a color-by-orientation map, and that passed through the two ROIs, were selected for fiber tracking and for further statistical analyses. All ROIs were drawn manually, blind to diagnosis. Average trace, length, and FA were calculated for the extracted tracts.

In some cases, seeding from the two ROIs resulted in short and anatomically inaccurate AC tracts. These cases produced tracts with an average fiber length plus standard deviation that was less than one voxel in length (1.7 mm). Four such scans were found (three normal controls and one schizophrenia patient) and excluded from further analyses, resulting in a final count of 48 cases.

2.4. Statistical Analysis

For statistical analyses we used the Statistical Package for Social Sciences (SPSS version 16.0). To test for group differences in FA within the AC, analysis of variance (ANOVA) was performed with age and level of education as covariates and group as the between-subject factor. Post-hoc independent T-tests were carried out to find differences in trace and FA within the AC between patients with schizophrenia and normal controls. We also performed correlational analyses between mean FA values and age in both groups. Pearson's correlational analyses of FA values with duration of illness, daily dose of drugs, SAPS scores, SANS scores, and Iowa Gambling Task scores were also carried out.

3. Results

There were no group differences in mean age, parental socioeconomic status, handedness, WRAT score, or gender (all males). Level of education and social economic status showed significant differences between two groups ($t=-2.76$, $df=42$, $p=0.01$ for level of education and $t=3.87$, $df=42$, $p<0.01$ for social economic status) (Table 1).

There was a group effect for AC FA ($F=9.80$, $p<0.01$) and for Trace ($F=8.59$, $p<0.01$). Mean trace was significantly increased and mean FA was significantly decreased in AC tracts in the schizophrenia group compared with normal controls ($t=3.04$, $df=28.9$, $p<0.01$ for trace and $t=-3.14$, $df=46$, $p<0.01$ for FA) (Fig. 2) (Table 2).

A significant negative correlation was found between mean FA and age in schizophrenics, but not in controls ($r=-0.484$, $p=0.01$ for schizophrenics, and $r=-0.19$; $p=0.40$ for controls) (Fig. 3). Patients with schizophrenia showed a trend for a positive correlation between Trace and age, but this trend was not significant ($r=0.39$, $p=0.06$ for schizophrenics and $r=0.35$, $p=0.10$ for controls). Schizophrenics showed a trend towards decreased FA with increased duration of illness ($r=-0.39$, $p=0.09$). No significant correlations of mean FA in the AC were found with socioeconomic status, antipsychotic medication dose, or duration of medication ($r=-0.12$, $p=0.58$ for socioeconomic status; $r=-0.30$, $p=0.168$ for medication dose; $r=-0.10$, $p=0.681$ for duration of medication).

Correlation analyses between clinical symptoms, examined using SANS and SAPS in schizophrenics, and mean FA were also performed. Mean FA was significantly positively correlated with positive symptoms (r=0.44, p=0.03 for global SAPS), but not with negative symptoms. (r=0.12, p=0.57 for global SANS). Trace was not significantly correlated with global SAPS (r=−0.24, p=0.26) or SANS (r=0.151, p=0.472) scores (Table 3).

For the Iowa Gambling Task, there were no significant differences between groups in net gambling score (p=0.83), total amount won (p=0.91), total amount lost (p=0.34), or total amount earned (p=0.17). We examined correlations between the Iowa Gambling Task and mean FA in subjects. FA was significantly negatively correlated with net gambling score [(C+D)-(A+B)] (r=−0.46, p=0.04) and total amount earned (r=−0.50, p=0.02) in schizophrenics, but not in normal controls (r=−0.21, p=0.56 for net gambling score; r=−0.43, p=0.22 for total amount earned). There were no significant correlation between Trace and Iowa Gambling Task scores (r=0.24, p=0.20 for net gambling score; r=24, p=0.20 for total amount earned) (Fig. 4).

4. Discussion

Our main finding is that patients with schizophrenia reveal a significant decrease in FA and an increase in trace in the AC compared with healthy controls. To the extent that FA is related to axonal integrity, density, caliber and myelination (Beaulieu, 1994), our findings of subnormal levels of FA in the AC suggest the presence of microstructural abnormalities in this fasciculus in patients with schizophrenia. Our results are consistent with those of Highley et al. (1999), who reported reduced fiber density in the AC in schizophrenia patients *postmortem*. With respect to our finding of higher trace in the schizophrenia patients, compared with controls, several previous DTI studies have suggested that increased trace is associated with immaturity of the brain (Neil et al., 1998) and structural brain disorders, such as cerebral ischemia (Kim et al., 2005) or hydrocephalus(Gideon et al., 1994). The changes in trace and FA in our study thus suggest that there are structural abnormalities in the AC in schizophrenia.

