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Structural integrity of grey and white matter in schizophrenic patients by diffusion tensor imaging

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Abstract

Background Schizophrenia is a chronic disabling mental illness. A novel magnetic resonance imaging (MRI) technique known as diffusion tensor imaging (DTI) is a non-invasive and does not need external contrast materials. It is capable of identifying anomalies in the white matter micro-structure of the brain. This work conducted the DTI in schizophrenic patients to evaluate altered structural integrity in grey and white matter.

Methods This prospective case control study was conducted on 25 schizophrenic patients selected from neuropsychiatric department, and 25 age/sex-matched healthy controls.

Results Schizophrenic patients showed diminished fractional anisotropy in fornix, corpus callosum, right cingulum, right superior and inferior occipito-frontal fasciculi. Increased mean diffusivity in right inferior occipito-frontal fasciculus, corpus callosum, right thalamus and right basal ganglia were noted in schizophrenic patients. Fractional anisotropy and mean diffusivity had a predictive value for detection of schizophrenic patients.

Conclusions DTI of white and grey matter tracts is considered a promising tool for diagnosis of schizophrenic patients which usually have prolonged illness, chronic course and poor outcome.

Keywords Schizophrenia, Diffusion tensor imaging, Fractional anisotropy (FA), Mean diffusivity (MD), Apparent diffusion coefficient (ADC)

Background

Hallucinations, delusions, and erratic behavior are hallmarks of schizophrenia, which is a chronic, incapacitating mental condition that places a significant load on healthcare resources. Even though schizophrenia has been the subject of much study, its pathophysiology is still unknown, in part because the illness is so heterogeneous and complicated [1].

Antipsychotic medication, substance usage, medical comorbidities (especially diseases linked to second-generation antipsychotics), and perhaps exacerbated aging impacts have all been long-term influences on individuals with chronic schizophrenia [2].

The pathophysiology of schizophrenia is complicated and involves several mechanisms that are dysregulated [3].

Schizophrenia affects the glutamatergic, dopaminergic, and gamma-aminobutyric acid (GABAergic) neurotransmitter systems, and interactions among these receptors play a role in the pathogenesis of the illness [4].

Diffusion tensor imaging (DTI), which measures water molecule diffusion, has made it possible to examine neural micro-structures in vivo [5].

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The Brownian motion hypothesis states that water molecule diffusion is isotropic. However, because of the cellular micro-structures in the brain, the mobility of molecules of water is anisotropic and may vary as a result of micro-structural alterations [6].

A relatively new method of neuro-imaging called DTI may be utilized to study the in vivo micro-structures of white matter. In order to evaluate the claim that DTI can distinguish between variations in the white matter of schizophrenic individuals and healthy control people, research on schizophrenia were conducted [7].

The purpose of this work conducted the DTI in schizophrenic patients to evaluate altered structural integrity in grey and white matter.

Methods

Study population

This prospective, case–control work was performed from January 2022 to December 2022 following permission from local Research Ethics Committee in our institute, on non-randomized sample of 25 schizophrenic patients who were drug naïve or patients who stopped their medication about 3 months prior to the time conducting the study, selected from neuropsychiatric department. Control group of twenty-five healthy persons with no medical or neurological disorders by history and examinations were selected (correlating to age and sex patients' group), all patients and healthy subjects provided written informed permission.

Inclusion criteria

Patients who clinically diagnosed as primary idiopathic schizophrenia or secondary to other organic lesions in the brain were included.

Exclusion criteria

In this study, patients who had metallic devices that are incompatible to MRI machine and patient with other mental psychiatric disorder were excluded. Also, this excluded patients who refused or their guardians to undergo the examination, claustrophobic patients from MRI machine and severely agitated irritable patients.

Data collection

MRI assessment by using MRI unit (General Electric, GE, healthcare, Chicago, Illinois, U.S.) 1.5 Tesla, to reduce participant movements, all participants were assessed while lying supine with a head-coil and a head supported cushion in place. The patient removed all metal objects like pins and earrings. Coronal, axial, and sagittal planes were taken. The matrix was 256 × 256, the field of vision was 220–240 mm, and the thickness of the slice had been 6 mm. Protocol for MRI was offered: Axial T1WI (TR 450 m/s and TE 15) axial and sagittal T2WI (TR 3612 m/s and TE 100 m/s) axial and/or coronal oblique FLAIR: (TR 6000, m/s and TE 120 m/s). DTI was performed using a single shot, spin-echo echo-planar sequencing with 60 encoding directions, a diffusion weighing factor of 800 s/mm2, TR and TE speeds of 10,951 m/s and 67 m/s, 2 excitations, 2 mm slice thickness, and a flip angle of 90°.

Data processing and analysis

Transferring all the diffusion tensors to the workstations. GE program designed for obtaining: Color orientations, apparent diffusion coefficient (ADC), fractional anisotropy (FA), and mean diffusivity maps was used to post-process images. The direction and architecture of the tracts are visible in the directionally encoded FA maps, wherein each of the 3 orthogonal planes is represented by a distinct color, with red representing right-to-left tracts, green representing antero-posterior tracts, and blue representing cranio-caudal tracts. The creation of a 7 display of tracts. A ROI (or seed) was established (placed) along the path of the tract in the (sagittal, axial, or coronal) plane to create 7 fiber tracts, color orientation maps, FA maps, ADC maps and mean diffusivity maps in single or consecutive sections. Regions of interest (ROIs) were drawn within identifiable white matter tracts affected and grey matter by schizophrenia, avoiding grossly cystic and necrotic regions. Color-coded DTI maps were analyzed, comparing the FA, ADC and mean diffusivity values with the same tracts in normal cases. Radiologists with more than 5 years' experience measured all previous parameters on work station.

Statistical study

The SPSS version 26 for Windows (IBM Corp., Armonk, New York, USA) was used for statistical analysis. The Shapiro–Wilk test for normality was run on quantitative data. When comparing two groups, the independent samples T test was used. Numerical parameters with a normal distribution were described as mean ± standard deviations (SD). The Mann–Whitney test was used to compare two sets of numerical parameters that didn't have a normal distribution. Median and interquartile range (IQR) were used to summarize these numerical data. The rank order correlation method of Spearman was used to examine correlations among parameters. Frequency (count and percentage) summaries were used to represent categorical parameters. Fisher's exact, Fisher–Freeman–Halton exact, or Pearson's Chi-square test for independence were used to analyze the relationships between categorical parameters. A receiver operating characteristics (ROC) curve analysis was performed to identify the measurements that significantly diagnosed cases and the optimal cutoff values. The significance level

was adopted at a p value < 0.05 For interpreting statistical test findings.

