Microstructural abnormalities of uncinate fasciculus as a function of impaired cognition in schizophrenia: A DTI study

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Neuropsychological studies have reported that attention, memory, language, motor and emotion processing are impaired in schizophrenia. It is known that schizophrenia involves structural alterations in the white matter of brain that contribute to the pathophysiology of the disorder. Uncinate fasciculus (UNC), a bundle of white matter fibres, plays an important role in the pathology of this disorder and involved in cognitive functions such as memory, language and emotion processing. Therefore, the present study aimed to investigate microstructural changes in UNC fibre in schizophrenia patients relative to controls and its correlation with neuropsychological scores.

Diffusion tensor imaging (DTI) and Hindi version of Penn Computerised Neuropsychological Battery test was performed in 14 schizophrenia patients and 14 controls. DTI measures [fractional anisotropy (FA) and mean diffusivity (MD)] from UNC fibre were calculated and a comparison was made between patients and controls. Pearson's correlation was performed between neuropsychological scores and DTI measures.Schizophrenia patients showed significantly reduced FA values in UNC fibre compared to controls. In schizophrenia patients, a positive correlation of attention, spatial memory, sensorimotor dexterity and emotion with FA was observed. These findings suggest that microstructural changes in UNC fibre may contribute to underlying dysfunction in the cognitive functions associated with schizophrenia.

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1. Introduction

Schizophrenia is a psychotic disorder which is associated with a wide spectrum of disturbances, including social, cognitive and emotional dysfunction. Several neuropsychological studies have shown deficits in working memory, verbal memory, language, motor and executive functions in schizophrenia (Green 1996; Penn *et al.* 1997; Rund and Borg 1999; Goldberg and Green 2002). These impairments in cognitive domains reflect the abnormal functioning of the brain in schizophrenia patients.

It is evident that schizophrenia involves structural alterations in the white matter of the brain that contributes to the pathophysiology of the disorder (Davis *et al.* 2003). Various neuroimaging studies have shown the structure–function relationship in a large number of brain regions which are affected in schizophrenia (Niznikiewicz *et al.* 2003; Waddington 2007). Literature has suggested that a disruption in connectivity between different brain regions, especially between the frontal and temporal lobes, may partly explain some of the primary symptoms of schizophrenia (Friston and Frith 1995; Deakin and Simpson 1997; Kubicki *et al.* 2002). The frontal and temporal lobes are connected via the uncinate fasciculus (UNC) which is considered as the major fibre tract (Ungerleider *et al.* 1989; Catani and Thiebaut de Schotten 2008). UNC plays a putative

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role in episodic memory, language, semantic retrieval and social emotional processing (Von Der Heide *et al.* 2013). It is also associated with higher level object perception and object memory (Murray *et al.* 2005).

Magnetic resonance imaging (MRI)-based diffusion tensor imaging (DTI) is a non-invasive method which have the ability to quantify the integrity of white matter fibre tracts that functionally connect different brain networks. DTI measures the strength and direction of water diffusivity in brain tissue to estimate the microstructural changes of fibre tracts in various pathological conditions using DTI indices [fractional anisotropy (FA), and mean diffusivity (MD)]. FA measures the amount of coherence of water diffusion and putatively reflects the amount of myelination in axonal bundles or the coherence of fibre tracts whereas MD measure overall displacement of diffusion in a particular region or voxel. Several studies have measured the FA values in the UNC of schizophrenia using DTI (Kubicki *et al*. 2002; Highley *et al*. 2002; Burns *et al*. 2003; Jones *et al*. 2006; Price *et al*. 2008; Voineskos *et al*. 2010; Kitis *et al*. 2012). Most of these studies reported decreased FA values in schizophrenia patients as compared with healthy controls (Burns *et al*. 2003; Price *et al*. 2008; Voineskos *et al*. 2010; Kitis *et al*. 2012) whereas few of them showed increased or no change in FA values in the schizophrenia patients (Kubicki *et al*. 2002; Highley *et al*. 2002; Jones *et al*. 2006).

