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Reduced integrity of superior longitudinal fasciculus and arcuate fasciculus as a marker for auditory hallucinations in schizophrenia: A DTI tractography study

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ABSTRACT

Aims and objectives: : The study aimed to assess and compare fractional anisotropy (FA) in bilateral superior longitudinal fasciculi (SLF) and arcuate fasciculi (AF) across schizophrenia with auditory hallucinations(AH), without AH, and healthy controls using diffusion tensor imaging (DTI) tractography.

Methodology: : Right-handed adult (18–50 years) individuals with DSM-5 diagnosis of schizophrenia with AH (group-I; $n = 30$) were compared to those without lifetime AH (group-II; $n = 32$) and healthy controls (group-III; $n = 30$). Severity of psychosis in groups-I and II was assessed using SAPS, SANS, and CGI-SCH, and psychopathology was assessed using PSYRATS. The FA was calculated for all images on DTI studio-version 3.0 using tractography technique.

Results: : All three groups were comparable for age, gender, education and illness-severity. Schizophrenia subjects with AH had significantly lower FA values in bilateral SLF and AF compared to those without AH and healthy controls. No difference was observed in corresponding FA values between schizophrenia without AH and healthy controls.

Conclusion: : White matter disruptions in bilateral SLF and AF appear to be specific to schizophrenia with AH and must be explored further as potential marker of AH, pending replication in other studies.

1. Introduction

Auditory hallucinations (AH) are one of the common psychiatric symptoms occurring across a range of disorders, including schizophrenia (Baethge et al., 2005; Ali, 2011). In clinical settings, persistent AH in schizophrenia interferes with daily activities and functioning in view of their intrusive and uncontrollable nature (Ali, 2011). Relatively less research has taken a symptom-based approach for exploring biological correlates of individual psychopathological symptoms, such as AH (Zmigrod et al., 2016). Further, diagnostic systems and subtypes keep on changing over time, making it important to have symptom-based perspectives in addition to a disorder-based approach.

Till date, several studies have used diffusion tensor imaging (DTI) to investigate anatomical connectivity in schizophrenia, but very few have extended this research to find the underlying associations specific to AH (Hubl et al., 2004; Shergill et al., 2007; Catani and Thiebaut de Schotten, 2008; Szeszko et al., 2008; Rotarska-Jagiela et al., 2010; Catani et al., 2011; Abdul-Rahman et al., 2012; Knöchel et al., 2012; de Weijer et al., 2013; Benetti et al., 2015; McCarthy-Jones and Oestreich, 2015; Ćurčić-Blake et al., 2015; Wigand et al., 2015). One of the early reports of diffusion abnormalities in AH found rather higher fractional anisotropy (FA) measure in left lateral arcuate fasciculus (AF), and left cingulum in patients of schizophrenia prone to AH compared to those without AH and healthy controls, suggesting possibility of alterations in connectivity between frontal and parieto-temporal speech-related areas (Hubl et al., 2004). Subsequent studies to take a symptom-based approach for AH in schizophrenia have shown conflicting findings (Hubl et al., 2004; Shergill et al., 2007; Catani and Thiebaut de Schotten, 2008; Szeszko et al., 2008; Rotarska-Jagiela et al., 2010; Catani et al., 2011; Abdul-Rahman et al., 2012; Knöchel et al., 2012; de Weijer et al., 2013; Benetti et al., 2015; McCarthy-Jones and Oestreich, 2015; Ćurčić-Blake et al., 2015; Wigand et al., 2015), with majority reporting a lower FA, while a few observed higher FA across schizophrenia with AH compared to those without AH or healthy controls in various white matter tracts (Hubl et al., 2004; Shergill et al., 2007; Catani and Thiebaut de Schotten, 2008; Szeszko et al., 2008; Rotarska-Jagiela

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Table 1
Socio-demographic profile of the study groups.