Results

No substantial variation among schizophrenic groups and control group as regards to sociodemographic data. The age of schizophrenic patients in this study ranged from 18–48 years with the median and interquartile range (IQR) 30.5 ± 8.8 years. While the age of control group ranged from 20 to 45 years with the median and interquartile range 31.6 ± 7.1 years. Schizophrenia male patients were (72%) and female patients (28%). About half of cases were smoker. The majority of cases were single (44%). Most of the studied cases had no family history of psychiatric diseases or history of addiction (Table 1).

Substantial variations were existed among schizophrenic patients and control group in fractional anisotropy of fornix, corpus callosum, right cingulum and both right superior and inferior occipito-frontal fasciculi (p value < 0.001). Comparing apparent diffusion coefficient and mean diffusivity between schizophrenic patients and control group showed no significant differences except in mean diffusivity of corpus callosum, right inferior occipito-frontal fasciculi, right thalamus and right basal ganglion (Table 2 and Fig. 1). Regarding fractional anisotropy of the fornix, corpus callosum and right cingulum of schizophrenic group had median values and interquartile range 0.48 [0.45–0.49], 0.40 [0.38–0.45] and 0.34 [0.30–0.38], respectively.

In the current study the median and interquartile range of fractional anisotropy, apparent diffusion coefficient and mean diffusivity values in right superior occipito-frontal fasciculus of schizophrenic patients were 0.33 [0.31–0.35], 0.81 [0.75–0.88] × 10^{-3} mm^2/s and 2.50 [2.10–3.00] × 10^{-9} mm^2/s and right inferior occipito-frontal fasciculi were 0.33 [0.30–0.37], 0.80 [0.78–0.84] × 10^{-3} mm^2/s and 2.70 [2.29–3.20] × 10^{-9} mm^2/s, respectively (Table 2 and Fig. 2).

Table 1 Comparison of sociodemographic characteristics of the studied patients (n:50)

	Groups				Tests of significance	
	Control (n = 25)		Patients (n = 25)		Test statistic	*p* value
Age (years)						
Median [IQR]	31.6 ± 7.1		30.5 ± 8.8		t = 0.475	0.637
Min–Max	20.0–45.0		18.0–48.0			
Gender						
Male	14	56.0%	18	72.0%	X^2_{ChS} = 1.389	0.239
Female	11	44.0%	7	28.0%		
Occupational						
No	14	56.0%	13	52.0%	X^2_{ChS} = 0.081	0.777
Yes	11	44.0%	12	48.0%		
Educational						
No	12	48.0%	14	56.0%	X^2_{ChS} = 0.321	0.571
Yes	13	52.0%	11	44.0%		
Marital status						
Single	10	40.0%	11	44.0%	X^2_{ChS} = 0.114	0.944
Married	8	32.0%	7	28.0%		
Divorced	7	28.0%	7	28.0%		
Family history of psychiatric disease						
No	21	84.0%	18	72.0%	X^2_{ChS} = 1.049	0.306
Yes	4	16.0%	7	28.0%		
Smoker						
No	12	48.0%	12	48.0%	X^2_{ChS} = 0.000	1.000
Yes	13	52.0%	13	52.0%		
Addiction						
No	21	84.0%	17	68.0%	X^2_{ChS} = 1.754	0.185
Yes	4	16.0%	8	32.0%		

Max maximum, *Min* minimum, *n* number, *IQR* interquartile range, *t* Independent samples *T* test, X^2_{ChS} Pearson's Chi-square test, X^2_{FFH} Fisher–Freeman–Halton exact test, Significance level is adopted at $p \leq 0.05$

Table 2 Comparison between Schizophrenic patients and control group regarding fractional anisotropy, apparent diffusion coefficient and mean diffusivity values of fornix, corpus callosum, right cingulum and right superior & inferior occipito-frontal fasciculi (n: 50)

	Groups		**Mann–Whitney test**	
	Control (n = 25)	**Patients (n = 25)**	**Z**	***p* value**
Fornix				
Fractional anisotropy				
Median [IQR]	0.48 [0.45–0.49]	0.25 [0.24–0.30]	6.085	< 0.001*
Min–Max	0.44–0.58	0.20–0.42		
Apparent diffusion coefficient × 10^{-3} mm^2/s				
Median [IQR]	1.90 [1.60–1.98]	1.88 [1.60–1.^{97}]	0.410	0.682
Min–Max	1.45–2.12	1.33–2.05		
Mean diffusivity × 10^{-9} mm^2/s				
Median [IQR]	4.80 [4.00–5.00]	4.30 [3.80–5.87]	0.253	0.800
Min–Max	2.00–6.50	2.38–6.74		
Corpus callosum				
Fractional anisotropy				
Median [IQR]	0.65 [0.58–0.69]	0.40 [0.38–0.45]	6.072	< 0.001*
Min–Max	0.55–0.73	0.20–0.50		
Apparent diffusion coefficient × 10^{-3} mm^2/s				
Median [IQR]	2.00 [1.88–2.01]	1.90 [1.50–2.00]	1.674	0.094
Min–Max	1.60–2.80	1.30–2.50		
Mean diffusivity × 10^{-9} mm^2/s				
Median [IQR]	4.00 [3.20–4.20]	5.67 [5.40–6.65]	6.069	< 0.001*
Min–Max	2.80–4.60	4.96–9.80		
Right cingulum				
Fractional anisotropy				
Median [IQR]	0.58 [0.55–0.62]	0.34 [0.30–0.38]	6.069	< 0.001*
Min–Max	0.52–0.68	0.24–0.50		
Apparent diffusion coefficient × 10^{-3} mm^2/s				
Median [IQR]	0.89 [0.85–0.95]	0.86 [0.78–0.92]	1.680	0.093
Min–Max	0.75–1.05	0.70–1.02		
Mean diffusivity × 10^{-9} mm^2/s				
Median [IQR]	2.50 [2.00–3.00]	2.55 [2.30–3.00]	0.253	0.800
Min–Max	1.50–3.50	1.88–5.47		
Right superior occipito-frontal fasciculus				
Fractional anisotropy				
Median [IQR]	0.55 [0.52–0.58]	0.33 [0.31–0.35]	6.078	< 0.001*
Min–Max	0.50–0.62	0.25–0.46		
Apparent diffusion coefficient × 10^{-3} mm^2/s				
Median [IQR]	0.84 [0.79–0.89]	0.81 [0.75–0.88]	1.090	0.276
Min–Max	0.75–1.25	0.70–1.40		
Mean diffusivity × 10^{-9} mm^2/s				
Median [IQR]	2.50 [2.00–2.80]	2.50 [2.10–3.00]	0.759	0.448
Min–Max	1.6–3.6]	1.9 -3.93		
Right inferior occipito-frontal fasciculus				
Fractional anisotropy				
Median [IQR]	0.58 [0.56–0.60]	0.33 [0.30–0.37]	6.079	< 0.001*
Min–Max	0.55–0.68	0.29–0.51		
Apparent diffusion coefficient × 10^{-3} mm^2/s				
Median [IQR]	0.80 [0.78–0.86]	0.80 [0.78–0.84]	0.409	0.682
Min–Max	0.76–1.20	0.73–1.09		
Mean diffusivity × 10^{-9} mm^2/s				
Median [IQR]	1.50 [1.33–1.60]	2.70 [2.29–3.20]	5.612	< 0.001*
Min–Max	1.20–2.90	1.94–4.53		

Table 2 (continued)

IQR interquartile range (25th–75th percentiles), *Max* maximum, *Min* minimum, *n* number

*Significant at $p \leq 0.05$

(See figure on next page.)

