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Diffusion Tractography of the Fornix in Schizophrenia

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Abstract

Background—White matter fiber tracts, especially those interconnecting the frontal and temporal lobes, are likely implicated in pathophysiology of schizophrenia. Very few studies, however, have focused on the fornix, a compact bundle of white matter fibers, projecting from the hippocampus to the septum, anterior nucleus of the thalamus and the mamillary bodies. Diffusion Tensor Imaging (DTI), and a new post-processing method, fiber tractography, provides a unique opportunity to visualize and to quantify entire trajectories of fiber bundles, such as the fornix, *in vivo*. We applied these techniques to quantify fornix diffusion anisotropy in schizophrenia.

Methods—DTI images were used to evaluate the left and the right fornix in 36 male patients diagnosed with chronic schizophrenia and 35 male healthy individuals, group matched on age, parental socioeconomic status, and handedness. Regions of interest were drawn manually, blind to group membership, to guide tractography, and Fractional Anisotropy (FA), a measure of fiber integrity, was calculated and averaged over the entire tract for each subject. The Doors and People test (DPT) was used to evaluate visual and verbal memory, combined recall and combined recognition.

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Conflict of Interest

None of the authors have any conflicts of interest that require disclosure.

Contributors

Jennifer Fitzsimmons, M.D., and Marek Kubicki, M.D., Ph.D. designed the study and wrote the protocol. Jennifer Fitzsimmons, M.D. also wrote the first draft of the manuscript. Marek Kubicki, M.D., Ph.D. and Carl-Fredrik Westin, Ph.D. supervised the MRI data acquisition and processing, and provided guidance on technical aspects of diffusion tensor imaging. Paul Nestor, Ph.D., Margaret Niznikiewicz, Ph.D., and Robert W. McCarley, M.D. managed the recruitment and collected clinical information of participants. Martha E. Shenton, Ph.D., Marek Kubicki, M.D., Ph.D., and Robert W. McCarley, M.D. supervised the statistical analyses and edited multiple iterations of the manuscript, they also provided guidance on the study design and implementation of the study. All authors contributed to and have approved the final manuscript.

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Results—Analysis of variance was performed and findings demonstrated a difference between patients with schizophrenia and controls for fornix FA ($P=0.006$). Protected post-hoc independent sample t-tests demonstrated a bilateral FA decrease in schizophrenia, compared with control subjects (left side: $P=0.048$; right side $P=0.006$). Higher fornix FA was statistically significantly correlated with DPT and measures of combined visual memory ($r=.554$, $p=.026$), combined verbal memory ($r=.647$, $p=.007$), combined recall ($r=.516$, $p=.041$), and combined recognition ($r=.710$, $p=.002$) for the control group. No such statistically significant correlations were found in the patient group.

Conclusions—Our findings show the utility of applying DTI and tractography to study white matter fiber tracts *in vivo* in schizophrenia. Specifically, we observed a bilateral disruption in fornix integrity in schizophrenia, thus broadening our understanding of the pathophysiology of this disease.

INTRODUCTION

Prior to the advent of Diffusion Tensor Imaging (DTI), most magnetic resonance imaging studies of schizophrenia focused on gray matter (see review in Shenton et al., 2001). With the advent of DTI, however, we are now able to focus more closely on white matter integrity in schizophrenia. This technique is relatively recent and it depends upon the motion of water molecules to provide structural information *in vivo* (Basser, 1994; Pierpaoli, 1996). More specifically, DTI is dependent upon the structural environment of the brain, which modifies water according to the type of tissue involved. For example, myelin sheaths and nerve fibers restrict the motion of water in directions that are perpendicular to the fiber tracts. Other tissue properties such as the density of axons and dendrites, axon diameter, thickness of myelin tissue, as well as the organization and orientation of fibers, all affect the diffusion of water in the brain and thus provide important information about tissue integrity. Moreover, DTI is particularly useful for evaluating brain tissue where water diffusion is anisotropic, or unevenly restricted in direction (e.g., white matter), as opposed to isotropic or non-restricted, or evenly restricted diffusion (e.g., cerebral spinal fluid, gray matter).