Our correlational findings between age and integrity of the AC in schizophrenia are similar to results of previous investigations with the cingulum, the uncinate fasciculus (Mandl et al., 2008; Rosenberger et al., 2008), and the whole-brain WM (Jones et al., 2006; Mori et al., 2007). Our finding, and that of others, that suggest negative correlations between age and white matter integrity support the hypothesis that the pathophysiology of schizophrenia may reflect progressive neurodegeneration (de Haan and Bakker, 2004; DeLisi, 1997). However, we observed no significant correlations between duration of illness and FA, suggesting that it is likely age rather than duration of illness that is relevant to the observed correlations. Longitudinal studies are, however, needed to clarify further whether or not white matter integrity reduction reflects disease progression. The latter is particularly important given that findings of a correlation between age and FA have been reported in normal controls (Kubicki et al., 2008; Sullivan and Pfefferbaum, 2006). Thus more research needs to be done that can tease apart what is age related effects that are seen in both normal controls and patients with schizophrenia, and to address the question of whether or not the age effects observed are different in schizophrenia and suggest disease progression. Furthermore, additional studies will be needed to clarify whether medication or disease progression affect the altered integrity of AC. Longitudinal and first-episode studies of AC integrity will help to clarify these issues.

Significant positive correlations were observed between patients' FA in the AC and severity of positive symptoms, as measured by total scores on SAPS. This is not the first time that positive correlations have been observed between FA and positive symptom severity in

schizophrenia patients. On the contrary, significant positive correlations have been reported in the corpus callosum (Hubl et al., 2004; Rotarska-Jagiela et al., 2008), cingulum bundle (Hubl et al., 2004), superior longitudinal fasciculus (Seok et al., 2007; Shergill et al., 2007), arcuate fasciculus (Hubl et al., 2004), and inferior fronto-occipital fasciculus (Szeszko et al., 2008). However, the present study is the first (to our knowledge) to report a significant positive correlation between positive symptom severity and FA in the AC in schizophrenia patients. With regards to the cause of this seemingly paradoxical yet consistently reported correlation, Whitford et al. (2010) have suggested that the answer may lie in the extent of the conduction delays that would be expected to arise from mild as opposed to severe white-matter damage. Specifically, Whitford et al. (2010) suggest that *mild conduction delays* (such as might be expected from mild FA reductions) could result in the aberrant neural synchronization (Andreasen et al., 1999) that has been proposed to underlie the symptoms of schizophrenia (Andreasen et al., 1999; Bartzokis, 2002). In contrast, *severe conduction delays* (such as might be expected from more severe FA reductions) could result in neural signals that are sufficiently disjointed so as to be unincorporable into a coherent phenomenological framework such as necessary for a coherent, systematized delusion, for example. Our results showed severe positive symptoms were related to minimally dysfunctional FA. However, we found negative symptoms were not related to FA, though AC FA reduction predicted higher negative symptom score as we predicted. Nonetheless, we need more functional studies about the relationship between specific symptoms of schizophrenia and white-matter tracts. Testing this speculation may provide a worthwhile avenue for future research.

Since it has been reported that the orbitofrontal cortex plays an important role in decision making processes (Krawczyk, 2002), we investigated the relationship between FA in the AC, which interconnects the orbitofrontal cortices (Di Virgilio et al., 1999; Peuskens et al., 2004), and its abnormalities in schizophrenia, and the Iowa Gambling Task. Our results indicate that such a relationship indeed exists, suggesting the notion that changes in interconnectivity of the AC affect decision making processes in schizophrenia. It is possible that altered interconnectivity of the AC may be related to the same pathology producing orbitofrontal cortex volume reduction, which has been shown to be associated with thought disorder in schizophrenia (Nakamura et al., 2008). It is unclear why FA is higher in patients with severe decision making impairment, however a similar result was found in an impulsivity study of schizophrenia (Hoptman et al., 2004), where FA was positively correlated with impulsivity in the left postcentral gyrus, right superior/middle temporal gyrus, and bilateral fusiform gyrus, which might compromise a fronto-temporal-limbic circuit. Additionally, patients with schizophrenia showed a pattern of compromised decision making that is somewhat different from orbitofrontal cortex lesion patients (Shurman et al., 2005). We therefore suspect that the AC plays a role in the patterns of decision making impairment in schizophrenia. Of further note, equivocal results have been found in terms of differences in Iowa Gambling Task performance between SZ and NC, with some studies showing significant differences (Kester et al., 2006; Ritter et al., 2004), but others not (Cavallaro et al. 2003; Evans, et al. 2005; Rodriguez-Sanchez et al. 2005). Regarding our study, we observed that patients with a large FA reduction had minimal decision making impairments, which could potentially account for the minimal Iowa Gambling Task differences between patients and controls.

While AC FA was associated with decision making and positive symptoms in our study, it is unclear whether schizophrenia symptoms and decision making are related. Some studies suggest decision making impairment of schizophrenia and negative symptoms are associated (Shurman et al., 2005), while some studies do not (Evans CE et al., 2005). Another study suggests that some negative symptoms are associated with frontal medial cortex dysfunction, as measured with a Theory of Mind test, but that there was not a significant

correlation between the Iowa Gambling Task and negative symptom scores (Martino DJ et al., 2007). To our knowledge, there is no evidence to suggest a relationship between decision making and positive symptom scores. However, regardless of whether decision making and clinical symptoms are related, AC integrity seems to be related to multiple symptoms in schizophrenia.