Fig. 1 A single female patient aged 22 years, patient came with neglected appearance suffering from lack of attention, insomnia and social withdrawal, her last attack was from 9 months and she stopped psychiatric treatment from 7 months. DTI Finding: (**A**) Sagittal color coded map of corpus callosum and fornix, (**B**) Sagittal color coded map of the right inferior occipito-frontal fasciculus. (**C**, **D**) Sagittal fractional anisotropy maps of fornix and corpus callosum with decreased FA values measuring 0.27, 0.41, respectively. (**E**) Sagittal fractional anisotropy maps of right occipito-frontal fasciculus with decreased FA values measuring 0.34, (**F**) Sagittal apparent diffusion coefficient map of fornix with no changes in its value measuring 1.66×10^{-3} mm^2/s. (**G**) sagittal images of diffusion coefficient, mean diffusivity of right inferior longitudinal fasciculus show increasing in mean diffusivity value measuring 3.2×10^{-9} mm^2/s

In grey matter, the fractional anisotropy of right thalamus and right basal ganglion, the median and interquartile range of schizophrenic patients were0.25 [0.22–0.28] and 0.20 [0.19–0.22] respectively versus control group 0.25 [0.20–0.32] and 0.25 [0.20–0.30] respectively (Table 3). Apparent diffusion coefficient of schizophrenic patients was 0.85 $[0.77–0.90] \times 10^{-3}$ mm^2/s for right thalamus and 0.78 $[0.76–0.84] \times 10^{-3}$ mm^2/s for right basal ganglion. Moreover, mean diffusivity of schizophrenic patients was 3.10 $[2.80–3.44] \times 10^{-9}$ mm^2/s for right thalamus and 3.00 $[2.84–3.49] \times 10^{-9}$ mm^2/s for right basal ganglion. There were substantial variations among schizophrenic patients and control group in fractional anisotropy of right basal ganglion (p value < 0.050) and mean diffusivity of both right thalamus and right basal ganglion (p value < 0.001) as shown in table (3) and Figs. 3, 4).

In the current study, there was no significant comparative correlation of apparent diffusion coefficient, fractional anisotropy, and mean diffusivity between white and grey matter in schizophrenic patients (Table 4).

ROC curve was plotted for all the measured apparent diffusion coefficient, fractional anisotropy, and mean diffusivity in different areas of white and grey matter to predict schizophrenic patients. ROC curve of fractional anisotropy revealed significant differences ($p < 0.001$) of fornix, corpus callosum, right cingulum, right superior occipito-frontal fasciculus and right inferior occipito-frontal fasciculus that cutoff values were $\leq 0.42, \leq 0.5, \leq 0.41, \leq 0.39$ and ≤ 0.51, respectively. The area under curve of the previous parameters were 0.924, 0.932, 0.910, 0.881 and 0.970, respectively. These parameters exhibited high accuracy in predicting schizophrenic patients with 96%, 96%, 92%, 92% and 92% of sensitivity (respectively). Moreover, area under curve and cutoff values of fractional anisotropy were (0.661 and 0.27) in right basal ganglion with p: < 0.048, respectively (Table 5).

Regarding to ROC of apparent diffusion coefficient, no substantial variations were existed among all parameters for prediction schizophrenic patients.

To predict of schizophrenic patients by receiver operating characteristic ROC curves, there were significant differences ($p < 0.001$) of mean diffusivity in corpus callosum, right inferior occipito-frontal fasciculus, right thalami and right basal ganglion. The sensitivity and specificity of mean diffusivity in corpus callosum (90% and 84%), right superior occipito-frontal fasciculus (40% and 76%), right inferior occipito-frontal fasciculus (96% and 88%), right thalamus (96.0% and 72%) and right basal ganglion (76% and70%), as shown in Table (5).

Discussion

Schizophrenia is the most common functional psychotic disease. Individuals with this disorder may be presented with a variety of manifestation (e.g., Delusions, hallucination, and dis-organization) cognitive and motivational dys-functions [8].