DTI studies of white matter in schizophrenia have focused on large white matter regions (e.g., Buchsbaum et al., 1998; Lim et al., 1999; Kumra et al., 2004), as well as on smaller brain regions of interest (e.g., Burns et al., 2003; Kubicki et al., 2003; Wang et al., 2004) (See also reviews in Kubicki et al., 2005; Kanaan et al., 2005). Most of these studies have used rotationally invariant indices of diffusion anisotropy, most commonly Fractional Anisotropy (FA), a measure of the fraction of the magnitude of the tensor that constitutes the anisotropic diffusion (Basser, 1995). Most have also focused on region of interest (ROI) or voxel based morphology (VBM) analyses, and it is only more recently that tractography measures have been used to evaluate white matter fiber tracts in the brain (e.g., Jones et al., 2006; Kanaan et al., 2006).

Of further note, white matter fiber tracts, especially those interconnecting the frontal and temporal lobes, have long been thought to be involved in schizophrenia (e.g., Wernicke 1906, and more recently Weinberger et al., 1992; McGuire et al., 1996). Recently, DTI studies in schizophrenia have focused on individual association fiber bundles and have reported abnormalities in the cingulum bundle (Kubicki et al., 2003; Sun et al., 2003; Wang et al., 2004; Mori et al., 2007; Fujiwara et al., 2007), uncinate fasciculus (Kubicki et al 2002; Burns et al., 2003), and arcuate fasciculus (Burns et al., 2003; Hubl et al., 2004). The corpus callosum has also been evaluated where abnormalities have also been reported in schizophrenia (Fong et al., 2000; Agartz et al., 2001; Ardekani et al., 2003; Kannan et al., 2006; Mori et al., 2007).

The current study focuses on the fornix, a compact bundle of white matter fibers projecting from the hippocampus to the septum, anterior nucleus of the thalamus and the mamillary bodies. This structure is involved in important brain functions such as spatial memory (e.g., Gaffan 1994; Parker and Gaffan 1997), memory retrieval (e.g., Calabrese et al., 1995), and

verbal memory (e.g., Calabrese et al., 1995; Mc Mackin et al., 1995). These are also all functions disturbed in schizophrenia, including spatial memory (e.g., Park and Holzman, 1992; Carter et al., 1996 and Park et al., 1999) memory retrieval (e.g., Anderson and Spellman, 1995) and verbal memory (e.g., Park and Holzman, 1992; Carter et al., 1998; Cohen et al., 1997; Callicott et al., 2000; Perlstein et al., 2001). Thus characterizing disruptions in fornix integrity might further our understanding of this disorder. It is nonetheless important to emphasize that the fornix is an integral part of both verbal and spatial memory networks, which also involves various other interconnected brain structures that we did not investigate here, including prefrontal cortex, temporal and limbic structures, as well as the parieto-occipital association cortex. Of further note, the hippocampus is one of the most frequently implicated brain structures that has been consistently reported to be abnormal in schizophrenia (e.g., Bogerts et al., 1985; Jeste and Lohr, 1989; Nelson et al., 1998; McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001; Heckers, 2001; Weiss et al., 2004), with volume reductions more prominent on the left side (see review in Shenton et al., 2001).

One of the main reasons for studying the fornix is because it is the main hippocampal output. Few studies have investigated the fornix in schizophrenia. Of those that have, Zahajszky and coworkers (2001), from our laboratory, found no MRI volumetric differences between healthy controls and patients with chronic schizophrenia. In contrast, Davies and coworkers (2001) showed an increase of cross-sectional area of the fornix in early onset schizophrenia. In the only post-mortem study evaluating the fornix, Chance and coworkers (1999) found increased fiber density in the left fornix in male subjects with schizophrenia.

To our knowledge there is only one DTI study of the fornix in schizophrenia (Kuroki et al., 2006). In this study, from our laboratory, the authors investigated a small, cross-sectional portion of the fiber tract, and found a decrease in fiber integrity in chronic schizophrenia subjects compared with controls. Recent advances in DTI post-processing-DT tractography, however, as proposed here, enable us to follow, and to quantify the entire tract, thus making it more reliable and more powerful, compared with region of interest or voxel-based analyses (Kanaan et al., 2005; Jones et al., 2005).

The main objective of the current study is to identify, separate and evaluate left and right fornix integrity in patients with chronic schizophrenia compared with healthy controls. Because previous work has demonstrated the relationship between verbal and spatial memory and fornix integrity (Nestor et al., 2007), we will also evaluate this relationship in schizophrenia.