Socio-demographic variables	Schizophrenia with auditory hallucinations (n = 30) Mean (S.D) or N (%)	Schizophrenia controls without auditory hallucinations (n = 32) Mean (S.D) or N (%)	Healthy controls (n = 30) Mean (S.D) or N (%)	Comparison (Kruskal wallis test, Chi-squared test) Statistic (df), p value
Age (years)	32.9 (9.3)	27.7 (6.8)	28.1(6.9)	H = 5.873 (2); 0.053
Gender				
Male	19 (63.3%)	16 (50%)	21 (70%)	χ^2 = 2.714 (2); 0.257
Female	11 (36.7%)	16 (50%)	09 (30%)	
Marital status				
Never married	16 (53.3%)	23 (71.9%)	19 (63.3%)	χ^2 = 5.527 (4); 0.237
Married	14 (46.7%)	07 (21.9%)	10 (33.3%)	
Separated/divorced	–	02 (06.2%)	01 (03.3%)	
Education				
Upto 10^{th}	14 (46.7%)	12 (37.5%)	07 (23.3%)	χ^2 = 3.607 (2); 0.165
Above 10^{th}	16 (53.3%)	20 (62.5%)	23 (76.7%)	
Occupational Status				
Professionals	01 (3.33%)	01 (03.1%)	09 (30.0%)	χ^2 = 33.975 (12); 0.001
Skilled workers	01 (3.33%)	02 (06.2%)	03 (10.0%)	
Unskilled workers	05 (16.7%)	02 (06.2%)	09 (30.0%)	
Unemployed	09 (30.0%)	13 (40.6%)	00 (00.0%)	
Others	14 (46.7%)	14 (43.8%)	09 (30.0%)	
Total family income (in Rupees per month)				
≤ 10,000	06 (20.0%)	05 (15.6%)	02 (07.7%)	χ^2 = 2.288 (2); 0.319
> 10,000	24 (80.0%)	27 (84.4%)	28 (93.3%)	
Religion				
Hindu	28 (93.3%)	26 (81.3%)	27 (90.0%)	χ^2 = 6.119 (6); 0.410
Others	02 (06.7%)	06 (18.7%)	03 (10.0%)	

H = Chi square coefficient (Kruskal walis test).
χ^2 = Pearson chi square coefficient (Chi square test).

Table 2
Clinical characteristics of the study groups I and II.

Clinical variables	Schizophrenia patients with auditory hallucination (n = 30) Mean (S.D) or N (%)	Schizophrenia patients without auditory hallucination (n = 32) Mean (S.D) or N (%)	Comparison (Mann Whitney U test, Chi square test) Test statistic (df); p value
Age of onset (years)	23.2 (8.3)	22.1 (5.7)	U = .463.000; 0.810
Duration of illness (years)	9.6 (7.3)	5.5 (4.1)	U = 331.000; 0.035
Premorbid personality traits			
Well adjusted	19 (63.3%)	23 (71.9%)	χ^2 = 2.128 (2); 0.345
Schizoid traits	07 (23.3%)	05 (15.6%)	
Others	04 (13.3%)	04 (12.5%)	
Past history of depression	9 (30%)	6 (18.8%)	χ^2 = 0.301 (1); 0.379
Family history of psychosis	3 (10%)	8 (25%)	χ^2 = 0.122 (1); 0.185
History of nicotine use	4 (13.3%)	5 (15.6%)	χ^2 = 2.035 (2); 0.361
Duration on treatment (years)	6.3 (7.1)	3.6 (3.2)	U = 418.500; 0.384
SAPS (0-20)	7.1 (2.6)	3.5 (1.9)	U = 116.500; < 0.001*
SANS (0-25)	6.6 (5.8)	7.3 (5.8)	U = 467.500; 0.858
PSYRATS-D (0-24)	12.5 (5.5)	11.3 (4.6)	U = 418.500; 0.379
PSYRATS-H (0-44)	29.8 (6.1)	–	–
CGI-SCH (severity)	4.4 (0.9)	4.2 (0.7)	U = 386.00; 0.158

SAPS = Scale for assessment of positive symptoms, SANS = Scale for assessment of negative symptoms, PSYRATS = Psychotic symptom rating scale (D = Delusion subscale, H= Hallucination subscale), CGI- Clinical global impression scale for schizophrenia.
H = Chi square coefficient (Kruskal walis test), χ^2= Pearson chi square coefficient (Chi square test), U = Mann whitney U coefficient (Mann whitney U test).

et al., 2010; Catani et al., 2011; Abdul-Rahman et al., 2012; Knöchel et al., 2012; de Weijer et al., 2013; Benetti et al., 2015; McCarthy-Jones and Oestreich, 2015; Wigand et al., 2015). Decreased FA in AF is one of more consistent findings reported in schizophrenia with AH.