In the present study, we performed DTI and neuropsychological test using Penn Computerised Neuropsychological Battery (CNB) in 14 schizophrenia patients and 14 healthy subjects in order to measure the integrity of fibres within the uncinate fasciculus (UNC), the most prominent of all white matter fibre tracts connecting the frontal and temporal lobes, and its correlation with neuropsychological scores.

2. Methods

The study was conducted at the NMR Research Centre, Institute of Nuclear Medicine and Allied Sciences (INMAS), Delhi, India and was approved by the Institutional ethics committee of Post Graduate Institute of Medical Education and Research (PGIMER), Dr. Ram Manohar Lohia Hospital (RMLH), New Delhi, India, and the Institutional Review Board, INMAS, Delhi, India. After complete description of the study to the participants, written informed consent was obtained from all the participants.

2.1 *Subjects*

A total of 14 schizophrenia patients and 14 healthy controls underwent MRI scans (table 1). Schizophrenia subjects were recruited from outpatients at Department of Psychiatry, PGIMER- RMLH, New Delhi.

We included patients aged between 25–45 years with a DSM-IV diagnosis of schizophrenia, interviewed using the Hindi version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger *et al.* 1994; Deshpande *et al.* 1998) after diagnostic review with a board certified psychiatrist. Patients with a history of alcohol/illicit substances or individuals with any neurological disorders that interfered with the diagnosis or cognitive evaluations were excluded. All patients were on antipsychotic medications at the timing of MRI acquisition.

All control subjects chosen for the study were recruited from the local community. During the entire study, none of the subjects displayed any clinical evidence of stroke, head injury, cardiovascular diseases, history of smoking, alcohol or drug dependence and psychiatric disorders. Both patients and controls showed no neurological abnormalities on conventional MRI scans.

2.2 *Neuropsychological assessment*

Neurocognitive functions of both controls and patients were assessed with a Hindi version of Penn Computerised Neuropsychological Battery (CNB) (Gur *et al.* 2001). The CNB includes neurocognitive domains known to be impaired among individual with schizophrenia (Sachs *et al.* 2004). The CNB, developed in the Brain Behaviour Lab at Penn, is a series of computerized tests that measure the accuracy and speed of performance in major domains of cognition, including social-cognition (Gur *et al.* 2001). Data are acquired in an automated fashion, reducing observer bias. It is also possible to measure both accuracy and response times. The construct validity of the Penn CNB has been established and it has been used extensively (Gur *et al.* 2001). The battery assesses the following neurocognitive domains: abstraction and mental flexibility (ABF), attention (ATT), working memory (WM), verbal memory (VMEM), face memory (FMEM), spatial memory (SPA), language (LAN), sensorimotor dexterity (SM), emotion processing (EMO). The verbal domains are available only in English. As many Indians did not speak English, the verbal domains were excluded. For each domain, three summary functions are calculated: (a) accuracy (number of correct responses) (b) speed (median reaction time for correct responses) and (c) efficiency (which reflects both accuracy and speed). The battery was administered in a fixed order using a web browser interface. Participants need not be computer literate to complete the Penn CNB, as the evaluations are straight forward. In addition, each participant is required to complete a practice session designed for familiarisation with the computer mouse and the video monitor.

2.3 *Imaging protocol*

Patients and controls underwent conventional MRI and DTI. Imaging was performed on a 3 tesla whole-body MRI system (Magnetom Skyra, Siemens, Germany) using a 16-channel head coil with 45 mT/m actively shielded gradient system. The conventional MR Imaging was performed to rule out any

Table 1. Demographic and clinical characteristics of subjects

	Schizophrenic patients (N= 14) (mean±SD)	Healthy controls (N = 14) (mean±SD)
Age (years)	34.14±7.60	32.36±5.57
Gender (Male/Female)	8/6	6/8
Years of education	9.7 ± 3.8	11.3 ± 3.3
Duration of Illness (in weeks)	451.1 ± 318.8	NA
SANS total score	11.61 ± 5.9	
SAPS total score	7.96 ± 4.3	
Antipsychotic equivalent dosage of CPZ, mg/day	507.14 ± 362.9	
Duration of antipsychotic drug taken (in weeks)	451.1 ± 318.8	

SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; CPZ: chlorpromazine.

structural abnormality using axial T2-weighted turbo spin echo sequence with repetition time (TR)/echo time (TE)/number of excitations (NEX) =5600ms/100 ms/1 and T1-weighted turbo inversion recovery sequence with TR/TE/NEX=2000 ms/12ms/1 with other parameters: field of view=220×220 mm^2, slice thickness = 4 mm with no interslice gap and number of slices=25. DTI data were acquired using a single-shot echo-planar spin-echo (SE) sequence with ramp sampling. Diffusion-weighted acquisition parameters were: b-factor = 0 and 1000 s/mm^2, slice thickness=3 mm with no interslice space, number of slices=45, FOV=230 mm×230 mm, TR=8800 msec, TE=95 ms, NEX=2 and number of gradient encoding directions = 30.

2.4 *Diffusion tensor tractography and data quantitation*

Segmentation of white matter structures Segmentation of white matter structures followed by diffusion tensor tractography (DTT) was performed using in-house developed JAVA based software (Rathore *et al.* 2011).

The purpose of segmentation of white matter structure was to facilitate the selection of regions of interest (ROIs) for DTT. The key idea of this method is to do a segmentation of the principal eigenvector (e1) field into stable voxels having a minimal e1 variation (curvature). Thus, a voxel P (i, j, k) is a member of the stable fibre mass (SFM), if there is a neighboring voxel Q (x, y, z) such that the principal eigenvectors e1's at P and Q point out to each other. Mathematically, it translates to the relation G (F (P)) =P, where F (P) =ROUND (P + e1(P) + 0.5u), u = (1, 1, 1), and G (Q) = ROUND (Q - e1(Q) + 0.5u), function ROUND standing for component wise 'integral part' operation.

The method first generates SFM and then segments volume by colouring voxel P according to the values the components (l, m, n) of the vector joining P and Q take: (±1,0,0) - red, (0,±1,0) - green, (0,0,±1) - blue, (±1,±1,0) - yellow, (0,±1,±1) - cyan, (±1,0,±1) –magenta, (±1,±1,±1) -white. A non-stable voxel is coloured grey and a voxel with FA < 0.15 remains black. Typical segmented axial, sagittal and coronal SFM coloured maps are generated, using which this method narrows down the ROIs selection for the standard tractography to pointing out to a colour segment inside a broader ROI (Rathore *et al.* 2011) (figure 1).

Diffusion tensor tractography Fibre assignment by continuous tracking algorithm (Mori *et al.* 1999) was used for reconstruction of fibres. An in-house-developed JAVA-based software (Rathore *et al.* 2011) was used to generate and quantify uncinate fasciculus (UNC) fibre tract. DTI measures were calculated for the entire fibre. The FA threshold of 0.15 was used for fibre tracking.

2.5 *Statistical analysis*

Multivariate Analysis of Variance (MANOVA) using General Linear Model was performed to measure the changes in neuropsychological scores between controls and schizophrenia patients. Student's independent *t*-test was performed to determine the changes in FA/MD values in UNC fibre tracts between controls and schizophrenia patients. In schizophrenia patients as well as healthy controls, Pearson's correlation coefficient was computed to study the correlation between the white mater tract specific DTI measures and neuropsychological scores. A p-value ≤0.05 was considered to be statistically significant. All statistical analysis was conducted using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL).