METHODS

Subjects

DTI-MRI data was acquired to evaluate the right and the left fornix in 36 male patients diagnosed with chronic schizophrenia and 35 male healthy individuals. The population consisted of schizophrenic patients from the Brockton Veterans Administration Medical Center. Patients were diagnosed with schizophrenia based on the (DSM-IV) criteria. Normal controls were recruited through newspaper advertisement. The study was approved by the local IRB at both the VA and Brigham and Women's Hospital. Following a description of the study, written informed consent was obtained from all subjects participating in the study. The clinical research interviews were conducted by a trained neuropsychologist. Groups were matched on age, gender (all males), handedness (Oldfield 1971), parental socio-economic status (PSES, Hollingshead 1965) and WRAT score for IQ (For details see Table 1).

All patients were receiving antipsychotic medication (typical antipsychotics 9 of the 36; atypical antipsychotics 24 of the 36) and both (3 of the 36). All medication dosages were converted to chlorpromazine equivalents (Bezch-libnyk-Butler et al., 1996; Stoll 2001).

Patients' mean duration of illness was 17.5+/- 10.4 years, with a mean age of onset of 21.1+/- 4.1. Patients had no history of neurological problems, drug or alcohol abuse (within the last year). Clinical symptoms were measured using the Scale for the Assessment of Positive Symptoms (SAPS- Andreasen 1984) and the Scale for Assessment of Negative Symptoms (SANS- Andreasen 1981). In addition to the inclusion/exclusion criteria for patients, normal controls and their first-degree relatives had no history of mental disorder, drug or alcohol addiction. Additionally, we administered, the Doors and People test (DPT) to evaluate visual memory, verbal memory, combined recall and combined recognition (Baddeley et al., 1994).

MRI processing and acquisition

Images of all subjects were acquired with a 1.5 Tesla System GE Echosped (General Electric Medical Systems, Milwaukee) using a Line Scan Diffusion MR imaging technique (Gudbjartsson et al 1996). This protocol is described in detail in our previous studies (Kubicki et al., 2003; Nakamura et al., 2005; Kuroki et al., 2006) and in contrast to single-shot EPI, which is reviewed in Kubicki et al. (2004). Briefly, we acquired coronal-oblique slices, aligned to the AC-PC line covering the entire brain. Six images with high diffusion-weighting (1000 sec/mm²) along six independent directions were collected. For low (5 sec/mm²) diffusion weighting, only two images were collected, because diffusion-related signal changes are minimal at low B values. The following scan criteria were used: field of view 220x165 mm, 128x128 scan matrix, slice thickness 4mm, interslice distance 1mm, NEX=1, TE (echo time) 64 msec, effective repetition time 2592 msec, scan time 60 sec/slice. The diffusion-weighted images were transferred to a workstation after reconstruction, where eigenvalue, eigenvector, and fractional anisotropy (FA) maps of the diffusion tensor were calculated. Motion-related artifact maps were also calculated, and later used for data correction.

Fiber Tracking

Fornix extraction and measurements were obtained using 3Dslicer software (www.slicer.org) and diffusion tensor tractography. Because the fornix is a small white matter structure and its fibers run close to other structures such as the corpus callosum and the anterior commissure, to segment the fornix is not a trivial issue. In order to ensure precise segmentation of the structure, we used multiple ROI method, which has been used before in several clinical tractography studies (e.g., Catani et al., 2002; Conturo et al., 1999; Jones et al., 2005). Five separate Regions of Interest (ROIs) were defined in order to tract the desired fibers, which are explained below. Only those pathways passing through all 5 ROIs were retained for further analysis. ROIs were manually drawn on the FA map, blind to diagnosis. The first ROI was placed on the most anterior coronal plane where the body of fornix is visible on the FA map, and then two more ROIs were placed on the next two consecutive slices using the corpus callosum, the contours of the lateral ventricles and the third ventricle, as landmarks. Finally, two additional ROIs, one on each side, were drawn on the two more posterior slices, including the hippocampus (tail), parahippocampal gyrus, and the crus fornicis (These ROIs can be seen in Figure 1). ROIs were drawn manually, with mean volumes being in the order of 8.30 cm² on the left, 8.10 cm² on the right and 2.91cm² for the anterior ROI. After fornix tracts were extracted, the average values of FA and mean diffusivity were calculated for the entire tract, separately for each side, and subjected to statistical analysis.

