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Fractional Anisotropic Changes of Corpus Callosum Associated with Antipsychotic Treatment in First-Episode Antipsychotic Drug-Naive Patients with Schizophrenia

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ABSTRACT:

Fractional anisotropic changes of corpus callosum associated with antipsychotic treatment in first-episode antipsychotic drug-naive patients with schizophrenia

Objective: Schizophrenia involves white matter abnormalities that might have a central role in the pathophysiology. Abnormal brain connectivity especially in prefrontal and temporal heteromodal cortex has been suggested as the leading structural impairment in patients with schizophrenia. In this study we examined the relationship between potential white matter changes and clinical response, as well as associations with antipsychotic treatment follow-up.

Methods: 18 first-episode schizophrenia (FES) patients were recruited from the outpatient unit of the GATA (Gulhane Military Medical Academy) Haydarpasa Research and Training Hospital, between June 2009-February 2010. Fourteen patients with FES were recruited, and 16 healthy control subjects were recruited from the community. Diffusion tensor MRI (DT-MRI) was obtained from participants at baseline and after 4 weeks of standard antipsychotic treatment. A color-coded fractional anisotropy map for each 11 patient was extracted from the 4-week follow-up and the baseline splenium and genu FA measurements. According to Basser and others major eigenvector linear maps were transformed into the color-coded maps. Differences in Positive and Negative Syndrome Scale (PANSS) scores and Brief Psychiatric Rating Scale (BPRS) scores between baseline and follow up were also evaluated.

Results: In this study; in the FES patients, both genu FA (p=0.001) and the splenium FA (p=0.013) values were statistically significantly lower than the healthy control group. There were mild FA increases respectively genu and splenium (p=0.533, p=0.318) in the FES patients after the treatment. But the FA changes did not correlate with the changes in clinical symptoms. A negative, moderate, statistically significant correlation (Pearson's r=-0.569, p=0.034) was found between baseline splenium FA values and BPRS scores. The duration of illness prior to treatment was negatively, weak, statistically non-significantly correlated (r=-0.066; p=0.846) between baseline and follow-up splenium FA changes.

Conclusions: The reduced mean Callosal FA (CFA) values might indicate myelination defects and problems in axonal transport. The existence of white matter changes even in first episode drug-naive schizophrenia patients supports the view that these problems occurs in earlier stages of development. Although the callosal FA changes did not correlate with symptom improvement or the dose of antipsychotic medication, there was a mild increase in follow-up FA measurements. These findings show that CC which is the main conduit of interhemispheric connection is affected distinctly in patients with schizophrenia. Further collaborative studies are needed to clarify the potential long-term effects of antipsychotics on white matter microstructure and also its reversibility.

Keywords: First-episode schizophrenia, fractional anisotropy, antipsychotic treatment, corpus callosum

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INTRODUCTION

Schizophrenia, which is a serious brain illness that affects 1% of the population worldwide, involves in psychotic abnormalities that indicates many abnormality in brain function such as assessing the reality, thoughts, emotions, and cognitions. Abnormal brain connectivity that especially in prefrontal and temporal heteromodal cortex has been suggested as the leading distortion in schizophrenia patients. It may explain some of its symptoms and cognitive deficits. Prefrontal cortex network connections choose the genu of corpus callosum (CC) and temporoparietal network connections choose the splenium of corpus callosum area for information transfer that proves the importance of CC once again[1]. CC has a basic role for high cognitive functions because of providing connections between two hemispheres.

Andreasen[2], described cortico-cerebellar-thalamic-cortical circuitry in schizophrenia and mentioned about "cognitive dysmetria" model which is caused by malfunctions in that circuitry. On the other side Goldman-Rakic[3] suggested that schizophrenia symptoms reflects impairments in complex circuits of brain and "working memory impairment" is the basic deficit, psychopathology also results from the lack of guidance by ideational representations to attitudes. The main idea in schizophrenia ethiopathogenesis is established on the clinical reflections of disconnectivity[4].

While the detection of connections between these areas were performed with postmortem studies, it is feasible for in vivo diffusion tensor magnetic resonance imaging (DT-MRI) depending on measuring Brownian motion of water molecules which indicates connections between cortical fibers in brain's white matter micro-structure, organisation, and cytoarchitecture. Diffusion becomes isotropic in a tissue, which is free from structural barriers like grey matter and becomes anisotropic [different oriented, fractional anisotropy (FA)] in heterogeneous structures such as white matter pathways[5].