There is a considerable overlap between the participant sample in the current paper and the sample presented in the Whitford et al., paper. Specifically, 16 (61.5%) of SZ patients and 11 (42.3%) of the HC participants were also investigated in the Whitford et al., paper. There is some evidence from the literature that the CC and AC are closely related in terms of their structural integrity. In a previous study about callosal agenesis (Fischer et al., 1992), there was hypertrophy of AC in patients with callosal agenesis, suggesting that AC may compensate for damage to the CC. Regarding the relationship between AC and CC in the present study, we correlated the AC Fractional Anisotropy results with the CC1 (genu) Fractional Anisotropy results from the Whitford et al., paper and observed a non-significant trend for a positive correlation ($r=0.32$, $p=0.10$), across both groups.

Our study is the first to measure AC integrity using tractography in schizophrenia. Tractography has shown higher sensitivity and specificity compared to ROI or voxel-based morphometry analysis (Kanaan et al., 2006). Though the AC plays an important role in interconnection of the two hemispheres, there are few studies that investigate its changes in schizophrenia. By using tractography to analyze AC fibers, we were able to define, extract and directly measure AC integrity and its relationship with clinical symptoms and age. We note, however, that a diffusion tensor model is not always adequate, especially in voxels containing complex crossing tracts from differently oriented fibers(Alexander et al., 2002; Tuch etl al., 2002). Nonetheless DTI is the most popular approach to tractography and fiber crossings are not such an issue with AC. Further studies should include a multi-tensor approach that may provide more information about AC tract and integrity. Since some studies have found that changes in FA might be related to medication dosage (Minami et al., 2003; Okugawa et al., 2004), and our schizophrenia subjects are all chronically medicated, an additional studies are needed to clarify whether the relationship between age and FA is due to a medication effect. Sex differences in fiber numbers or cross sectional areas in the AC have also been reported (Allen and Gorski, 1991; Highley et al., 1999). In the current study, however, we only investigated changes in male subjects. We therefore need a larger, mixed-sex cohort to obtain a full interpretation of AC pathology in schizophrenia.

5. Conclusions

Reduced connectivity within the anterior commissure in schizophrenia was found in our study using high resolution DTI and a tractography approach. Our study found that age affected the reduced interhemispheric connectivity in schizophrenia, and interconnectivity of the AC was positively correlated with positive symptoms as well as decision making impairment. These results can help us understand the functional anatomy of the brain by understanding further the relationship between symptoms and interconnectivity of the AC in the pathophysiology of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported, in part, by grants from the National Institute of Health (K05 MH070047 and R01 MH 50740 to MES, R01 MH 40799 to RWM, P50MH 080272-CIDAR award- to RWM, MES), the Department of

Veterans Affairs Merit Awards (MES, RWM), the VA Schizophrenia Center Grant (RWM/MES). This work was also supported, in part, by the National Alliance for Medical Image Computing (NA-MIC), the latter a grant supported through the National Institutes of Health Roadmap for Medical Research, Grant U54 EB005149 (MK), and by an Overseas-Based Biomedical Training Fellowship from the National Health and Medical Council of Australia (NHMRC 520627) through the University of Melbourne (TW).

Role of funding source: All of the study sponsors had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

Acioly MA, Carvalho CH, Tatagiba M, Gharabaghi A. The parahippocampal gyrus as a multimodal association area in psychosis. J Clin Neurosci. 2010; 17:1603–1605. [PubMed: 20817470]

Agartz I, Andersson JL, Skare S. Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. Neuroreport. 2001; 12:2251–2254. [PubMed: 11447344]

Alexander DC, Barker GJ, Arridge SR. Detection and modeling of non-Gaussian apparent diffusion coefficient profiles in human brain data. Magn Reson Med. 2002; 48:331–340. [PubMed: 12210942]

Allen LS, Gorski RA. Sexual dimorphism of the anterior commissure and massa intermedia of the human brain. J Comp Neurol. 1991; 312:97–104. [PubMed: 1744245]

Andreasen, NC. Scale for the Assessment of Negative Symptoms. University of Iowa College of Medicine; Iowa City, IA: 1981.

Andreasen, NC. Scale for the Assessment of Positive Symptoms. University of Iowa College of Medicine; Iowa City, IA: 1984.

Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol Psychiatry. 1999; 46:908–920. [PubMed: 10509174]

Ardekani BA, Nierenberg J, Hoptman MJ, Javitt DC, Lim KO. MRI study of white matter diffusion anisotropy in schizophrenia. Neuroreport. 2003; 14:2025–2029. [PubMed: 14600491]

Bartzokis G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. Neuropsychopharmacology. 2002; 27:672–683. [PubMed: 12377404]

Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed. 1995; 8:333–344. [PubMed: 8739270]

Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994; 66:259–267. [PubMed: 8130344]

Beaulieu C, Allen P. Determinants of anisotropic water diffusion in nerves. MRM. 1994; 31:394–400.

Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994; 50:7–15. [PubMed: 8039375]

Bechara A, Damasio H, Tranel D, Anderson SW. Dissociation Of working memory from decision making within the human prefrontal cortex. J Neurosci. 1998; 18:428–437. [PubMed: 9412519]

Burns J, Job D, Bastin ME, Whalley H, Macgillivray T, Johnstone EC, Lawrie SM. Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. Br J Psychiatry. 2003; 182:439–443. [PubMed: 12724248]

Casanova MF. The temporolimbic system theory of paranoid schizophrenia. Schizophr Bull. 1997; 23:513–5. [PubMed: 9327514]

Cavallaro R, Cavedini P, Mistretta P, Bassi T, Angelone SM, Ubbiali A, Bellodi L. Basal-corticofrontal circuits in schizophrenia and obsessive-compulsive disorder: a controlled, double dissociation study. Biol Psychiatry. 2003; 54:437–443. [PubMed: 12915288]

Chan KC, Khong PL, Lau HF, Cheung PT, Wu EX. Late measures of microstructural alterations in severe neonatal hypoxic-ischemic encephalopathy by MR diffusion tensor imaging. Int J Dev Neurosci. 2009; 27:607–615. [PubMed: 19505567]

Crespo-Facorro B, Kim J, Andreasen NC, O'Leary DS, Magnotta V. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. Biol Psychiatry. 2000; 48:110–119. [PubMed: 10903407]

de Haan L, Bakker JM. Overview of neuropathological theories of schizophrenia: from degeneration to progressive developmental disorder. Psychopathology. 2004; 37:1–7. [PubMed: 14988644]

DeLisi LE. Is schizophrenia a lifetime disorder of brain plasticity, growth and aging? Schizophr Res. 1997; 23:119–129. [PubMed: 9061808]

Demeter S, Ringo JL, Doty RW. Morphometric analysis of the human corpus callosum and anterior commissure. Hum Neurobiol. 1988; 6:219–226. [PubMed: 3350703]

Demeter S, Rosene DL, Van Hoesen GW. Fields of origin and pathways of the interhemispheric commissures in the temporal lobe of macaques. J Comp Neurol. 1990; 302:29–53. [PubMed: 2086614]

Di Virgilio G, Clarke S, Pizzolato G, Schaffner T. Cortical regions contributing to the anterior commissure in man. Exp Brain Res. 1999; 124:1–7. [PubMed: 9928783]

Evans CE, Bowman CH, Turnbull OH. Subjective awareness on the Iowa Gambling Task: the key role of emotional experience in schizophrenia. J Clin Exp Neuropsychol. 2005; 27:656–664. [PubMed: 16019642]

Falkai P, Bogerts B, Schneider T, Greve B, Pfeiffer U, Pilz K, Gonsiorzcyk C, Majtenyi C, Ovary I. Disturbed planum temporale asymmetry in schizophrenia. A quantitative post-mortem study. Schizophr Res. 1995; 14:161–176. [PubMed: 7710997]

Fischer M, Ryan SB, Dobyns WB. Mechanisms of interhemispheric transfer and patterns of cognitive function in acallosal patients of normal intelligence. Arch Neurol. 1992; 49:271–277. [PubMed: 1536630]

Foong J, Maier M, Clark CA, Barker GJ, Miller DH, Ron MA. Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. J Neurol Neurosurg Psychiatry. 2000; 68:242–244. [PubMed: 10644799]

Fujiwara H, Namiki C, Hirao K, Miyata J, Shimizu M, Fukuyama H, Sawamoto N, Hayashi T, Murai T. Anterior and posterior cingulum abnormalities and their association with psychopathology in schizophrenia: a diffusion tensor imaging study. Schizophr Res. 2007; 95:215–222. [PubMed: 17664062]

Gideon P, Thomsen C, Gjerris F, Sorensen PS, Henriksen O. Increased self-diffusion of brain water in hydrocephalus measured by MR imaging. Acta Radiol. 1994; 35:514–519. [PubMed: 7946670]

Herweh C, Akbar M, Wengenroth M, Blatow M, Mair-Walther J, Rehbein N, Nennig E, Schenk JP, Heiland S, Stippich C. DTI of commissural fibers in patients with Chiari II-malformation. Neuroimage. 2009; 44:306–311. [PubMed: 18849000]

Highley JR, Esiri MM, McDonald B, Cortina-Borja M, Cooper SJ, Herron BM, Crow TJ. Anomalies of cerebral asymmetry in schizophrenia interact with gender and age of onset: a postmortem study. Schizophr Res. 1998; 34:13–25. [PubMed: 9824873]

Highley JR, Esiri MM, McDonald B, Roberts HC, Walker MA, Crow TJ. The size and fiber composition of the anterior commissure with respect to gender and schizophrenia. Biol Psychiatry. 1999; 45:1120–1127. [PubMed: 10331103]

Hollingshead, AB. Two Factor Index of Social Position. Yale University Press; New Haven, CT: 1965.

Hoptman MJ, Ardekani BA, Butler PD, Nierenberg J, Javitt DC, Lim KO. DTI and impulsivity in schizophrenia: a first voxelwise correlational analysis. Neuroreport. 2004; 15:2467–2470. [PubMed: 15538176]

Hubl D, Koenig T, Strik W, Federspiel A, Kreis R, Boesch C, Maier SE, Schroth G, Lovblad K, Dierks T. Pathways that make voices: white matter changes in auditory hallucinations. Arch Gen Psychiatry. 2004; 61:658–668. [PubMed: 15237078]

Hulshoff Pol HE, Schnack HG, Mandl RC, Cahn W, Collins DL, Evans AC, Kahn RS. Focal white matter density changes in schizophrenia: reduced inter-hemispheric connectivity. Neuroimage. 2004; 21:27–35. [PubMed: 14741639]

Jastak, S.; Wilkinson, G. The wide range achievement test—(WRAT-III). 3rd. Wilmington: Jastek; 1993.