Interrater Reliability

Interrater Reliability was calculated using an intraclass correlation coefficient for 7 cases, selected from the 71 cases at random, and redrawn using the same criteria, by a second rater blinded to diagnoses (KS). Intraclass correlation coefficients (Cronbach's Alpha) achieved 0.985 for the right and 0.971 for the left fornix.

Sensitivity tool

Because DTI scans are noisier and of lower resolution than the anatomical (structural) scans, fiber tractography usually produces a small percentage of extraneous “unwanted” fiber traces, that either need to be ignored, or removed. We developed a tool (currently part of the “slicer” package www.slicer.org) that can perform unbiased (automated) elimination of these fibers. This tool (described in detail in San Jose Estepar et al., 2006). For each point along the fiber, the sensitivity is computed by placing a Gaussian Kernel at that location and convolving the ROI image with the kernel. The output of the convolution is a value between 0 and 1, with higher values achieved by fibers running closer to the middle of the ROI. In addition, in order to accommodate fibers running in different orientations within single ROI, we use here an anisotropic kernel, with its width being proportional to the geodesic distance between the Diffusion Tensor at the fiber location and the neighbor tensors. In effect, if the principal diffusion directions (PDD) of the neighboring tensors are parallel to the PDD of the tensors at the fiber location, the kernel is an isotropic Gaussian with a $\text{std}= 1.5$ pixels. If the PDD of the neighboring tensors is not parallel, then the kernel width is reduced in a proportional way given by the geodesic distance between the tensors. Figure 2 demonstrates how the sensitivity tool can automatically eliminate erroneous fiber tracts (Figure 2).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS v.12.0). To test for group differences in FA within the fornix, analysis of variance (ANOVA) was performed, with side as the within- subject factor, and group as the between- subject factor. Protected post-hoc independent sample t-tests were then used to evaluate differences between groups on the left and on the right side.

RESULTS

There were no group differences in gender (all males) or handedness (all right), and mean age did not differ either between normal subjects and schizophrenics (39.5, $\text{SD}= +/-9.3$, versus 39.8, $\text{SD}= +/-9.06$). Parental socioeconomic status also showed no significant difference (2.75, $\text{SD}= +/-1.34$ versus 3.06, $\text{SD}= +/-0.983$) and there was no difference between groups on IQ (.133, $\text{SD}= +/-0.129$). (Table1).

There was a group effect for Fornix FA in both left ($F=4.049$; $df=1,69$; $p=0.048$) and right FA ($F=7.902$; $df=1,69$; $p=0.006$). Further post-hoc protected T-tests showed decreased FA in the left ($t [69] =2.012$, $p=0.048$) and the right ($t [69] =2.811$, $p=0.006$) fornix in schizophrenia, compared with control subjects.

We also observed a side effect ($F=3.846$; $df=1$; $p=0.054$), but no side x group interaction ($F=1.242$; $df=1$; $p=0.269$). Both groups were characterized by mean FA values greater on the right side than on the left (Figure 3), however only control subjects showed this difference to be statistically significant ($t [34]= -1.986$, $p=0.055$ for NC, and ($t[35]= -.665$, $p=0.510$ for SZ).

No correlation between FA measures and medication dosage were found. Pearson’s correlation showed FA Left + CPZ equivalent= $.230$ ($p=.212$) and FA Right + CPZ equivalent= $.0459$ ($p=.806$).

Associations were found for the control group, with higher FA of the fornix correlating statistically significantly with DPT (Doors and people Test described in detail in Nestor et al., 2007) measures of combined visual memory ($r=.554$, $p=.026$), combined verbal memory ($r=.647$, $p=.007$), combined recall ($r=.516$, $p=.041$) and combined recognition ($r=.710$, $p=.002$).

No such statistically significant correlations were found in the patient group. (Table 2) (Figure 4).