AF is a large white matter bundle that arches around lateral sulcus, and connects the two main language areas, that is Broca's and Wernicke's areas. AF has a long segment, which directly connects Broca's and Wernicke's areas, and two short segments, which indirectly connect the anterior and posterior language areas via the inferior parietal lobule. Altogether, they constitute the dorsal language stream which is involved in phonemic aspects of language (Johns, 2014).AF, in turn, is a part of larger superior longitudinal fasciculus (SLF). SLF, though initially considered synonymous with AF, have recently been found to have four components connecting frontal and opercular areas with the superior parietal lobe (SLF-I), the angular gyrus (SLF-II), the supramarginal gyrus (SLF-III), and the superior temporal gyrus (SLF-IV) (Madhavan et al., 2014). SLF-IV is now viewed as AF, due to its apparent connections with Broca's and Wernicke's area (Madhavan et al., 2014). Over the last few years, different anatomical models of SLF have been proposed, each of which emphasize the importance of tracts connecting the fontal region to not only temporal region, but also parietal region, which are eventually involved in semantic processing (Catani and Jones, 2005; Glasser and Rilling, 1991; Price, 2010). Abnormalities in AF have been reported in schizophrenia with AH, though, data on changes in SLF as a whole is scant.

The current study aimed to measure and compare the fractional anisotropy (FA) values through DTI using tractography among schizophrenia patients with AH, without AH and healthy controls in two predefined white matter fasciculi viz. (i) arcuate fasciculus (AF); and (ii) superior longitudinal fasciculus (SLF); and to correlate FA with

Table 3
Fractional anisotropy measures of the study groups.

Fasciculi	Schizophrenia with auditory hallucinations (N = 30) Mean (SD)	Schizophrenia controls without auditory hallucinations (N = 32) Mean (SD)	Healthy controls (N = 30) Mean (SD)	Comparison (Kruskal walis test) H (df = 2); p value	Post hoc analysis* (Dunn- Bonferroni)
Superior Longitudinal Fasciculus (R)	0.4843 (0.1793)	0.5119 (0.0279)	0.5040 (0.0236)	**17.540; < 0.001****	**I < II (p < 0.001), I < III (p = 0.005)**
Superior Longitudinal Fasciculus (L)	0.4801 (0.2265)	0.5201 (0.0254)	0.5125 (0.0229)	**32.753; < 0.001****	**I < II (p < 0.001), I < III (p < 0.001)**
Arcuate fasciculus (R)	0.4841 (0.0280)	0.5174 (0.0321)	0.5110 (0.0271)	**17.381; < 0.001****	**I < II (p = 0.003), I < III (p < 0.001)**
Arcuate fasciculus (L)	0.4935 (0.0254)	0.5289 (0.0298)	0.5249 (0.0242)	**23.357; < 0.001****	**I < II (p < 0.001), I < III (p < 0.001)**

(R) = Right, (L) = Left.
H = Chi square coefficient (Kruskal walis test).
*p values were adjusted for multiple comparisons by Sidak corrections (adjusted p value = 0.02).

clinical variables in patients of schizophrenia with/ without AH.

2. Methods

2.1. Recruitment

Ethical clearance was taken from Institute Ethics Committee at AIIMS (All India Institute of Medical Sciences), New Delhi. A written informed consent was taken from participants prior to their inclusion. Study subjects were recruited from the Department of Psychiatry and DTI was carried out at the Department of Neuroimaging and Interventional Neuroradiology at same institute. The DTI was done free of cost for all research participants by provision of institute support.

Right-handed individuals between the age group 18–50 years, diagnosed as schizophrenia as per DSM-5 criteria with total duration of illness ≥ 2 years were taken in the patient groups (group I and II) and compared with control group (group III).

Group I had 'significant' auditory verbal hallucinations (operationally defined as hallucinations ≥50% of days in current month, lasting for several minutes at least at a time, and present during previous exacerbation/s of illness. Group II had 'absence' of AH (operationally defined as a score of 0 for AH on scale for assessment of positive symptoms (SAPS), with no previous AH, and no lifetime AH as reported by family /next of kin) Group III consisted of healthy controls (i.e. no psychiatric diagnosis and no family history of psychiatric illness).