There are many schizophrenia studies in which corpus callosum was examined with DT-MRI. In a small part of these studies; an increasing in callosal FA (Fractional Anisotropy) values[6], a stability in some of them[7,8] and a decreasing FA values in large part of them[9-11] were detected. These differences in acquired findings may be attributed to a lack of excluding of diagnosis complexity, chronic course of disease and changes that related to applied treatments. Though, these studies did not perform a second evaluation of white matter structure at follow-up. Follow-up imaging studies can provide more information than cross-sectional studies, as they allow anatomical changes over time that may relate to treatment after-effect. For that reason, the studies particularly consisting of untreated first episode schizophrenia patients were in a limited number due to fact that both heterogenous form of patient samples and adaptation difficulties to study.

Therefore, the clinical studies of antipsychotic medications become important that demonstrate the effects ot medications in patients with schizophrenia, especially by using DT-MRI measures. Unfortunately, there are only few studies about effects of antipsychotic medications using DT-MRI technique.

Only six published longitudinal studies on the effects of antipsychotics using DT-MRI were found with diverging results[12-17].

Garver et al.'s study is the first study, in a small sample, reported that patients with chronic schizophrenia who responded to antipsychotics (risperidone, ziprasidone, or haloperidol) (n=8), assessing them 28 days after by using DT-MRI. They measured mean diffusivity (Dm) within whole brain and found significant decrease in Dm in the right pyramidal tract, left temporal lobe, and cingulate gyrus, and reduced white matter microstructural integrity compared to the non-responders (n= 5). In contrast, Ozcelik-Eroglu et al. assessed schizophrenia patients (n=16) with DT-MRI after 12 weeks of treatment with clozapine. They reported that clozapine appeared to increase FA values in widespread brain regions, especially in the corpus callosum, fronto-thalamic, and fronto-temporal regions. In addition, first episode drug-naive psychosis patients (n=28) were reported to have a significantly increased FA of to

the matter in the anterior thalamic radiation compared with controls (n=28), following 6 weeks of amisulpride treatment, and dose of amisulpride was correlated positively by FA changes in the right corticospinal tract[17]. Differences in results of FA changes in patients with schizophrenia may be related to methodological differences in brain imaging, clinical differences, and the possible effects of antipsychotics on their brains.

After all, morphometric magnetic resonance imaging was used to perceive the implications of the antipsychotics' effects on gray and white matters. But in those studies, findings might have many possible interpretations[18]. Hence, distinguishing between the effects of medication and pathogenesis would present a difficulty. Therefore, problematic pathogenesis of schizophrenia makes DT-MRI studies more important.

In this present study, using DT-MRI we aimed to examine the pre and posttreatment white matter microstructural changes in splenium and genu regions of corpus callosum in patients who were diagnosed with first episode schizophrenia patients according to the DSM-IV-TR. We hypothesized that FA values that would be changed, after the antipsychotic treatment in first episode schizophrenia patients.

MATERIAL AND METHODS

Participants

Between June 2009 and February 2010, unfortunately, due to the difficulty of finding first episode drug-naive psychosis, 18 patients with psychotic spectrum disorders were recruited from the outpatient unit of the Gulhane Military Medical Academy (GATA) Haydarpasha Research and Training Hospital for usual treatment. The healthy subjects were recruited among hospital personnel and their relatives. Patients (n=18) who were diagnosed with first episode psychosis (n=7) or schizophreniform disorder (n=11) and met inclusion criteria were included. Patients with schizophreniform disorder for initial diagnosis were followed up for at least 6 months and confirmed to meet the DSM-IV diagnosis criteria for schizophrenia. Patients who were included in the study were hospitalized for a month, all laboratory tests and measurements were implemented before beginning of the antipsychotics, then standard antipsychotic treatments [Risperidone (n=12, 5.77±1.21 mg/d), Paliperidone (n=2, 10.55±2.12 mg/d) were initiated for all patients. The duration of untreated psychosis (DUP) was measured from the onset of the first psychiatric symptoms to the first assessment. Also, by using SCID-II assessments, additional diagnoses for personality disorder were excluded. Two of the 18 patients were excluded because of being diagnosed with short term psychotic disorder and two patients were unable to participate due to incompatibility to the MRI environment. Three participants with schizophrenia were excluded from the study because of unsatisfactory imaging data because of head and body motion in the follow-up MRI scan. The DT-MRIs were obtained from participants at baseline and after 4 weeks of standard antipsychotic treatment follow up. Region of Interest (ROI) based FA measurements of splenium and genu were assessed with "color-coded fractional anisotropy maps" for each 11 patient.