3. Results

3.1 *Neuropsychological scores*

Table 2 shows neuropsychological test summary scores for the control and patient groups for each of the broad cognitive domains sampled: abstraction and mental flexibility (ABF),

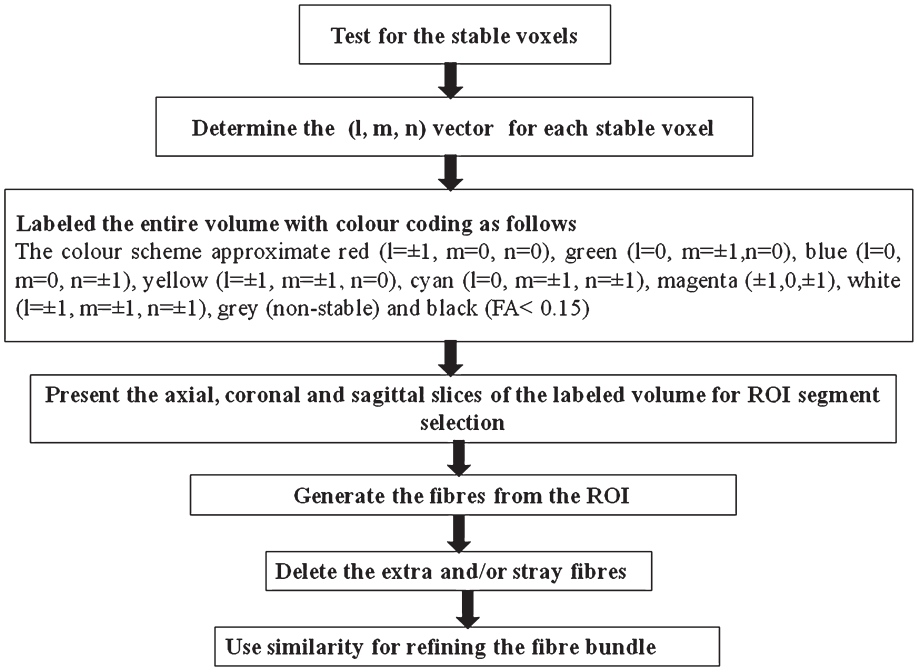

Figure 1. Flow chart explaining the algorithm used for fibre tracking, ROI: Region of interest.

attention (ATT), working memory (WM), face memory (FMEM), spatial memory (SPA), sensorimotor dexterity (SM), emotion processing (EMO). Patients with schizophrenia scored significantly lower than control subjects across neuropsychological summary measures.

3.2 *DTI measures*

Table 3 shows mean ± SD of FA and MD values in UNC fibre tract in both patients and controls. The result revealed significantly reduced FA values in both left and right UNC fibre tracts in the patient group (RUNC; 0.31 ± 0.03, LUNC; 0.32 ± 0.03) as compared to control subjects (RUNC; 0.35 ± 0.05, LUNC; 0.35 ± 0.05) (RUNC; p=0.005, LUNC; p=0.031) (figure 2).

Schizophrenia patients also showed increased MD values in UNC fibre tract compared to controls, though it could not achieve statistical significance.

3.3 *Correlation between DTI measures and neuropsychological scores*

Table 4 shows Pearson correlations for DTI measures of UNC and neuropsychological tests as indexed by the CNB. Schizophrenia patients showed positive correlation between attention, spatial memory, sensorimotor dexterity and emotion with FA values in UNC. In controls, no significant correlation was observed between any of the neuropsychological test and FA values.

MD values did not show any correlation with neuropsychological score in schizophrenia patients as well as control subjects.

4. Discussion

The present study demonstrates altered DTI indices as a result of microstructural changes in UNC fibre tracts and its correlation with neuropsychological functions in schizophrenia patients compared with healthy controls. There are some studies which have shown correlation of altered DTI indices in UNC fibre with memory function in schizophrenia (Nestor *et al.* 2004; Nestor *et al.* 2008; Szeszko *et al.* 2008). Besides this, our study showed correlation of altered FA in UNC fibre with attention, sensorimotor dexterity and emotion processing in schizophrenia patients as compared to healthy controls.