Those with unclear or uncertain AH, current major psychiatric disorder (other than schizophrenia in the patient groups), lifetime major psychiatric disorder (except schizophrenia and major depression in patient groups; except nicotine dependence in all), intellectual disability, significant medical/neurological condition or those with standard MRI contraindications (e.g. metal implant) were excluded.

2.2. Clinical Assessments

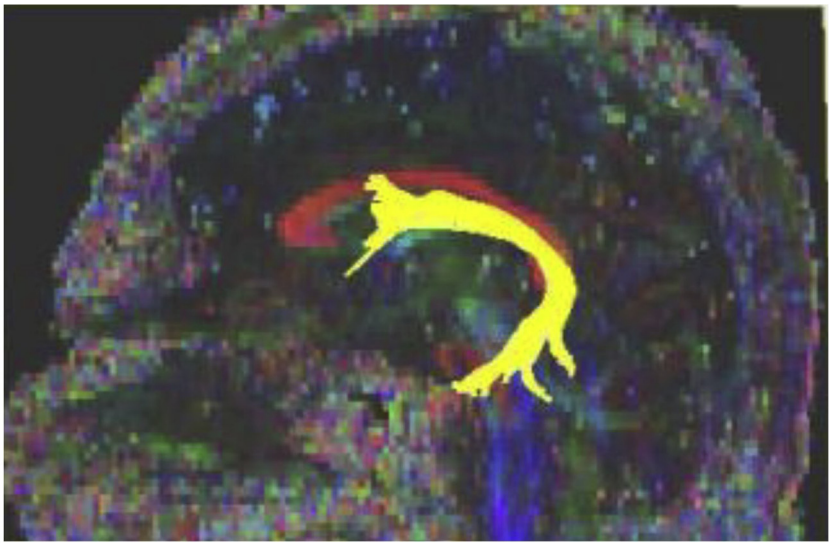
After screening the eligible subjects by MINI version 7.0.0 (Sheehan et al., 1998) and Edinburgh's handedness inventory (Oldfield, 1971), the subjects were taken up for clinical assessment. A semi-structured proforma was used to gather relevant demographic and clinical details. The SAPS and SANS (scale for the assessment of negative symptoms) were used for grading severity of positive and negative symptoms respectively (Andreasen, 1984, 1983). Psychotic Symptom Rating Scale (PSYRATS) (Haddock et al., 1999) was applied to assess for severity of hallucinations and delusions. In addition, Clinical Global Impression-Schizophrenia scale (CGI-SCH scale) (Haro et al., 2003) assessed the overall severity of psychosis.

2.3. Study procedure

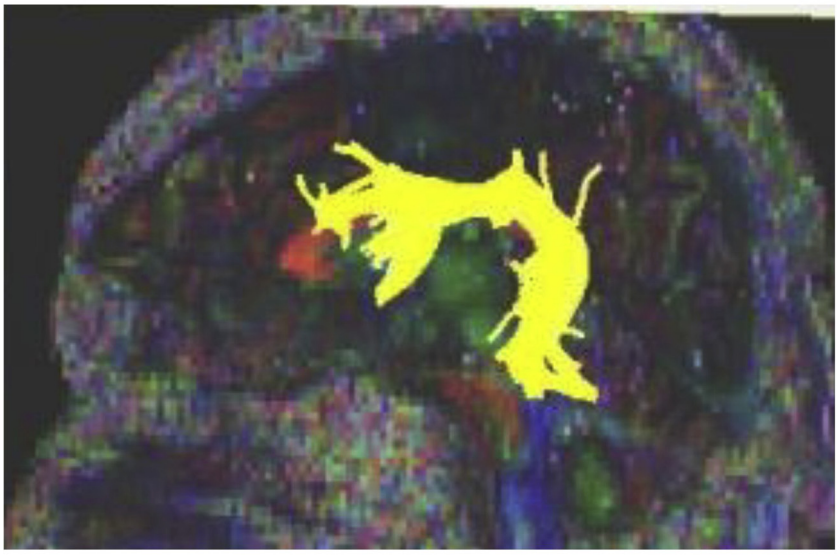
Patients were recruited from out-or inpatient settings into group I and II, as per selection criteria and controls (group III) were recruited from among healthy, non-biological relatives/friends of patients, with a minimum target sample of 30 per group. Assessment instruments were applied in a single session and diffusion tensor MR imaging was done within a week by appointment.