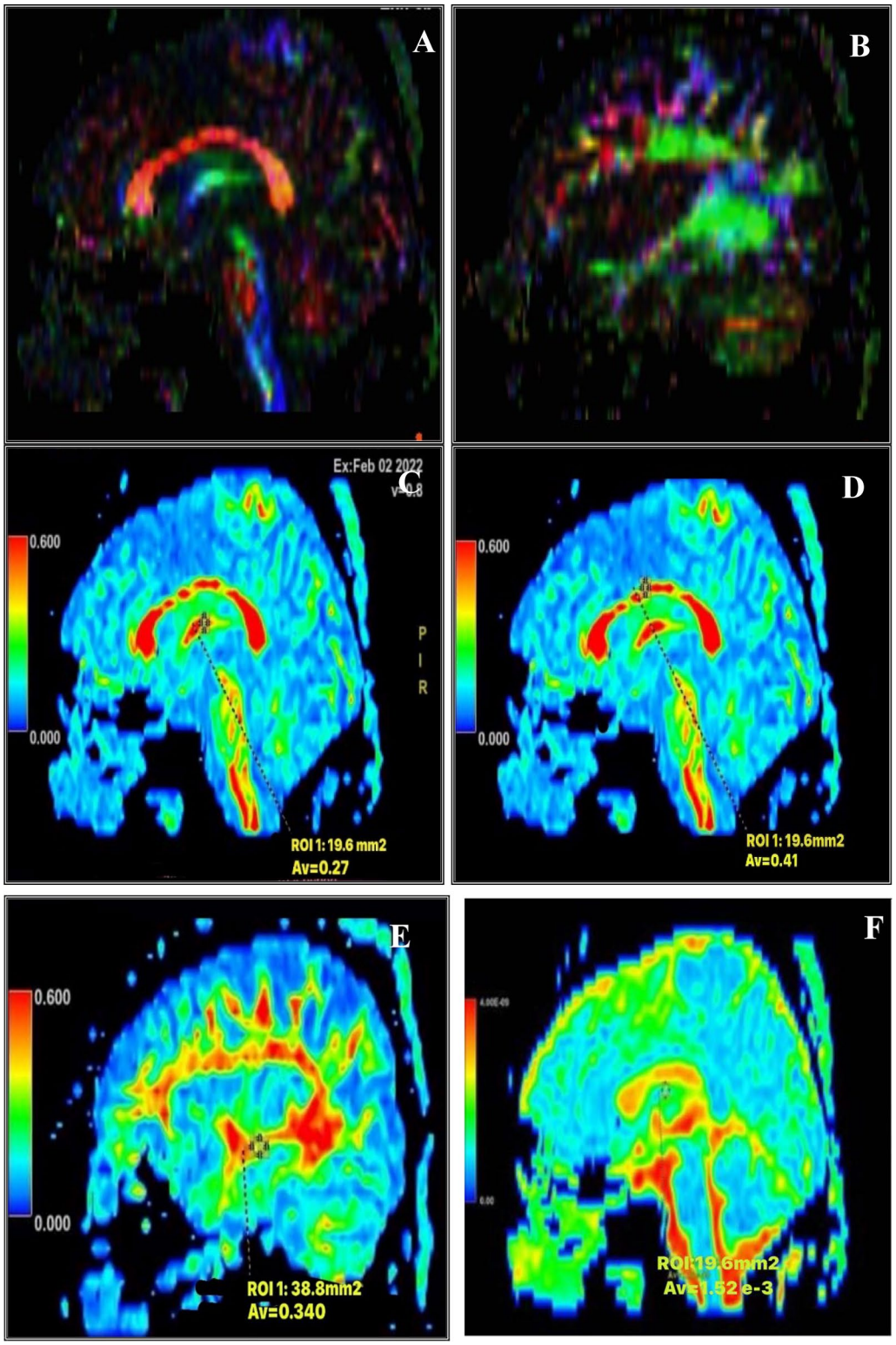

Fig. 1 (See legend on previous page.)

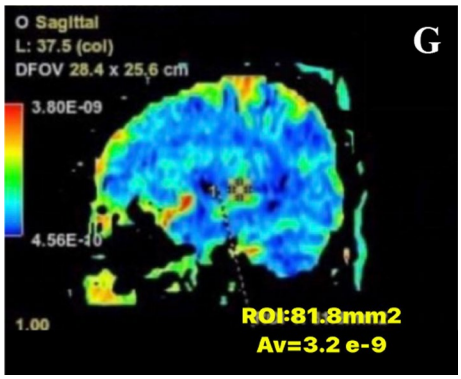

Fig. 1 continued

The aim of this study conducted the DTI in schizophrenic patients to evaluate altered structural integrity in grey and white matter.

Schizophrenic patients who did not receive any treatment or patients who stopped their medication about 3 months prior to the time conducting the study (not receiving antipsychotic medications) to exclude the effect of medications on clinical manifestations and DTI results.

In the current study, there were no substantial differences among schizophrenic and control group regarding the sociodemographic data. These findings may be attributed to selection of control group correlated schizophrenic group. Excluded patients were above 50 years to minimize the probability of associated vascular changes or involutional brain changes that may influence the DTI results [9].

In the current study, most of the studied cases had no family history of psychiatric diseases this finding inconsistence with Nuhu et al. [10] who said that early onset schizophrenia is associated with strong genetic predisposition, this may be explained by Egyptian community who refusing acceptance of mental illness and consider it as stigma. Moreover, most of patients in this study had no history of addiction while substance use problems are widespread in individuals with schizophrenia and significantly exacerbate their overall clinical course, according to Khokhar et al. [11]. Abusing drugs is a substantial risk factor for psychosis, according to Green and Glausier [12], but additional environmental and biological variables also affect the likelihood of becoming schizophrenic. Educated patients in this study represented by 44% and 48% only of schizophrenic group had a job. These findings may be explained by Martini et al. [13] who mentioned in their research that people with milder symptoms had a better chance of obtaining a job.

The majority of cases were single 44% while both married and divorced represented by 28% for each, Li [14] demonstrated that people with schizophrenia who live in communities have a greater risk of social disorder if they have a negative marital situation. Considerations of public health investments in the prevention and treatment of mental illnesses should take these impacts into account.

In the present study, fractional anisotropy in fornix, corpus callosum, right cingulum, right superior and inferior occipito-frontal fasciculi were decreased in schizophrenic group. This schizophrenic disease's etiopathogenesis is still not completely known. A general drop in brain volume, initially in the temporal-lobe and later in the parietal and frontal lobes, enlarged ventricular space, and a reduction in white matter volume were all seen in MRI investigations on individuals suffering from schizophrenia [15]. Histopathological assessments appear to support this, as post-mortem examinations of schizophrenia patients have revealed decreased numbers of neuroglia cells, issues with their structure of myelin sheath, deterioration in the mitochondria, decreased presynaptic follicles, and neural atrophy [16].

The temporal cortex, the prefrontal cortex, and their connecting fibers play an essential component in the etiology of schizophrenia, according to several investigations. The prefrontal cortex is in a unique position to regulate a wide range of cognitive processes, including working memory, declarative memory, rule-learning, making plans, solving problems, recognizing novel stimuli, consideration control, motivational control, language control, suppression of reactions, making decisions, control of emotions, and social cognition. This is due to the prefrontal cortex's profound connections with nearly all cortical and sub-cortical areas [17]. The inferior fronto-occipital fasciculus, cingulum, anterior thalamic-radiations, fornix, arcuate fasciculus, and uncinate fasciculus are the primary white matter fibers that link the pre-frontal cortex to other regions of the cerebrum. Schizophrenia's etiopathogenesis may be significantly impacted by structural and functional issues within