Jones DK, Catani M, Pierpaoli C, Reeves SJ, Shergill SS, O'Sullivan M, Golesworthy P, McGuire P, Horsfield MA, Simmons A, Williams SC, Howard RJ. Age effects on diffusion tensor magnetic resonance imaging tractography measures of frontal cortex connections in schizophrenia. Hum Brain Mapp. 2006; 27:230–238. [PubMed: 16082656]

Kanaan RA, Shergill SS, Barker GJ, Catani M, Ng VW, Howard R, McGuire PK, Jones DK. Tract-specific anisotropy measurements in diffusion tensor imaging. Psychiatry Res. 2006; 146:73–82. [PubMed: 16376059]

Kester HM, Sevy S, Yechiam E, Burdick KE, Cervellione KL, Kumra S. Decision-making impairments in adolescents with early-onset schizophrenia. Schizophr Res. 2006; 85:113–123. [PubMed: 16733084]

Kim HJ, Choi CG, Lee DH, Lee JH, Kim SJ, Suh DC. High-b-value diffusion-weighted MR imaging of hyperacute ischemic stroke at 1.5T. AJNR Am J Neuroradiol. 2005; 26:208–215. [PubMed: 15709115]

Kopp N, Michel F, Carrier H, Biron A, Duvillard P. Hemispheric asymmetries of the human brain. J Neurol Sci. 1977; 34:349–363. [PubMed: 591994]

Krawczyk DC. Contributions of the prefrontal cortex to the neural basis of human decision making. Neurosci Biobehav Rev. 2002; 26:631–664. [PubMed: 12479840]

Kubicki M, Styner M, Bouix S, Gerig G, Markant D, Smith K, Kikinis R, McCarley RW, Shenton ME. Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. Schizophr Res. 2008; 106:125–131. [PubMed: 18829262]

Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. Biol Psychiatry. 2003; 54:1171–1180. [PubMed: 14643084]

Kwon JS, McCarley RW, Hirayasu Y, Anderson JE, Fischer IA, Kikinis R, Jolesz FA, Shenton ME. Left planum temporale volume reduction in schizophrenia. Arch Gen Psychiatry. 1999; 56:142–148. [PubMed: 10025438]

Mandl RC, Schnack HG, Luigjes J, van den Heuvel MP, Cahn W, Kahn RS, Hulshoff Pol HE. Tract-based Analysis of Magnetization Transfer Ratio and Diffusion Tensor Imaging of the Frontal and Frontotemporal Connections in Schizophrenia. Schizophr Bull. 2008

Martino DJ, Bucay D, Butman JT, Allegri RF. Neuropsychological frontal impairments and negative symptoms in schizophrenia. Psychiatry Res. 2007; 152:121–128. [PubMed: 17507100]

Minami T, Nobuhara K, Okugawa G, Takase K, Yoshida T, Sawada S, Ha-Kawa S, Ikeda K, Kinoshita T. Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. Neuropsychobiology. 2003; 47:141–145. [PubMed: 12759557]

Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol. 1999; 45:265–269. [PubMed: 9989633]

Mori T, Ohnishi T, Hashimoto R, Nemoto K, Moriguchi Y, Noguchi H, Nakabayashi T, Hori H, Harada S, Saitoh O, Matsuda H, Kunugi H. Progressive changes of white matter integrity in schizophrenia revealed by diffusion tensor imaging. Psychiatry Res. 2007; 154:133–145. [PubMed: 17276660]

Nakamura M, Nestor PG, Levitt JJ, Cohen AS, Kawashima T, Shenton ME, McCarley RW. Orbitofrontal volume deficit in schizophrenia and thought disorder. Brain. 2008; 131:180–195. [PubMed: 18056163]

Neil JJ, Shiran SI, McKinstry RC, Schefft GL, Snyder AZ, Almli CR, Akbudak E, Aronovitz JA, Miller JP, Lee BC, Conturo TE. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. Radiology. 1998; 209:57–66. [PubMed: 9769812]

Okugawa G, Nobuhara K, Minami T, Tamagaki C, Takase K, Sugimoto T, Sawada S, Kinoshita T. Subtle disruption of the middle cerebellar peduncles in patients with schizophrenia. Neuropsychobiology. 2004; 50:119–123. [PubMed: 15292664]

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971; 9:97–113. [PubMed: 5146491]

Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet. 2003; 361:281–288. [PubMed: 12559861]

Peuskens D, van Loon J, Van Calenbergh F, van den Bergh R, Goffin J, Plets C. Anatomy of the anterior temporal lobe and the frontotemporal region demonstrated by fiber dissection. Neurosurgery. 2004; 55:1174–1184. [PubMed: 15509324]

Price G, Bagary MS, Cercignani M, Altmann DR, Ron MA. The corpus callosum in first episode schizophrenia: a diffusion tensor imaging study. J Neurol Neurosurg Psychiatry. 2005; 76:585–587. [PubMed: 15774453]

Ringo JL, Sobotka S, Diltz MD, Bunce CM. Eye movements modulate activity in hippocampal, parahippocampal, and inferotemporal neurons. J Neurophysiol. 1994; 71:1285–1288. [PubMed: 8201422]