2.4. MRI Data acquisition

MR imaging were performed on a 3 T MR unit (Ingenia; Philips Medical Systems, Netherlands) using a 32-channel head coil. DTI were performed by using a single-shot echo-planar sequence with the array sensitivity – encoding technique. Motion-probing gradient orientations were applied along at least 32 directions, and the b factor was set at 1000s/mm^2. The acquisition parameters used were as follows: TR/TE, 8,000/83.3 ms; bandwidth, 143 kHz; matrix size, 128 × 128; section thickness, 2 mm without intersection gap; FOV, 30 × 30 cm; and NEX,



(a) Left arcuate fasciculus



(b) Left superior longitudinal fasciculus

Fig. 1. (a–b): DTI tracts formed by tractography on DTI studio software.

2.

2.5. MRI Data analysis

The DTI datasets were transferred to a PC with windows platform and were processed using the analysis software DTI studio v3.0 developed and distributed by Prof Mori's laboratory (Godzilla.kennedykrieger.org, 2019). Images were first realigned using the AIR program, in order to remove any potential small bulk motions that occurred during the scans (Woods et al., 1998a, b). Subsequently, all diffusion-weighted images were visually inspected for apparent artefacts due to subject motion and instrumental malfunction. The six elements of the diffusion tensor were calculated for each pixel using multi-variate linear fitting. After tensor diagonalization, three eigen values and eigen vectors were obtained and FA maps were calculated. The eigen vector associated with the largest eigen value were used as an indicator for fibre orientation. In the DTI colour maps, red, green, and blue colours were assigned to right- left, anterior-posterior, and superior-inferior orientations, respectively.

2.6. Fibre tracking and Region of Interest (ROI) drawing strategy

We used tractography-based method to detect minor changes by analysing specific tracts in schizophrenia patients with AH, without AH, and healthy controls. Quantitative tract-based measurements of FA were obtained for two white matter fasciculi bilaterally i.e. AF and SLF.

For 3D tract reconstruction, the fibre assignment by continuous tracking or FACT method (Mori et al., 2019; Xue et al., 1999) were used with FA threshold 0.2 and an inner product threshold of 0.75, which prohibited angles larger than 41° during tracking. The fibre tracking