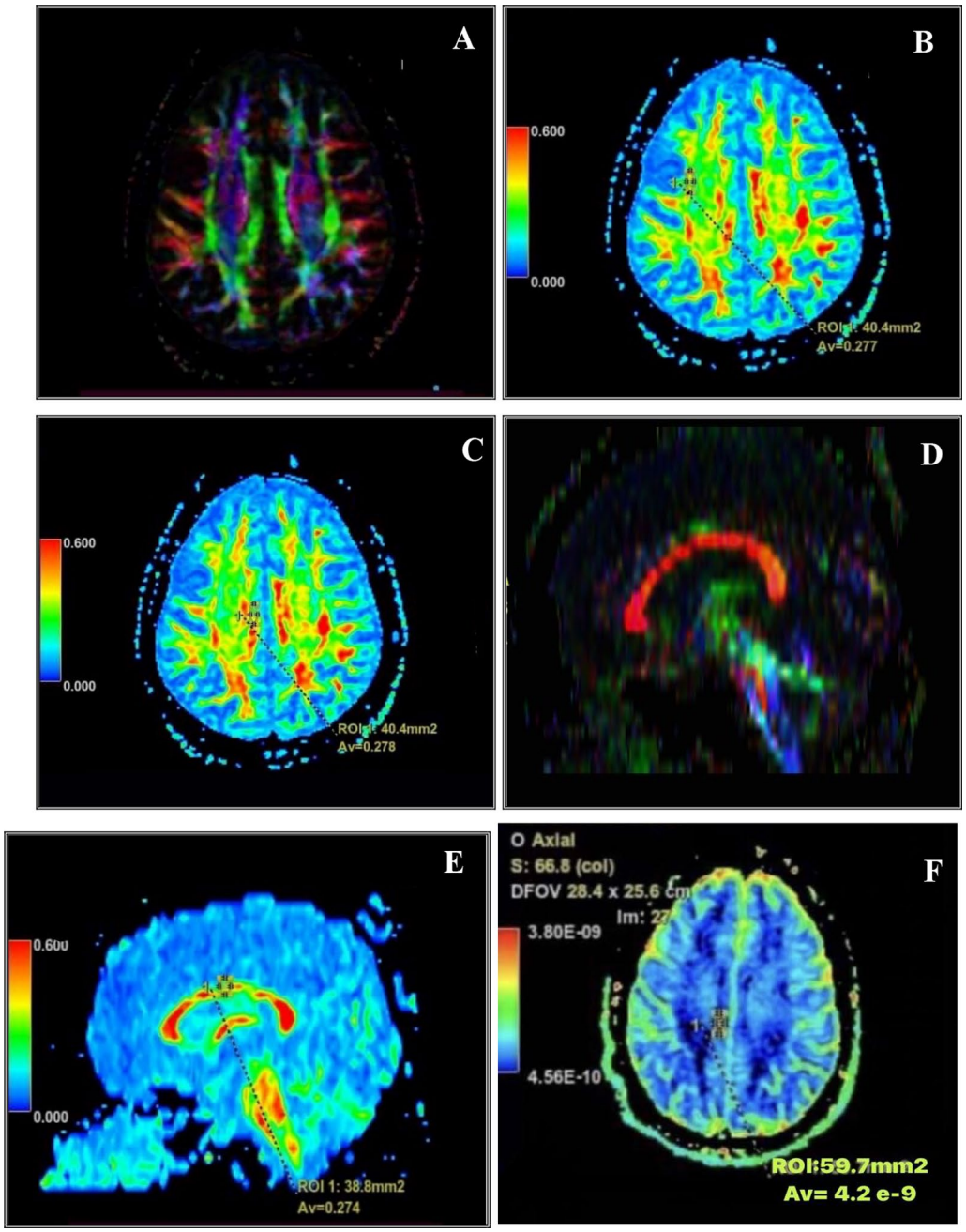

Fig. 2 Twenty-eight female patient who had psychic trauma after failure in collage from 5 years, she admitted with social isolation and disorganized speech and flat effect she stopped her treatment from 5 month and her last attack was from 9 months. DTI Finding: Affection of right cingulum, right superior occipito-frontal fasciculus and corpus callosum. (**A**) Axial color coded maps of both cingulum and superior occipito-frontal fasciculi, (**B**) Axial fractional anisotropy maps of the right superior occipito-frontal fasciculus showing decreased Fa value measuring 0.27. (**C**) Axial fractional anisotropy maps of the right cingulum with decreased FA value 0.278, (**D**) Sagittal color coded maps of corpus callosum, (**E**) decreased FA value of corpus callosum in sagittal fractional anisotropy maps measuring 0.274. (**F**) axial mean diffusivity map of right cingulum showing increasing in its value measuring 4.2×10^{-9} mm^2/s

these frameworks [18, 19]. According to Kelly et al. [7] decreased FA in coherent fiber bundles might signify aberrant fiber packing or coherence, or it could indicate problems with axonal integrity and/or myelination. Wu et al. [20] considering that FA could indicate the connection of the nerve fibers in the brain's white matter, a decrease in FA denotes impairment to the integrity of the localized brain white matter and a decrease in nerve fiber

Table 3 Comparison between schizophrenic patients and control group regarding fractional anisotropy, apparent diffusion coefficient and mean diffusivity values of right thalami and right basal ganglia

	Groups		Mann–Whitney test	
	Control (n = 25)	Patients (n = 25)	Z	*p* value
Right thalamus				
Fractional anisotropy				
Median [IQR]	0.25 [0.20–0.32]	0.25 [0.22–0.28]	0.897	0.370
Min–Max	0.20–0.39	0.17–0.37		
Apparent diffusion coefficient $\times 10^{-3}$ mm^2/s				
Median [IQR]	0.89 [0.79–0.93]	0.85 [0.77–0.90]	1.371	0.170
Min–Max	0.75–1.01	0.70–0.97		
Mean diffusivity $\times 10^{-9}$ mm^2/s				
Median [IQR]	2.30 [2.00–2.70]	3.10 [2.80–3.44]	5.167	< 0.001*
Min–Max	1.80–3.00	2.50–3.80		
Right basal ganglion				
Fractional anisotropy				
Median [IQR]	0.25 [0.20–0.30]	0.20 [0.19–0.22]	1.961	0.050*
Min–Max	0.12–0.35	0.08–0.27		
Apparent diffusion coefficient $\times 10^{-3}$ mm^2/s				
Median [IQR]	0.80 [0.76–0.88]	0.78 [0.76–0.84]	0.934	0.350
Min–Max	0.75–1.20	0.71–0.99		
Mean diffusivity $\times 10^{-9}$ mm^2/s				
Median [IQR]	1.80 [1.50–2.20]	3.00 [2.84–3.49]	5.981	< 0.001*
Min–Max	1.20–2.70	2.50–4.20		

IQR interquartile range (25th–75th percentiles), *Max* maximum, *Min* minimum, *n* number

*Significant at $p \leq 0.05$

connections. Prior study has demonstrated that the middle frontal lobe (complex of the hippocampus-amygdala and entorhinal cortex), the hippocampal sulcus, the superior frontal gyrus, the frontal lobe, the corpus callosum and the cingulate gyrus are the primary structure areas where individuals with schizophrenia have abnormalities.