Discussion

Fornix Integrity and Schizophrenia

In this study, fiber integrity of the fornix was measured in patients with chronic schizophrenia and in normal controls. Our results showed bilateral reduction of FA (indicative of white matter integrity) in the fornix of patients with schizophrenia compared to normal control subjects. Although we did not find neuropsychological correlations with measures of FA for the fornix in schizophrenic patients, we did find statistically significant correlations between fornix integrity and combined visual and verbal memory and combined recall and recognition in the control group. Previous studies also failed to demonstrate a significant fornix-declarative memory relationship in patients with schizophrenia (Nestor et al., 2007). Reduced FA in the fornix thus may be more associated with executive failures but not to memory anomalies in schizophrenia. The significant correlation in this study that we reported in controls, however, between episodic memory and FA in the fornix, is consistent with considerable evidence demonstrating that the fornix, a subcortical white matter tract carrying axons to and from the hippocampus, plays a vital role in normal episodic memory in the human brain (Graffan, 2005; Squire Zola-Morgan, 1991).

Few Studies of Fornix in Schizophrenia

Despite the important role of the fornix as the largest connection of the hippocampus with other brain structures, there are only a few studies that have evaluated this structure and its relationship to hippocampal volumes in schizophrenia. Our investigation includes only white matter measures. Because of the anatomical relationship between fornix and hippocampus, where the fornix serves as an important connective pathway carrying axons to and from the hippocampus, it is important to examine both gray and white matter measures in future studies in order to understand further the relationship between hippocampus and fornix.

The only postmortem study that investigated the fornix in schizophrenia was the study by Chance et al. (1999), who found a higher fiber density on the left side in men with schizophrenia than in comparison subjects, with no significant differences in the total number of fibers. The subjects in his study were older and only descending columns of the fornix were analyzed. An imaging study was later conducted by Zahajsky and coworkers (2001), who used structural MRI to measure and compare fornix volumes between patients with schizophrenia and controls, and where no significant differences in total volume between groups was observed, although these investigators were able to identify correlations between fornix and hippocampus volumes. Finally, the only study investigating fornix integrity in schizophrenia using Diffusion Tensor Imaging was a previous study conducted in our laboratory, which found reduced FA in the fornix in the schizophrenia patients compared with normal control subjects. This study, however, was limited to a small part of the fornix, the body of the fornix, and thus the entire structure was not included *in vivo* in schizophrenia.

Implications of Bilateral Fornix Findings in Schizophrenia

We reported bilateral findings for reduced FA in patients with schizophrenia compared with healthy controls. Of further note, anisotropic asymmetry differences were observed for the fornix for right-higher-than left anisotropy in healthy controls but not in patients with schizophrenia. The absence of anisotropy asymmetry differences in the fornix in patients is interesting although it is unclear what it means (i.e., lack of lateralization for fornix structure and function in schizophrenia?) and thus further investigation is needed. In fact, the relevance of brain asymmetry and schizophrenia is still poorly understood, although a number of studies

have characterized differences in brain asymmetries between patients with schizophrenia and controls (e.g., Bartley et al., 1993; Crow et al., 1989, 1997, 2000; DeLisi et al., 1994; Hoff et al., 1992). The fornix, in fact, is one of several structures where asymmetry abnormalities have been reported. Future studies are thus needed to clarify further asymmetry, or the lack thereof, in the fornix in schizophrenia.

Fiber Tractography to Quantify Fornix Anisotropic Diffusion

Fiber Tractography itself is a new approach to DTI data analysis (e.g., Mori et al., 1999; Basser et al., 2000; Catani et al., 2002). This new approach makes it possible to observe and to quantify white matter properties along the entire fiber bundles. This technique was introduced in 1999 (Mori et al.), and has been shown since to solve some of the problems associated with difficulties in the manual definition of long tracts (Kannan et al., 2005). Fiber tractography also has higher specificity and sensitivity compared to the conventional approach of using measurements from manually drawn ROIs (see Kannan et al., 2005). More specifically, after tracts are generated, they are used as labels to quantify fractional anisotropy, considered to be a measure of axonal integrity, density and myelination (Beaulieu 2002). This technique has also proven to be sensitive to white matter changes in different pathological conditions such as Multiple Sclerosis (Wilson et al., 2003) and Congenital Hemiparesis (Glenn et al., 2003).

Our findings using fiber tractography indicate abnormalities in the integrity of the fornix, which provides connectivity between the hippocampus and other brain regions. This kind of relationship has been demonstrated before in epilepsy. Kuzniecky et al. (1999), for example, found fornix atrophy in epilepsy patients with unilateral hippocampal atrophy and in a higher proportion in patients with bilateral hippocampal atrophy.