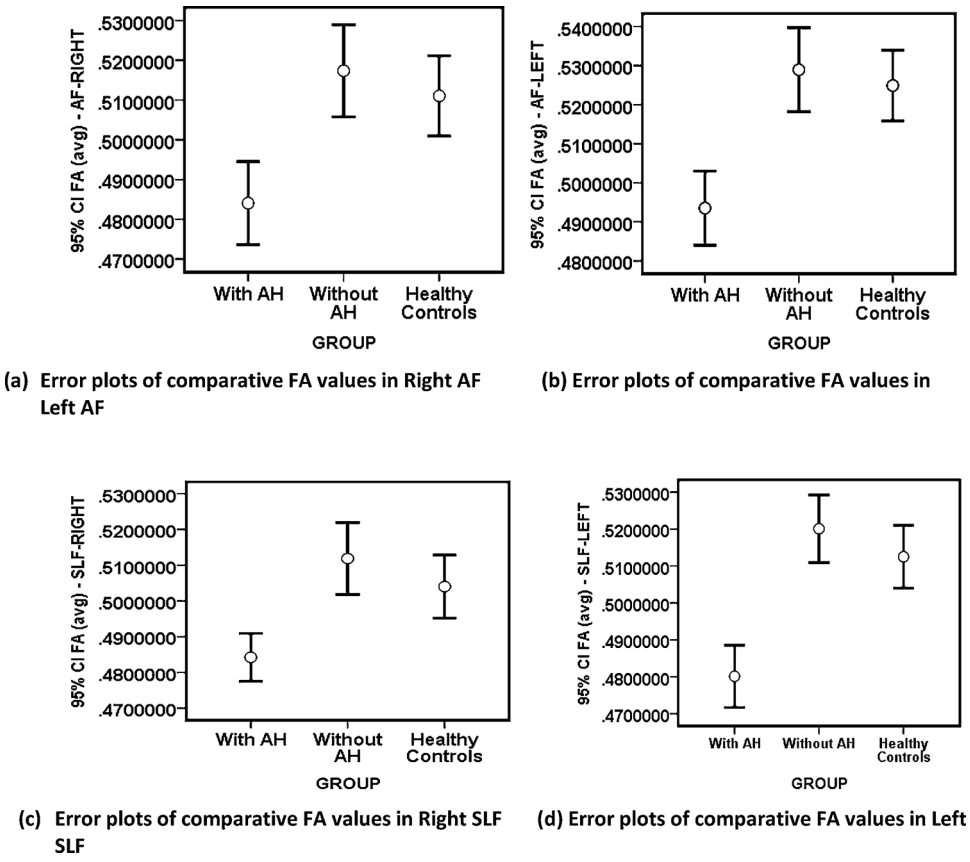


Fig. 2. (a to d): Error plots of comparative FA values in arcuate and superior longitudinal fasciculus between the three groups (with auditory hallucinations (AH), without AH, Healthy controls) depicting significantly lower FA values in group I as compared to group II and III.

was performed on DTI studio v3.0. A multi-ROI approach was used to reconstruct tracts of interest, which exploits existing anatomical knowledge of tract trajectories. Tracking was performed from all pixels inside the brain (brute-force approach) and results penetrating the manually defined ROIs were assigned to the specific tracts associated with the ROIs (Conturo et al., 1999). When multiple ROIs were used for a tract of interest, we employed three types of operations, namely "AND", "CUT", and "NOT", the choice of which depends on the characteristic trajectory of each tract. Individual tracts were then selected by requiring fibres to pass through manually placed ROIs on DTI colour maps, according to protocols specific for each tract in DTI studio v3.0 (Wakana et al., 2007). Any anatomically implausible fibres were removed using exclusion ROIs.

2.7. Statistical analysis

Statistical analysis was carried out using SPSS 20.0. adjusted p values were calculated by Sadik's correction using the formula $[1-(1-\alpha)^{1/n}]$ where $\alpha = 0.05$ (i.e. the p value) and $n = 3$ (i.e. the number of comparisons). FA values were exported from DTI studio and analysed in SPSS similar to what has been carried out in previous studies (Mahapatra et al., 2017; Lim et al., 2017).

3. Results

3.1. Socio-demographic and clinical profile

No significant difference was observed with respect to age, gender, educational qualification, or family income across the three groups (Table 1). The AH and non-AH groups differed significantly in terms of duration of illness (9.6±7.3years, 5.5±4.1years; $U = 331.000$, $p = 0.035$). The score on SAPS was understandably different across AH and non-AH groups (7.1+2.6, 3.5+1.9; $U = 116.500$, $p < 0.001$). There were no significant differences with respect to other clinical variables (Table 2).

3.2. DTI data

Table 3 shows the FA values of different tracts across the three groups. The tracts are depicted in Fig. 1 (a–b) as per tractography technique in DTI studio. Significant differences in FA values were found between the three groups in right SLF ($H = 17.540$; df = 2, $p < 0.001$), left SLF ($H = 32.753$; df = 2, $p < 0.001$), right AF ($H = 17.381$; df = 2, $p < 0.001$), and left AF ($H = 23.357$, df = 2, $p < 0.001$).

Post-hoc pair-wise comparisons showed that FA was significantly lower in schizophrenia patients with AH group compared to schizophrenia patients without AH group which in turn had no significant difference as compared to healthy control group [Fig. 2 (a–d)]. Fig. 2 (a–d) shows the error plots of FA values in SLF and AF across the three groups, depicting significantly lower FA values in group I as compared to group II and III in all the tracts. As can be seen in Fig. 2 (a–d), there is no point of overlap between group I and other two groups depicting significant difference of group I from group II and III. Group II and III overlap as there is no significant difference in FA values between these two groups.

No differences were noted in FA values for gender. The relationship of FA values with sociodemographic and clinical variables was explored within groups I & II. No relationship was found between FA values and age of individuals, severity of psychosis/ hallucinations, total duration of illness or treatment duration.