In our research, corpus callosum and right inferior occipito-frontal fasciculi mean diffusivity in schizophrenia individuals raised. In 2015, Spalletta et al. [21], observed that MD was higher in those with schizophrenia than in controls. It is interesting to note that the higher MD in schizophrenia was caused by both slightly higher axial and radial diffusivity. Furthermore, Scheel et al. [22] discovered that schizophrenia also had higher radial diffusivity. Scan results from structural MRIs that focused on myelin water fractions revealed signs of demyelination. Decreased speed of processing may be linked to decreased diffusion characteristics in schizophrenia, which has been found to be impacted by defective myelination, which affects the transport of information throughout the brain. Therefore, structural anomalies may have a distinct influence on the functional deficits in schizophrenia [23, 24].

As regards ADC value there was no significant changes has found in all examined tracks in this study, between schizophrenic patients and control cases, ADC alterations are not a reliable indicator of abnormalities in the grey or white matters in schizophrenia, according to several studies. Fractional anisotropy (FA) alterations may be a more accurate sign of white matter dysfunction in this condition than alterations in other metrics [25].

In the current study, there was no significant correlation of fractional anisotropy between white and grey matter in schizophrenic patients. Martinez-Heras et al. [25] mentioned that the ideas of non-isotropic and isotropic diffusion serve as the basis for DTI. Water molecules flow in each of the 3 directions. Isotropic diffusion happens whenever molecules of water spread out evenly in each of the 3 directions, while anisotropic diffusion occurs when they spread out unequally. Free molecules of water travel in an isotropic manner in white matter. This is due to the fact that in the tracts of the white matter, the myelin sheath that surrounds the white matter allows the molecules of water to travel lesser perpendicular and further along a fiber bundle's long axis. Maximal diffusivity correlates with the direction of the white matter fiber tract.

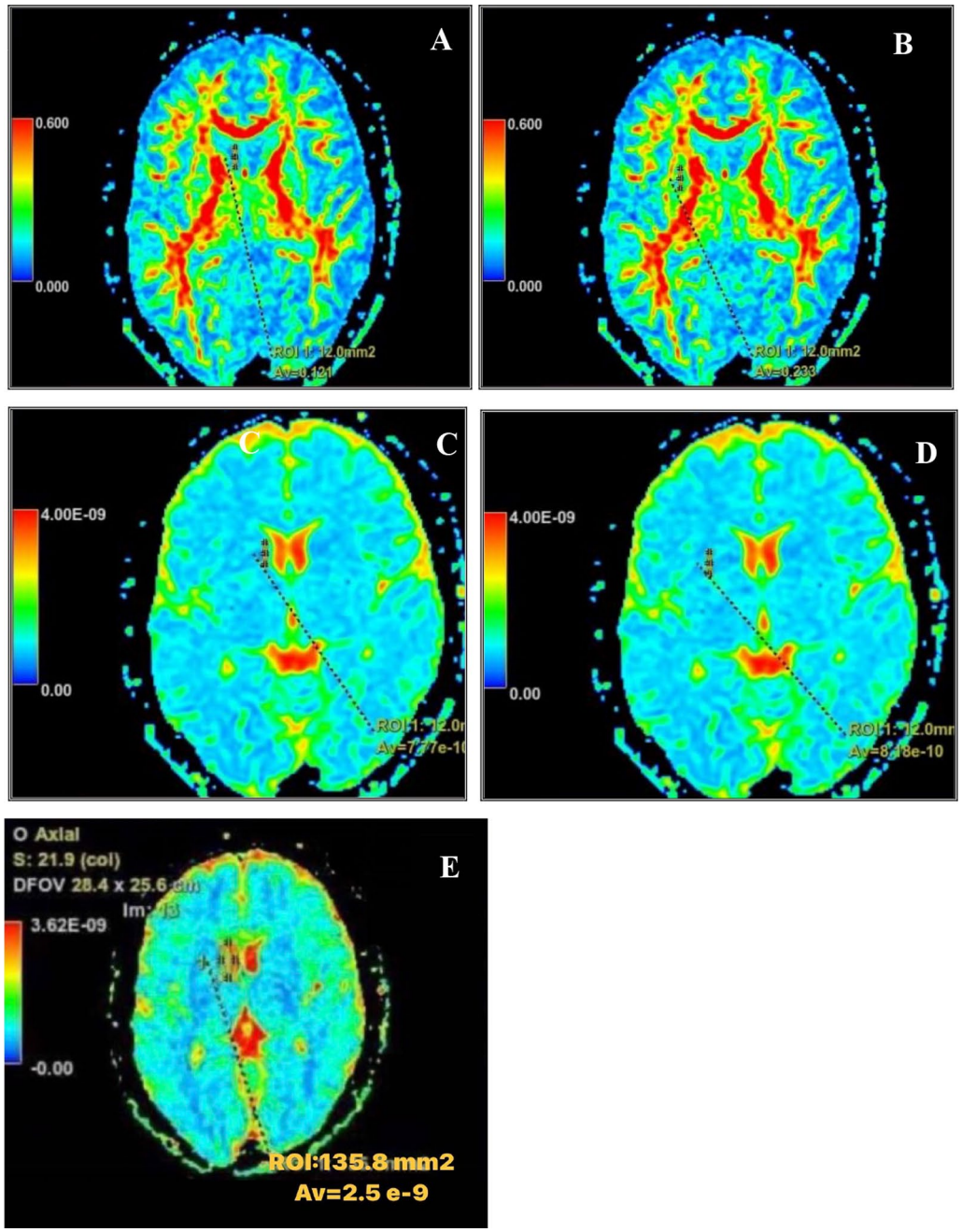

Fig. 3 A single female patient aged 43 years, came with attack of disorganized speech, aggression and grandiosity she was diagnosed with schizophrenia from 5 years, her last attack was from 2 years and she stopped her treatment from 7 months. DTI Finding: Affection of Right basal ganglion and right arcuate fasciculus fibers. **A**, **B** Axial fractional anisotropy maps of the right caudate and putamen nuclei with decreasing values measuring 0.121 and 0.233 respectively, **C**, **D** average values of the right caudate and putamen nuclei in axial apparent diffusion coefficient maps measuring (0.77 and 0.81) $\times 10^{-3}$ mm2/s. **E** Axial image of diffusion coefficient of mean diffusivity map of the right caudate with average values measuring 2.5×10^{-9} mm^2/s

DTI detects the spreading of molecules of water in tissues, which may happen either unrestrictedly (i.e., in an isotropic fashion) or restrictedly (i.e., in an anisotropic manner) by certain barriers, such as cell membranes. Most often, fractional anisotropy (FA), radial diffusivity, mean diffusivity (MD), and axial diffusivity are used to measure diffusion. DTI enables the reconstruction,