Finally, this study included participants who had completed 14 baseline, 11 both baseline and follow-up patients and 16 healthy control groups who had no organic or psychiatric disease and whose age, gender, and education level were matched with the patient group. All evaluations of healthy control subjects were performed by the researchers who work as clinicians. Patients' family histories were received and patients were examined mentally, physically, and neurologically. Initially liver, kidney and thyroid functions of all patients were examined. Besides this, structural brain abnormalities are evaluated during the DT-MRI measurements. Differences in Positive and Negative Syndrome Scale (PANSS) scores and Brief Psychiatric Rating Scale (BPRS) scores between baseline and follow-up were also evaluated.

To be eligible, criteria of involvement for either patients or healthy control subjects were as follows: between 18-45 years old, using right hand (for this evalution Edinburg Handedness Inventory was used), first time presentation to a psychiatry clinic for psychiatry, elementary school graduate at minimum, except for abusing of nicotine or caffeine having no DSM-IV-TR Axis I and Axis II comorbidity, a written consent form approval (by patients or by first degree relatives).

The exclusion criteria were as follows: having clinically significant medical or neurological illnesses, having received antipsychotic treatment at the time of presentation and having used benzodiazepine prior to longer than two weeks, necessity for ECT (electroconvulsive therapy), an incompatibility to the MRI environment and communication problems due to physical and neurological illnesses.

The study was initiated after submitting the study protocol to Istanbul Clinical Studies Ethics Board with Number 3 and received approval (Number of decision: 2009-CC-040/11.12.2009) and prospectively planned data was started to be assessed retrospectively.

Magnetic Resonance Imaging

A 1.5 T MR scanner (Siemens® avanto, Erlangen, Germany) with a protected magnetic field gradient 22 mT/m and a polarized circular convoluted helmet was used. Head movements were reduced with standard foam and immobilization. In sagittal plan which was used as scanning sequence T1 weighted images were acquired, T1 MR (TR:1940, TE:3.1, FOV:250 mm, NEX:1, matrix:246x256, section thickness:1 mm, space:0.3 mm), in axial plan T1, T2 weighted (TR:3820, TE:98, FOV:230 mm, NEX:2, section thickness:3 mm, space:1 mm), and after routine brain scanning with images, diffusion weighted images were acquired by means of two different b values used in three axes (x,y,z). DT-MRI sequences were acquired (here multivariate linear regression was used) from diffusion weighted imaging (DWI) sets which was acquired from different b matrix values (0-1000 sec/mm²) practiced in each three axis. Axial sections for DT-MRI were positioned based on the AC-PC (Anterior-posterior commissure) line over sagittal primary image. Images in 30 direction were received with the usage of WVHEAD bandage and EPI (Echo Planar Imaging) sequence (TR:3014, TE:96, FOV:230 mm, NEX:4, matrix size:128x128). Diffusion was selected as b=1000 sec/mm² in tensor sequence, section thickness 5 mm, section space 1.5 mm. For DT-MRI voxel dimension was 1.8x1.8x5 mm. and 20 section were acquired in total. For each patient it lasted 16 seconds included MR imaging and diffusion tensor sequence. Diffusion tensor images from each patient were transfered to the workstation (Siemens® syngo VE27A SL0109 Syngo multimodality Workplace AG 2007) and analyzed.

DT-MRI Image Analysis

FA maps were calculated with Siemens® syngo VE27A SL0109 Syngo Multimodality Workplace AG 2007 according to Basser and others[19]. Major eigenvector linear maps were transformed into the color codes. Thereby FA maps with color codes were acquired along the ways of right-left (red), anterior-posterior (green) and superior-inferior (blue) which had the largest eigenvector. In ROI measurements, fixed topographic circular probes were selected for reducing a probable CSF (Cerebrospinal Fluid) and grey matter combination. Additionally in the first place, automatic boundary value filtration was used on nondiffusion weighted (b=0) ecoplanar axial images. In the second stage, in advance of measurements a 3D correction (Eddy Current Correction) is implemented to remove artifacts of emerged images. ROI's radiuses were determined 2 mm in genu, 3 mm in splenium (Figure 1). Also paid attention to utilization of this determined regions from tractography. Genu and splenium regions where ROI was going to be placed were determined 5 mm above of minimum level genu and splenium which comes out obviously in axial sections across z axis.