4. Discussion

To the best of our knowledge, this is the first DTI tractography study from South Asia to examine white matter integrity in schizophrenia subjects with AH, comparing them to those without AH and healthy controls. In the present study, motion-probing gradient orientations were applied along 32 directions, which strengthened its estimation of the DTI parameters (Wakana et al., 2007). A multi-ROI approach was used, to reconstruct tracts of interest based on anatomical knowledge of white matter tracts, which is considered an ideal technique since specific ROIs can be strategically located based on known fibre trajectories.

One of the main findings from the study points to a decreased connectivity in the bilateral AF as well as SLF among schizophrenia patients with AH. Further, the FA values in right AF of schizophrenia patients with AH were decreased by 6.4% and 5.3% compared to patients without AH and healthy controls respectively. The percentage decrease for FA values in left AF of AH group was 7.8% and 6.7% compared to patients without AH and healthy controls respectively. Similar percentage differences for bilateral SLF was 5.4% and 3.9% for right sided tract and 7.7% and 6.3% for left sided tract. Reduced FA coefficients have been reported to be a marker of disruptions in the microstructural integrity of white matter axonal tracts specifically, although these parameters by themselves are insufficient to point towards the cause e.g. loss of myelin etc. of such microstructural disruption (Wakana et al., 2007).

Findings from current study support the evidence from prior studies pointing to alterations in connectivity between frontal and parieto-temporal speech-related areas, including AF (Abdul-Rahman et al., 2012; de Weijer et al., 2013; McCarthy-Jones and Oestreich, 2015). A recent meta-analysis with five DTI studies that compared schizophrenia with AH and healthy controls, gathering a total of 256 DTI data points (106 for AH positive and and 150 for healthy controls), demonstrated a reduced FA in the left AF bundle of schizophrenia patients with AH (Lavigne and Woodward, 2018). The finding of bilaterally reduced FA in SLF as seen in the present study is supported by findings from the previous study by Curcic-Blake and colleagues, which found a reduced FA in bilateral SLF, among other tracts (Ćurčić-Blake et al., 2015). Further, in that study the severity of hallucinations correlated negatively with white matter integrity in the fronto-temporal white matter tracts (Ćurčić-Blake et al., 2015). Another study by Shergill observed that the propensity to experience AH in schizophrenia was associated with relatively increased FA in SLF. Overall, SLF remain less studied in the context of AH (Shergill et al., 2007; Rotarska-Jagiela et al., 2010).

Precise hypothesis for pathogenesis of AH remains a matter of debate, however the disrupted connectivity between frontal and parieto-temporal speech-related areas may likely explain the AH. The dysfunctional networks are hypothesized to be responsible for AH during the generation and monitoring of inner speech (Hubl et al., 2004). During the inner speech, these alterations may lead to abnormal coactivation in regions related to the acoustical processing of external stimuli, which may account for the patients' inability to distinguish self-generated thoughts from external stimulation. Other recent functional neuroimaging studies found a hypercoupling of activity in speech-perception-specific brain networks which may play a role in the generation of AH, though such hypercoupling was found to be specific for perceived speech but not for inner verbal thought generation (Whitford et al., 2012). Others have hypothesized that a poor myelination in frontal white matter fasciculi may result in conduction delays in efference copies triggered by willed actions, leading to delays in suppression of the sensory consequences of the willed actions and consequent ambiguity leading to a significant prediction error. Perception of salience in a self-generated thought or action leads to confusion as to its origins and, consequently responsible for phenomena such as AH (Zhang et al., 2018). However, other studies have shown equivocal findings in this regard (Whitford et al., 2012). AH in schizophrenia may be accompanied by white matter abnormalities in more wide-spread tracts connecting the language, auditory and memory or limbic networks (Psomiades et al., 2016). As the current study focused on pre-selected tracts, it remains unclear if schizophrenia with AH is associated with more global, as opposed to local, FA reductions in the brain.

Findings from present study indicate that a significantly reduced FA in AF and SLF may be a biomarker for AH in patients with schizophrenia. Moreover, there was a higher percentage decrease in the left-sided tracts pointing to a somewhat higher left-sided loss of integrity. It is known that the speech-relevant areas are located in left hemisphere in > 90% of right-handed individuals (Catani et al., 2007; Vernooij et al., 2007).