Advantages and Limitations of the Study

There are some limitations that require further studies. First, we don't know the effect of antipsychotic medication on DTI measures, although we found no significant correlation between FA measures and medication dosage. There are, nevertheless, only a few other studies that have evaluated this relationship, although different results have been obtained, with some reporting an association (Minami et al., 2003) and others not (Buchsbaum et al., 1998; Foong et al., 2000). It is possible that long-term treatment with antipsychotics also affects schizophrenics and thus further longitudinal studies might clarify this issue. Second, FA is observed to change as a function of the normal aging process (Pfefferbaum et al., 2005; Salat et al., 2005). Our study, however, included subjects who were younger compared to the participants of normal aging studies, and thus further studies are needed to compare FA changes in patients with schizophrenia and normal controls. We note, however, that Rosenberger et al. (2008), in our group, showed a negative correlation between FA in a group of 20–55 year olds compared to a group of healthy controls in the same age range. Moreover, medication dosage was not correlated with this finding. These findings thus suggest that white matter integrity may show progressive changes even in a restricted age range in patients with schizophrenia. Third, while our sample size was large and it provided adequate power, the subject population included only men and thus studies are needed that include both men and women in order to evaluate gender effects. Finally, further studies should be conducted in first episode patients as well as longitudinal studies in order to help identify whether or not abnormalities in schizophrenia are static or progressive in nature.

Conclusion

We used DTI and a tractographic approach to make measurements of fractional anisotropy in a specific white matter tract and found this to be a useful tool. Our results point to bilateral disruption in the fornix integrity in schizophrenia. Considering the role of the fornix in

connecting key brain structures involved in superior cognitive functions, this study can help broaden our understanding of the pathophysiology of schizophrenia.

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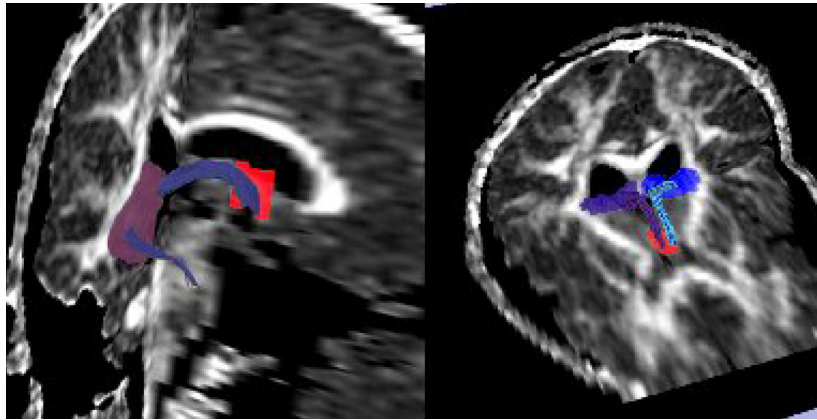


Figure 1.
ROIs used to extract the fornix, along with the tracts (purple- right fornix, blue- left fornix).
Middle ROIs were placed bilaterally.

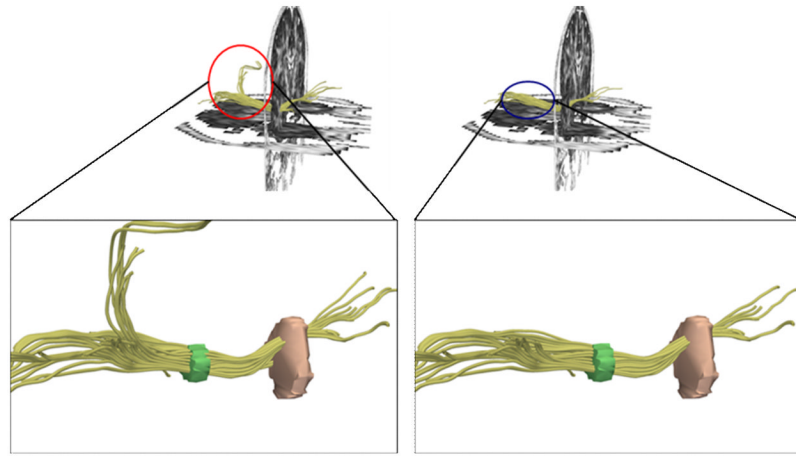


Figure 2. Figure demonstrating application of “sensitivity” tool to extract fibers of interest. Tool was able to exclude anatomically incorrect fibers (left panel before, right after tool application).