The UNC is a white matter fibre tract that connects the anterior temporal lobe with the medial and lateral orbitofrontal cortex (Ungerleider *et al.* 1989; Catani and Thiebaut de Schotten 2008). It is suggested that the information transmission properties of any white matter fibre tract can be predicted by the function of the regions that it connects. At the same time, the functions of cortical regions are determined by their pattern of white matter input and output

Table 2. A summary of group means and SDs of the neuropsychological scores in schizophrenia patients and controls subjects which showed significant differences

Domains	Controls	Patients	p-Value
	Accuracy		
Abstract and mental flexibility	−0.08 ± 0.87	−1.87 ± 0.62	0.001
Attention	0.37 ± 0.27	−1.10 ± 1.44	0.001
Face memory	0.76 ± 1.42	−0.91 ± 0.93	0.001
Spatial memory	0.97 ± 1.03	−0.68 ± 0.51	0.001
Working memory	0.53 ± 0.67	−1.55 ± 1.35	0.001
Spatial ability	0.39 ± 0.56	−0.36 ± 0.53	0.006
Sensorimotor	0.70 ± 0.21	−0.38 ± 1.47	0.011
Emotion	0.05 ± 0.92	−0.75 ± 1.03	0.039
	Speed		
Abstract and mental flexibility	− 0.25 ± 0.88	−1.51 ± 1.62	0.017
Attention	− 0.12 ± 0.80	−1.12 ± 1.48	0.035
Face memory	0.69 ± 1.72	−1.04 ± 2.61	0.049
Spatial memory	0.69 ± 0.56	−0.79 ± 2.18	0.020
Working memory	0.18 ± 0.74	−0.85 ± 1.32	0.014
Spatial ability	0.15 ± 0.88	−2.78 ± 3.60	0.008
Sensorimotor	0.95 ± 0.64	−0.03 ± 1.16	0.011
Emotion	0.87 ± 0.77	−1.77 ± 2.81	0.002
	Efficiency		
Abstract and mental flexibility	− 0.22 ±0.89	−2.08 ± 0.68	0.001
Attention	0.37 ± 0.43	−1.75 ± 2.05	0.001
Face memory	1.05 ± 1.67	−0.95 ± 0.97	0.001
Spatial memory	1.15 ± 1.13	−0.75 ± 0.63	0.001
Working memory	0.52 ± 0.67	−1.49 ± 1.23	0.001
Spatial ability	0.09 ± 0.82	−1.13 ± 0.75	0.003
Sensorimotor	0.94 ± 0.46	−0.48 ± 1.70	0.006
Emotion	0.44 ± 1.15	−0.81 ± 1.22	0.010

(Passingham *et al.* 2002; Von Der Heide *et al*. 2013). By virtue of the geographic placement and connectivity of UNC, it is assumed that the UNC is associated with the limbic system and involved in emotion and episodic memory (Von Der Heide *et al.* 2013). Several studies have shown decreased FA values in the UNC of schizophrenia (Burns *et al.* 2003; Price *et al.* 2008; Voineskos *et al.* 2010; Kitis *et al.* 2012). In concordance with these studies, our findings also revealed significantly decreased FA values in UNC fibre in schizophrenia patients relative to healthy controls. MD values also increased in UNC fibre tract in patient group, but it was not statistically significant. The decreased FA values in UNC fibre might be due to demyelination, decreased neuronal fibre density, or directional coherence in this fibre tract.

It is suggested that disrupted uncinate fasciculus integrity in schizophrenia may be related to impaired memory and social

Table 3. A summary of group means and SDs of the fractional anisotropy (FA) and Mean diffusivity (MD) values from the UNC white matter tracts of brain from the controls and schizophrenia patients (N = 14)

DTI Indices	Fibre bundles	Controls	Schizophrenics	p-Value
FA	RUNC	0.35 ± 0.05	0.31 ± 0.03	0.005*
	LUNC	0.35 ± 0.05	0.32 ± 0.03	0.031*
MD	RUNC	0.88 ± 0.05	0.90 ± 0.04	0.320
	LUNC	0.87 ± 0.04	0.89 ± 0.04	0.182

UNC, uncinate fasciculus. p-Values show the level of statistical significance.