Ritter LM, Meador-Woodruff JH, Dalack GW. Neurocognitive measures of prefrontal cortical dysfunction in schizophrenia. Schizophr Res. 2004; 68:65–73. [PubMed: 15037340]

Rodríguez-Sánchez JM, Crespo-Facorro B, Perez-Iglesias R, González-Blanch C, Alvarez-Jimenez M, Llorca J, Vázquez-Barquero JL. Prefrontal cognitive functions in stabilized first-episode patients with schizophrenia spectrum disorders: a dissociation between dorsolateral and orbitofrontal functioning. Schizophr Res. 2005; 77:279–288. [PubMed: 15950437]

Rosenberger G, Kubicki M, Nestor PG, Connor E, Bushell GB, Markant D, Niznikiewicz M, Westin CF, Kikinis R, A JS, McCarley RW, Shenton ME. Age-related deficits in fronto-temporal connections in schizophrenia: a diffusion tensor imaging study. Schizophr Res. 2008; 102:181–188. [PubMed: 18504117]

Rotarska-Jagiela A, Schonmeyer R, Oertel V, Haenschel C, Vogeley K, Linden DE. The corpus callosum in schizophrenia-volume and connectivity changes affect specific regions. Neuroimage. 2008; 39:1522–1532. [PubMed: 18096406]

Seok JH, Park HJ, Chun JW, Lee SK, Cho HS, Kwon JS, Kim JJ. White matter abnormalities associated with auditory hallucinations in schizophrenia: a combined study of voxel-based analyses of diffusion tensor imaging and structural magnetic resonance imaging. Psychiatry Res. 2007; 156:93–104. [PubMed: 17884391]

Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res. 2001; 49:1–52. [PubMed: 11343862]

Shergill SS, Kanaan RA, Chitnis XA, O'Daly O, Jones DK, Frangou S, Williams SC, Howard RJ, Barker GJ, Murray RM, McGuire P. A diffusion tensor imaging study of fasciculi in schizophrenia. Am J Psychiatry. 2007; 164:467–473. [PubMed: 17329472]

Shurman B, Horan WP, Nuechterlein KH. Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. Schizophr Res. 2005; 72:215–224. [PubMed: 15560966]

Stoll. The Psychopharmacology References Card Antipsychotic Treatment Guide. McLean Hospital; Belmont, MA: 2001.

Sullivan EV, Pfefferbaum A. Diffusion tensor imaging and aging. Neurosci Biobehav Rev. 2006; 30:749–761. [PubMed: 16887187]

Sun Z, Wang F, Cui L, Breeze J, Du X, Wang X, Cong Z, Zhang H, Li B, Hong N, Zhang D. Abnormal anterior cingulum in patients with schizophrenia: a diffusion tensor imaging study. Neuroreport. 2003; 14:1833–1836. [PubMed: 14534430]

Szeszko PR, Robinson DG, Ashtari M, Vogel J, Betensky J, Sevy S, Ardekani BA, Lencz T, Malhotra AK, McCormack J, Miller R, Lim KO, Gunduz-Bruce H, Kane JM, Bilder RM. Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. Neuropsychopharmacology. 2008; 33:976–984. [PubMed: 17581532]

Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magn Reson Med. 2002; 48:577–582. [PubMed: 12353272]

Whitford TJ, Kubicki M, Schneiderman JS, O'Donnell L, King R, Alvarado JL, Khan U, Markant D, Nestor PG, Niznikiewica M, McCarley RW, Westin CF, Shenton ME. Corpus callosum abnormalities and their association with psychotic symptoms in patients with schizophrenia. Biological Psychiatry. 2010; 68:70–77. [PubMed: 20494336]

Witelson SF, Goldsmith CH. The relationship of hand preference to anatomy of the corpus callosum in men. Brain Res. 1991; 545:175–182. [PubMed: 1860044]