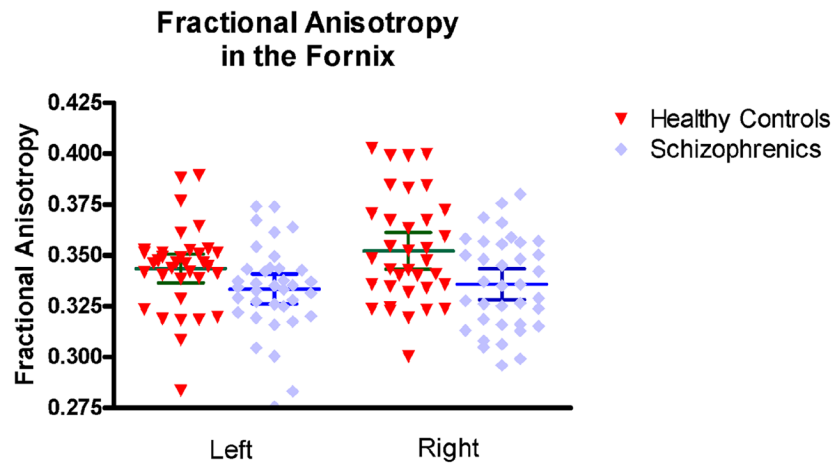


Figure 3.
Results of Fractional Anisotropy comparison.

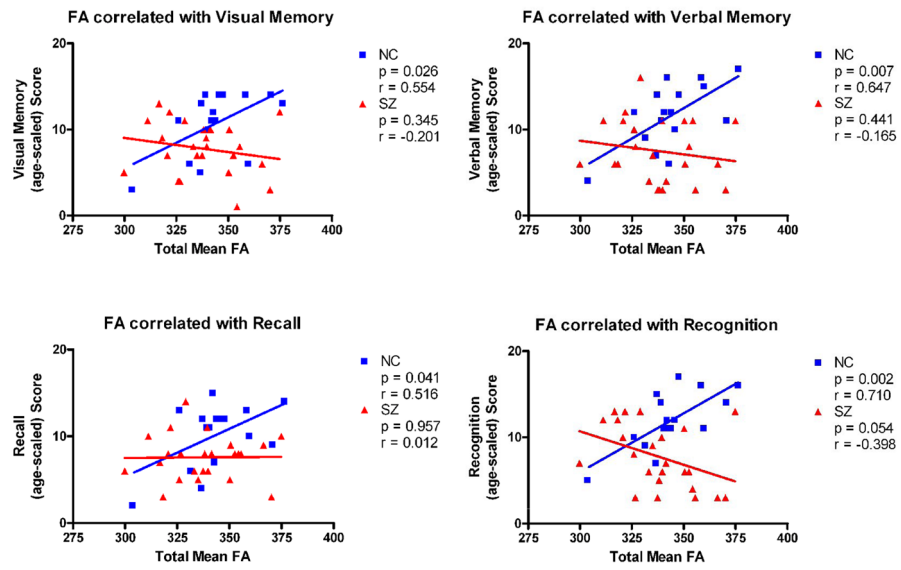


Figure 4. Scattergrams for fornix FA and Doors and People Test (DPT) measures of visual, verbal, recall and recognition memory for normal controls and patients with schizophrenia.

Table 1

Demographic data

	Mean (standard deviation)		p value
	Schizophrenics n=36	Controls n=36	
Sex (%male)	100%	100%	-
Age	39.89 (9.06)	39.59 (9.32)	0.897
PSES	3.06 (.983)	2.75 (1.34)	0.278
Handedness (%right)	100%	100%	-
WRAT	97.29 (13.03)	109.38(11.11)	0.133

Table 2

Doors and People Test (DPT) correlation between neuropsychological and brain measures for patients with schizophrenia (SZ) and normal controls (NC).

	NC		SZ	
	r	p	r	p
Combined Visual Memory	0.554	0.026*	-.201	.354
Combined Verbal Memory	0.647	0.007*	-.165	.441
Combined Recall	0.516	0.041*	0.012	.957
Combined Recognition	0.71	0.002*	-.398	.054

* P < .05.