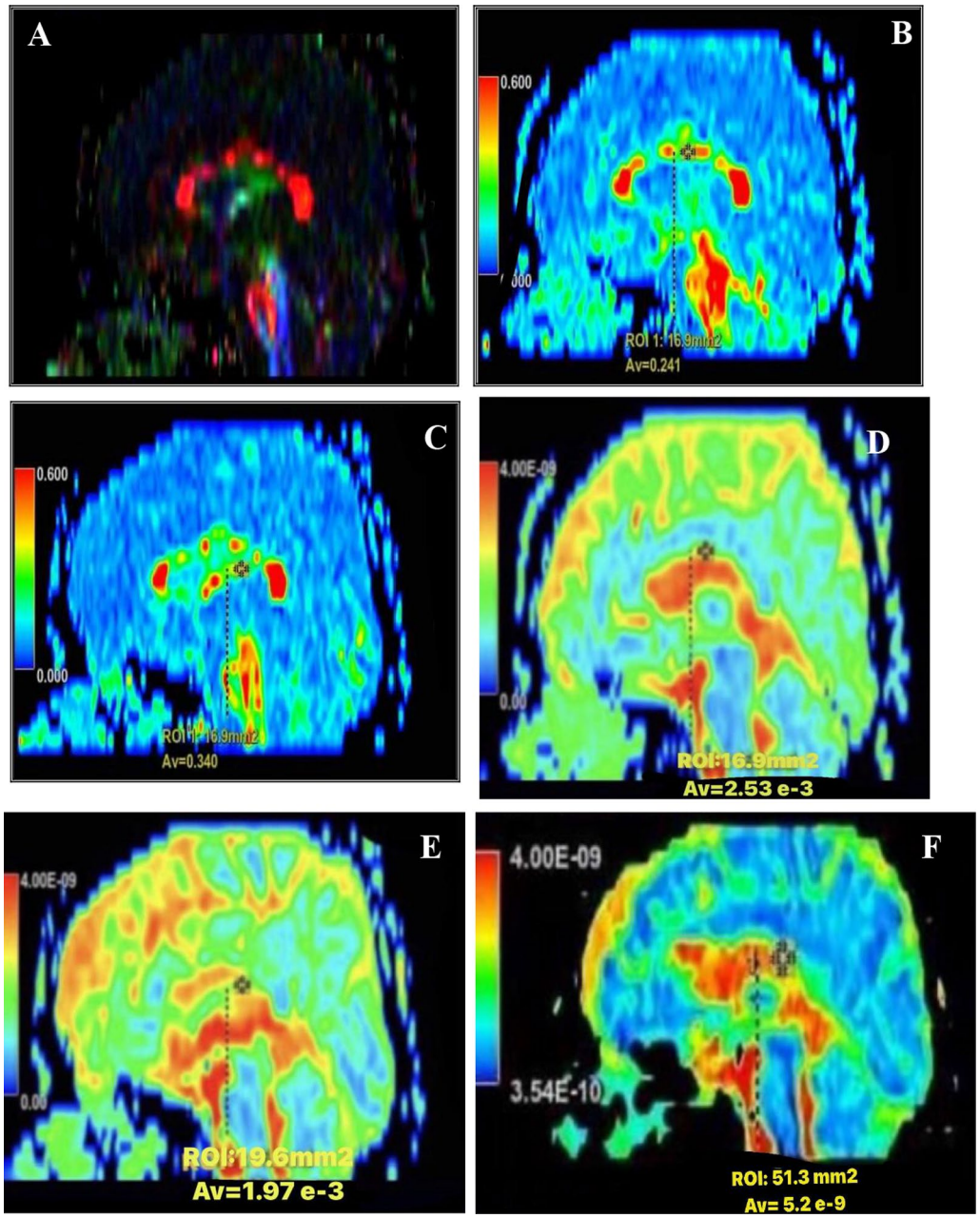

Fig. 4 23-year-old single male showed severe symptoms of hallucinations and delusions at his admission time to psychiatric department, he did not experience any psychiatric disorders before. DTI Finding: Affection of fibers of corpus callosum and fornix. **A** Sagittal color orientation map of corpus callosum and fornix, **B**, **C** Sagittal fractional anisotropy maps of corpus callosum and fornix with decreasing values measuring 0.241 and 0.34 respectively, **D**, **E** Average values of the corpus callosum and fornix in sagittal apparent diffusion coefficient maps measuring (2.53 & 1.97) $\times 10^{-3}$ mm^2/s. **F** Sagittal images of diffusion coefficient of mean diffusivity maps of the corpus callosum shows high value measuring 5.2×10^{-9} mm^2/s

visualization, and assessment of specific white matter properties [26].

To predict schizophrenic patients in this study, receiver operating characteristic curve was plotted for all the measured apparent diffusion coefficient, fractional anisotropy, and mean diffusivity in different areas of white and grey matter. In the current study, ROC (Receiver operating characteristic) curve of fractional anisotropy revealed significant differences ($p < 0.001$) of fornix,

Table 4 Correlation of fractional anisotropy, apparent diffusion coefficient and mean diffusivity measurements between white and grey matter in schizophrenic patients

	Right thalamus	Right basal ganglion
Fractional anisotropy		
Fornix		
Rs	0.156	0.344
p value	0.458	0.092
Corpus callosum		
Rs	− 0.333	0.229
p value	0.104	0.270
Right cingulum		
Rs	− 0.093	0.322
p value	0.660	0.116
Right superior occipito-frontal fasciculus		
Rs	− 0.130	0.095
p value	0.537	0.651
Right inferior occipito-frontal fasciculus		
Rs	− 0.084	− 0.018
p value	0.689	0.934
Apparent diffusion coefficient		
Fornix		
Rs	− 0.369	− 0.319
p value	0.069	0.120
Corpus callosum		
Rs	− 0.010	0.277
p value	0.962	0.181
Right cingulum		
Rs	0.210	− 0.188
p value	0.314	0.369
Right superior occipito-frontal fasciculus		
Rs	0.111	− 0.353
p value	0.598	0.084
Right inferior occipito-frontal fasciculus		
Rs	0.309	0.249
p value	0.133	0.230
Mean diffusivity		
Fornix		
Rs	0.335	− 0.081
p value	0.102	0.701
Corpus callosum		
Rs	0.206	0.036
p value	0.322	0.864
Right cingulum		
Rs	0.054	0.107
p value	0.798	0.612
Right superior occipito-frontal fasciculus		
Rs	0.383	− 0.047
p value	0.059	0.822
Right inferior occipito-frontal fasciculus		
Rs	0.027	0.075
p value	0.898	0.722

Table 4 (continued)

rs coefficient of Spearman's rank order correlation; moderate: $r = 0.3–0.7$; strong: $r > 0.7$

*Significant at $p \leq 0.05$

corpus callosum, right cingulum, both right superior and inferior occipito-frontal fasciculi. These parameters exhibited high accuracy in predicting schizophrenic patients. Receiver operating characteristic curve of apparent diffusion coefficient, there were no substantial variations in all parameters for prediction of schizophrenic patients.