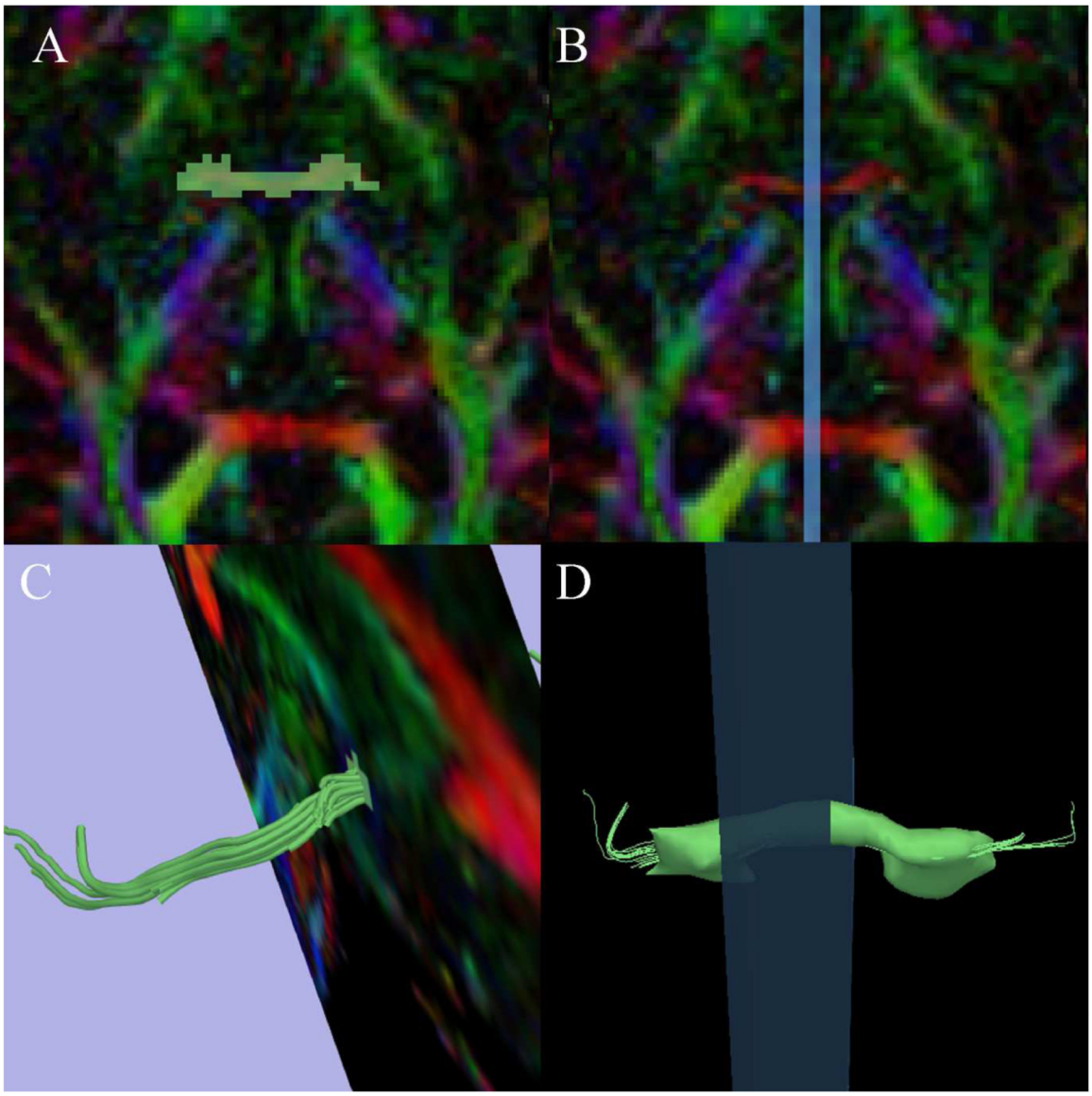

Fig. 1.

ROIs to draw the AC and Tractography. (A) In the color-by-orientation images, the ROI (indicated in green) was drawn on the red voxels (i.e., representing right-left diffusion). (B) Because anterior commissure fibers pass through the midline, a second ROI (indicated in blue) was drawn in the midsagittal plane (C). (D) Anterior commissure fibers were extracted from the two ROIs.

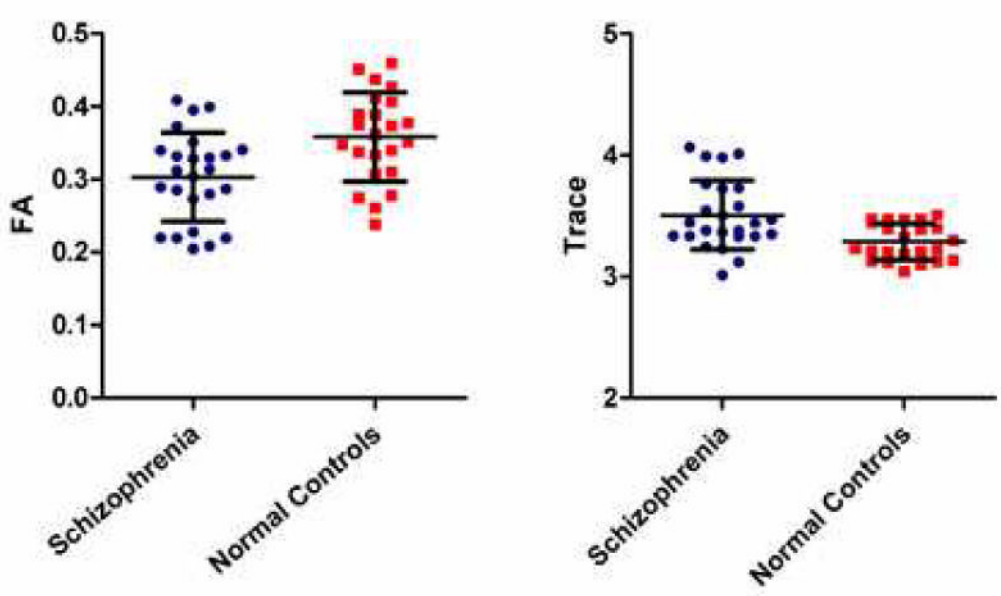

Fig. 2.
Results of FA and Trace comparison.