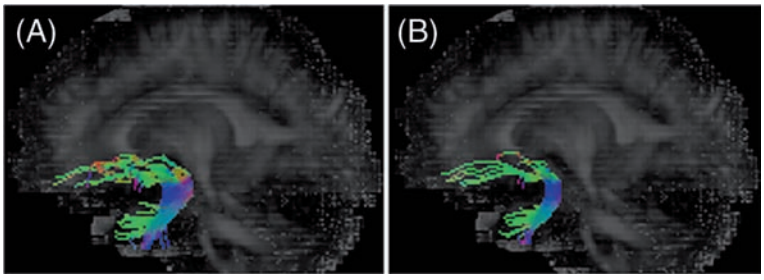

Figure 2. Projection of the UNC on the mid-sagittal plane in age-matched control and schizophrenia patient. 3D tractography image shows thinning of fibre bundle in patient (**B**) as compared with control (**A**).

cognition (Voineskos *et al.* 2010; Von Der Heide *et al.* 2013). There are studies which have shown correlation of DTI changes in UNC fibre with memory functions in schizophrenia patients (Nestor *et al.* 2004; Nestor *et al.* 2008; Szeszko *et al.* 2008). Szeszko *et al.* (2008) have reported that lower FA in UNC correlated significantly with worse memory functioning in patients with recent onset schizophrenia. Similarly, Nestor *et al.* (2008) showed lower FA in UNC is associated with worse declarative-episodic verbal memory in schizophrenia patients.

Table 4. Summary of the Pearson's correlation coefficient (r) between neuropsychological scores and FA values of UNC fibre tracts in controls and schizophrenia patients which showed significant correlation.

Fibre Bundles	Controls		Patients	
	Accuracy vs FA			
	r-Value	p-Value	**r**-Value	p-Value
Attention				
RUNC	0.188	0.519	0.598	0.024*
LUNC	0.023	0.937	0.572	0.033*
Spatial memory				
RUNC	-0.004	0.990	0.843	0.009*
Sensorimotor Dexterity				
RUNC	0.144	0.623	0.685	0.007*
	Efficiency vs FA			
Attention				
RUNC	0.273	0.346	0.574	0.032*
LUNC	0.116	0.693	0.563	0.036*
Spatial memory				
RUNC	0.003	0.992	0.873	0.001*
Sensorimotor Dexterity				
RUNC	0.167	0.568	0.607	0.021*
Emotion				
RUNC	0.167	0.568	0.425	0.053*

p-Values shows the level of statistical significance and asterisk indicate significant correlation between groups (*$p<0.05$).

In line with these studies, we also found a positive correlation between reduced FA values in UNC and memory functions.

In addition to correlation of altered FA values with memory functions, we also found a significant positive correlation between FA values in UNC fibre and attention, sensorimotor dexterity and emotion processing in schizophrenia patients. Healthy controls did not show any significant relationship between FA values and neuropsychological scores. The uncinate fasciculus (UNC) fibre tract connects the frontal and temporal lobes (Ungerleider *et al.* 1989; Kubicki *et al.* 2002; Catani and Thiebaut de Schotten 2008), that are involved in various cognitive functions such as attention, language, motor control and emotion processing (Miotto *et al.* 1996; Semendeferi *et al.* 1997; Patterson *et al.* 2007; Olson *et al.* 2007). These cognitive functions such as attention, motor function and emotion processing, are known to be impaired in schizophrenia (Gur *et al.* 2001; Goldberg and Green 2002). Our findings suggest that microstructural alteration in UNC fibre may contribute to underlying dysfunction associated with these cognitive functions in schizophrenia patients.

There are some limitations in the present study. Our sample size is relatively small; a greater number of subjects would yield more statistically significant results. Secondly, all the patients were on antipsychotic medications. Inclusion of a third group consisting of first-episode patients without medical history will be helpful to determine the potential effect of pharmacological treatment in schizophrenia. Although the effect of age on FA/MD values were reported in the literature, but we did not find any significant correlation between age and FA/MD values in both patient and control group.

5. Conclusion

In conclusion, our study reveals correlation of reduced FA values in UNC fibre with attention, sensorimotor dexterity and emotion in addition to memory in schizophrenia patients. These findings suggest that microstructural changes in UNC fibre may contribute to underlying dysfunction in the cognitive functions associated with schizophrenia.

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