Splenium and genu ROIs were placed by two

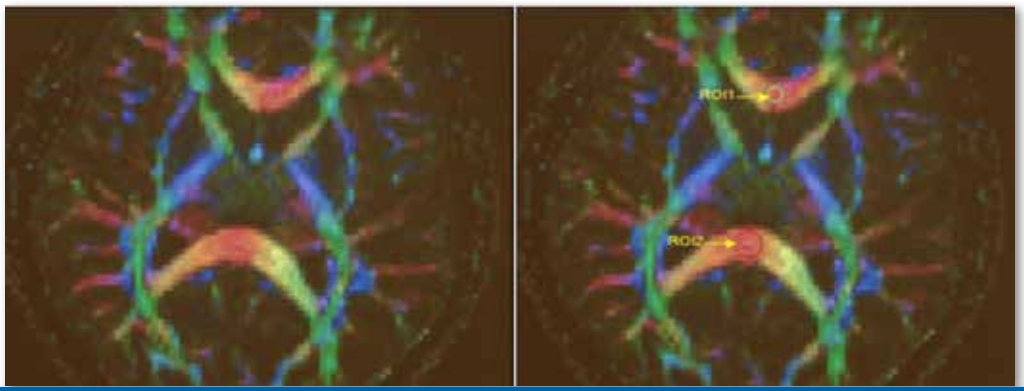

Figure 1: ROI placement in color-coded FA map in the same subject

independent researcher who had no information about patients and healthy controls. ROIs were placed to the FA map sections at maximum thickness and brightness. The circular margins were kept within the red colour intensity on color coded maps, indicating fibers with left–right direction and the highest anisotropy. Hereby FA values were calculated accurately.

Statistical Analysis

Acquired parameters from the study were analyzed by using package program SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL). Study parameters were expressed with mean±standard deviation and percent values. Group differences were assessed at baseline using independent group Student's t-tests or χ^2-tests, whereas longitudinal changes between the baseline and follow-up time points in patients' group was examined using paired Student's t-tests and Mann-Whitney test. Significance value for all statistical analyses was accepted as $p<0.05$. Mean Callosal FA was exported to SPSS to examine in relation to clinical symptom scores (using a cutoff value of $p<0.05$; two-tailed) using Pearson's correlations.

RESULTS

All of the the study subjects were men. In terms of age (22.7±2.25 and 22.1±2.11 respectively) and education level (10.2±2.51 and 10.4±2.47

Table 1: The sociodemographic data of the subjects and splenium-genu region of CC's FA values

	FES 0 (n=14)	HC (n=16)	Statistical tests (FES 0 versus HC)	FES 1 (n=11)	Statistical tests (FES 0 versus FES 1)
Age (years±SD)	22.7±2.25	22.1±2.11	t=-0.902, p=0.375	22.8±2.31	t=-0.35, p=0.972
Education (years±SD)	10.2±2.51	10.4±2.47	t=0.176, p=0.862	10.5±2.61	t=0.482, p=0.635
Gender (male;%)	14(100%)	16(100%)	-	11(100%)	-
Handedness (Right handed;%)	14(100%)	16(100%)	-	11(100%)	-
DUP (months±SD) (months; median and quartiles 25; 75)	2.28±1.68 2; 1; 3	-	-	2.36±1.77 2; 1; 3	z=-0.56, p=0.956*
Economic Status (Low;%)	8 (57.1%)	1 (6.3%)	χ^2=10.35, p=0.006	6(54.5%)	χ^2=0.051, p=0.821
Family history (for schizophrenia, positive;%)	4 (28.6%)	0 (0.0%)	χ^2=5.27, p=0.037	4(36.3%)	χ^2=3.741, p=0.053
Interval (months±SD)				1.27±0.41	
Genu FA	0.690±0.124	0.834±0.042	t=4.1, p=0.001	0.711±0.133	t=-0,646, p=0.533
Splenium FA	0.764±0.112	0.852±0.031	t=2.8, p=0.01	0.790±0.056	t=-1.051, p=0.318

FES0/1: Baseline/Followup First Episode Schizophrenia, HC: Healthy Controls, Mean±SD: Mean±Standart Deviation, DUP: Duration of Untreated Psychosis, *: Mann-Whitney test.