The FA values in schizophrenia patients without AH were not significantly different from healthy controls. This findings has been variable in the available DTI studies on schizophrenia (Catani et al., 2011; McCarthy-Jones and Oestreich, 2015; Ćurčić-Blake et al., 2015). It is possible that the schizophrenia patients without AH may have white matter disruptions in other brain areas compared to healthy controls, however the focus of present study remained on AF and SLF wherein no significant difference was noted.

From the clinical methodology perspective, available studies have defined the status of AH for study groups in a non-uniform manner. While some authors have constituted the primary group to be having lifetime history of hallucinations (McCarthy-Jones and Oestreich, 2015; Wigand et al., 2015), others have separated current and past history of hallucinations into separate groups (Ćurčić-Blake et al., 2015; Oestreich and McCarthy-Jones, 2016). We used a rigorous criteria for inclusion in the AH group in order to clearly establish the phenomenon to be indeed a hallucination and included current AH to minimize the recall bias, wherein pseudohallucination or other phenomenon might have been misconstrued as AH. Most of the previous studies had a relatively modest sample size (between 39–66), which might reduce the power of the study and limit generalization of the findings (Hubl et al., 2004; Knöchel et al., 2012; Ćurčić-Blake et al., 2015; Wigand et al., 2015; Mulert et al., 2012).

The study has several strengths, like a relatively larger sample, symptom-based approach, rigorous selection criteria, relatively stable diagnosis of schizophrenia (with at least two years of illness duration would most likely allow the neurobiological changes to set in, if they are consequential), utilising 32-channel head coil (which provides better resolution of images) on a 3-tesla MR imaging machine with tractography method of analysing diffusion tensor images. Replication of such studies can assist in identifying the specific areas to be targeted in patients who continue to have persistent AH.

The study findings must be interpreted with certain limitations in mind. The AH group had a relatively longer duration of illness compared to non-AH group, which might have influenced the findings. Presence of another comparator group (e.g. depressive disorder or bipolar disorder with AH) may have helped to study these findings for AH across multiple diagnosis. In DTI Studio, fiber tracking is performed based on deterministic tractography without taking crossing-fiber into considerations, which could potentially affect the findings. Moreover, the investigators analysing the images were not blind to the patients' group status. As the study did not use a whole-brain approach, it remains unclear whether the white matter disruption is specific to these regions or is a part of a global finding. Other possible factors that could influence white matter, including hydration and nutrition, and effect of anti-psychotic medication were not explored. The findings of reduced FA most likely reflect an alteration in white matter connectivity, and it is difficult to interpret the physiological significance of these findings. The specific cellular abnormalities that underlie differences in FA cannot be concluded from this study. The accuracy of the diffusion tensor and, in turn, the reliability of the data derived from it are influenced by the signal-to-noise ratio, image resolution, image distortion due to magnetic susceptibility effects, and motion artefacts. All four factors are interrelated and are influenced by the acquisition parameters (including the field strength and number of directions) (Sexton

et al., 2009). Also, while the findings were significant in whole SLF and one sub-part of it, it was not feasible to study other sub-parts in the current study due to logistics. It would be worthwhile to see in further studies if whole SLF is affected or only the part connecting the language areas.

To summarize, what has emerged from this study is a reduced integrity of select white matter tracts in schizophrenia patients with AH in comparison to those without AH and healthy controls. The low FA in AF and SLF should be investigated as a potential marker for AH in schizophrenia. Future research needs to replicate these findings in larger samples and in diverse clinical populations. Such studies might help to determine the potential targets for interventions in patients with persistent AH and might open the possibilities of subtyping of schizophrenia in newer ways.

Author contribution

Nishtha Chawla: Conception and design of study, acquisition of data, analysis of data, drafting the manuscript and figures, manuscript editing

Raman Deep: Conception and design of study, acquisition of data, drafting the manuscript and figures, manuscript editing.

Sudhir K. Khandelwal: Conception and design of study, acquisition of data, drafting the manuscript and figures, manuscript editing.

Ajay Garg: Conception and design of study, acquisition of data, drafting the manuscript and figures, manuscript editing.

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Declaration of Competing Interest

There is no conflict of interest to declare for any of the authors.

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Appendix A. Supplementary data

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