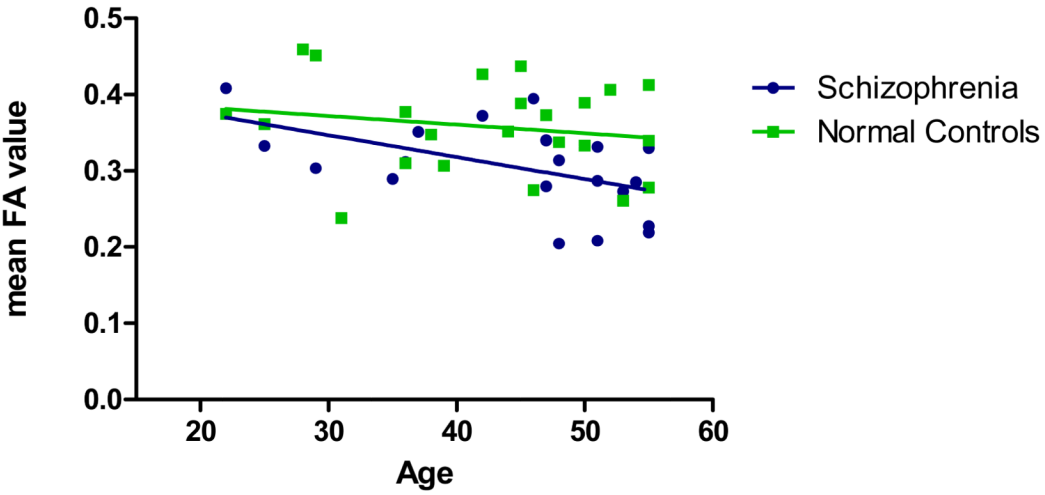

Fig. 3.

A scatter plot between mean FA and age. Blue dots represent patients with schizophrenia and green dots represent normal controls. Solid line indicates a regression line for schizophrenia ($r=0.484$; $p<0.01$) and the dashed line indicates a regression line for normal controls ($r=0.19$; $p=0.40$).

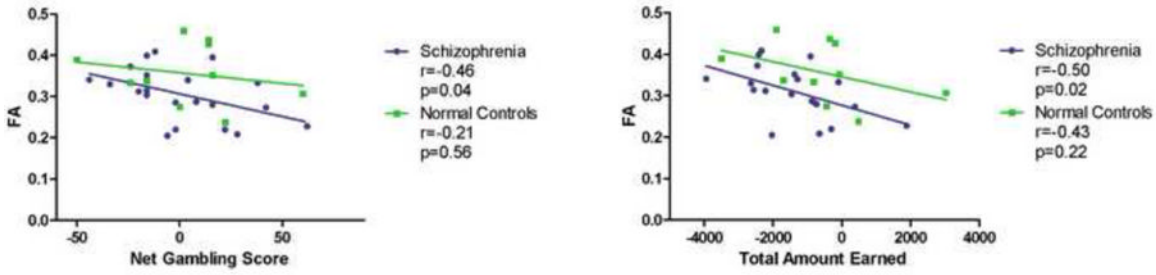

Fig. 4.

Correlation analyses between Iowa Gambling Tasks and FA of AC. In schizophrenia group (blue circles), FA was significantly correlated with net gambling score [(C+D)-(A+B)] ($r=-0.46$; $p=0.04$), total amount won ($r=0.51$; $p=0.02$), total amount lost ($r=0.52$; $p=0.02$), and total amount earned ($r=-0.50$; $p=0.02$). In normal controls (green squares), FA was not significantly correlated with all parameters.

Table 1

Demographic data

Variable	Mean (SD)	
	Patients with Schizophrenia (N=25)	Controls (N=23)
Age (yr)	44.69 (9.69)	42.22 (10.06)
Sex (% male)	100	100
Level of Education (yr)*	13.18 (1.84)	14.79 (2.01)
Socioeconomic Status*	3.44 (1.08)	2.26 (0.87)
Parental Socioeconomic Status	2.61 (1.12)	2.28 (1.27)
Handedness[a]	0.72 (0.24)	0.74 (0.20)
WRAT	98.6 (14.23)	103.5 (11.70)
Age of Onset	22.76 (5.02)	
Medication dose[b]	357.6 (264.4)	
SANS: Sum of Score	11.42 (7.32)	
SAPS: Sum of Score[c]	9.17 (4.07)	

*P <0.01.

[a]Ratio of (right-left)/(right+left) on handedness inventory.

[b]Chlorpromazine equivalent; In 2 patients medication dose was unavailable.

[c]In 1 patient clinical symptom scores were unavailable.

Table 2
Mean fractional anisotropy and trace in the anterior commissure

Variable	Mean (SD)		P-value
	Patients with Schizophrenia (N=25)	Controls (N=23)	
FA	0.303 (0.061)	0.358 (0.061)	<0.01
Trace[a]	3.59 (0.48)	3.29 (0.15)	<0.01

[a] $\times 10^3$ mm^2/s

Table 3

Correlation between FA, Trace in anterior commissure and clinical symptoms in schizophrenia.

Clinical measure	Number of subjects	Pearson's correlation coefficients	P-value
FA			
Sum of Global SAPS Score	24	0.444	0.030 *
Sum of Global SANS Score	25	0.121	0.565
Trace			
Sum of Global SAPS Score	24	-0.238	0.260
Sum of Global SANS Score	25	0.151	0.472

* P<0.05