For prediction of schizophrenic patients by receiver operating characteristic ROC curves, there were significant differences ($p < 0.001$) of mean diffusivity in right inferior occipito-frontal fasciculus, corpus callosum, thalamus, basal ganglion. The level of sensitivity and specificity of mean diffusivity were (90% and 84%) in corpus callosum, (96% and 88%) right inferior occipito-frontal fasciculi, (96.0% and 72%) right thalamus and (76% and 70%) right basal ganglion.

Little data were known about the prediction of schizophrenia using DTI, but in 2005 Kubicki et al. [27] mentioned that the fornix, the corpus callosum, bilaterally in the cingulum bundles, superior occipito-frontal fasciculus, right inferior occipito-frontal fasciculus, internal capsule, and left arcuate fasciculus showed reduced diffusion anisotropy in schizophrenic individuals. The results also imply that some of the anomalies may be related to myelin/axonal disintegrate and that the diffusion aberrations in schizophrenic are probably caused by aberrant coherence or organization of the fiber tracts.

To differentiate between schizophrenic patients from controls, Kambeitz et al. [28] found that DTI parameters had 80.3% sensitivity (95% confidence interval (CI): 76.7–83.5%) and 80.3% specificity (95% CI 76.9–83.3%). In comparison with structural MRI investigations, which had sensitivity of (76.4%, 95% CI 71.9–80.4%) and specificity of (79.0%, 95% CI 74.6–82.8%).

However, Ardekani et al. [29] reported that fifty individuals with schizophrenia and 50 healthy participants, matched by gender and age had DTI along with high-resolution structural MRI. The classifier successfully recognized 94% of the test set instances utilizing the FA maps (96% sensitivity and 92% specificity). When the MD maps were used as inputs to the classifier, it was able to identify between schizophrenia sufferers and healthy participants in the test dataset with 98% accuracy (96% sensitivity and 100% specificity). Combining FA and MD data had no appreciable impact on accuracy (96% sensitivity and specificity). Automated algorithms for pattern-recognition may be utilized in conjunction with patterns of water self-diffusion in the brain measured by DTI to accurately

Table 5 Performance of receiver operating characteristic ROC curves of mean diffusivity in different areas of white and grey matter to predict schizophrenic patients

	AUC	95% CI	*p* value	Cutoff	Sensitivity (%)	Specificity (%)
Fractional anisotropy						
Fornix	0.924	0.920–0.956	< 0.001*	≤ 0.42	96.0	96.0
Corpus callosum	0.932	0.929–0.998	< 0.001*	≤ 0.5	96.0	96.0
Right cingulum	0.910	0.902–0.977	< 0.001*	≤ 0.41	92.0	92.0
Right superior occipito-frontal fasciculus	0.881	0.872–0.990	< 0.001*	≤ 0.39	92.0	90.0
Right inferior occipito-frontal fasciculus	0.970	0.929–0.988	< 0.001*	≤ 0.51	92.0	90.0
Right thalamus	0.574	0.426–0.712	0.384	≤ 0.3	72.0	76.0
Right basal ganglion	0.661	0.513–0.789	0.048*	≤ 0.27	60.0	48.0
Mean diffusivity $\times 10^{-9}$ mm^2/s						
Fornix	0.521	0.375–0.664	0.807	$\leq 4.7\times10^{-9}$	72.0	82.0
Corpus callosum	0.972	0.929–0.976	< 0.001*	$> 4.6\times10^{-9}$	90.0	84.0
Right cingulum	0.521	0.375–0.664	0.805	$> 2.86\times10^{-9}$	38.0	56.0
Right superior occipito-frontal fasciculus	0.562	0.415–0.702	0.450	$> 2.8\times10^{-9}$	40.0	76.0
Right inferior occipito-frontal fasciculus	0.95	0.865–0.996	< 0.001*	$> 1.7\times10^{-9}$	96.0	88.0
Right thalamus	0.926	0.815–0.981	< 0.001*	$> 2.5\times10^{-9}$	96.0	72.0
Right basal ganglion	0.993	0.915–0.962	< 0.001*	$> 2.5\times10^{-9}$	76.0	70.0

AUC area under the curve, *CI* confidence interval of AUC, *p p* value from a test comparing the AUC to the null hypothesis of AUC = 0.5, *NPV* negative predictive value, *PPV* positive predictive value

*Significant at $p \leq 0.05$

identify between those suffering from schizophrenia and healthy control participants.

The diagnostic accuracy with ROC exploration of data is a base for direct future researches because the purpose of the current work was to differentiate between schizophrenic patients and control volunteers.

The current study was limited by a short period of time with a relative small sample size, underestimation of number.

Conclusions

Only DTI allows for in vivo calculating and visualizing of fiber-tract trajectories. White matter tract DTI is thought to be a potential method for diagnosis of schizophrenic patients which usually have prolonged illness, chronic course and poor outcome.

Recommendation

Using mean diffusivity and fractional anisotropy of white matter as a tool for diagnosis of schizophrenic patients.

Early diagnosis and management of schizophrenia, to obtain better outcome, and decreasing the period of untreated illness with its associated long standing negative symptoms.

Need further studies using mean diffusivity and fractional anisotropy of white matter for differentiation between schizophrenic patients and different psychiatric disorder.

Need to compare patients during illness and after cure for better assessment of functional changes in reward processing.

Abbreviations

ADC	Apparent diffusion coefficient
CI	Confidence interval
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
GABAergic	Gamma-aminobutyric acid
IQR	Interquartile range
MD	Mean diffusivity
MRI	Magnetic resonance imaging
ROC	Receiver operating characteristic curve
ROIs	Regions of interest
SD	Standard deviations

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Author contributions

All authors have read and approved the manuscript" and ensure that this is the case.

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Availability of data and materials
The authors confirm that all data supporting the finding of the study are available within the article and the raw data supporting the findings were generated and available at the corresponding author on request.

Declarations

Ethics approval and consent to participate
Informed written consents were taken from the patients and healthy volunteers, the study was approved by ethical committee of Tanta University hospital, faculty of medicine (approval code: 35114/12/21).

Consent for publication
All participants included in the research gave written consent to publish the data included in the study. Authors accepted to publish the paper.

Competing interests
The authors declare that they have no competing of interests.

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