Table 2: Splenium and Genu FA versus FES0/1 FA correlation with BPRS,PANNS scores and antipsychotic dosage

	GenuFA (r;p)	SpleniumFA (r;p)	BPRS (r;p)	Statistical tests (FES0 GenuFA versus FES1GenuFA)	Statistical tests (FES0 SpleniumFA versus FES1 SpleniumFA)
Genu FA	-	0.482 (0.007)	-0.174 (0.553)		
Splenium FA	0.482 (0,007)	-	-0.569 (0.034)		
BPRS	-0.174 (0.553)	-0.569 (0.034)	-	r=-0.087, p=0.800	r=-0.137, p=0.689
PANSS Total	-0.263 (0.364)	-0.234 (0.420)	-	r=-0.310, p=0.354	r=-0.583, p=0.060
Risperidone n=9 (Mean±SD;mg) 5.77±1.21	-	-		r=0.340, p=0.370	r=0.494, p=0.176
Paliperidone n=2 (Mean±SD;mg) 10.55±2.12	-	-		-	-

FES0/1: Baseline/Followup First Episode Schizophrenia, r: Pearson's r, Correlation is significant at the 0.05 level.

respectively) between first episode schizophrenia group and control group, we found no statisticly significant differences (p=0.375). First episode schizophrenia group's economic level was lower than healthy controls (p=0.022). The mean duration of untreated psychosis was 2.28 months (SD: ±1.68, range: 0.5-7, quartiles: 1; 2; 3). Family history for schizophrenia was identified as 28.6% (Table 1).

In the first episode schizophrenia group, FA value of corpus callosum's genu region was 0.690±0.124 and 0.834±0.042 for the control group. Splenium region's FA value was 0.764±0.112 for the first episode schizophrenia group and 0.852±0.031 for the control group. In the first episode schizophrenia group, FA values both in genu (p=0.001) and splenium (p=0.01) were lower than the control group. Follow-up measurements of corpus callosum's genu and splenium region's FA values were found respectively 0.711±0.133 and 0.790±0.056 for the FES group. There were mild fractional anisotropy increases respectively genu and splenium (p=0.533; p=0.318) among FES patients following treatment.

A negative, moderate, statistically significant correlation (Pearson's r=-0.569, p=0.034) was found between baseline splenium FA values and BPRS scores. The duration of illness prior to treatment was negatively, weak, statitically nonsignificantly correlated (r=-0.066, p=0.846) between baseline and follow-up splenium FA changes.

There were no statistically significant correlations between the change in genu and splenium FA values and the improvement in clinical symptoms, PANSS total (r=-0.310, p=0.354, r=-0.583, p=0.060 respectively) and BPRS score (r=-0.087, p=0.800, r=-0.137, p=0.689 respectively) after about 1(1.27±0.41) month of treatment. Moreover, there were no statistically significant correlations between the change in genu and splenium FA values and the dose of antipsychotic (risperidone; 5.77±1.21 mg/d) medications (r=0.340, p=0.370; r=0.494, p=0.176) (Table 2).

DISCUSSION

In this present DT-MRI study, we found the callosal FA changes did not correlate significantly with symptom improvement or the dose of antipsychotic medication, there was a mild increase in follow-up FA measurements. Also, in FES patients group FA values of corpus callosum were found to be lower than that of healthy control group especially in genu was found. Also a negative correlation was found between BPRS scores and baseline splenium FA values.

Antipsychotic medication effects of on DTI measurements studies have usually found no relationship between FA values and dose of antipsychotic medications[14,20,21], as small sample sizes and lack of long-term longitudinal designs have limited interpretation.

In addition, Wang et al.[14] reported that there

was a significant decrease in absolute FA values in the white matter in 35 first-episode drug-naive patients with schizophrenia and after 6 weeks of antipsychotic treatment that did not correlate with symptom reduction. On the other hand, Serpa et al.[22] showed that antipsychotic treatment increased the fractional anisotropy values especially in the internal capsule. In another study, in a sample of chronic patients, assessed response 4 years after the brain imaging, and found that responders (n=23) had lower callosal fractional anisotropy compared with non-responders (n=26)[13].

In line with 3 recent longitudinal studies over 12 and 6 weeks that indicated clozapine treatment, assorted other atypical antipsychotic agents and mono-antipsychotic treatment were appeared to increase FA values also improved white matter integrity. In this studies; associative tracts, such as the left uncinate, fornix, cingulum and superior longitudinal fasciculus, and commissural tracts such as the corpus callosum were the most affected tracts in WM with schizophrenia patients[15-17].

Among the several possible explanations for the WM FA changes in patients with schizophrenia, antipsychotic medication is expected to be the major factor. There are some studies explaining how antipsychotics might effect white matter integrity, however, they suggest that antipsychotics' effects would be on oligodendrocytes by prosperity of myelination, especially for risperidone[23,24]. In addition to this, low FA values in schizophrenia patients might also depend on atypical myelination or axonal abnormalities. Depending on destruction in myelin of fibers and other axonal cellular elements; isotropy value increases, anisotropy value decreases so, and it means that the degree of FA changes surrogate for fibres tract organization[25]. They have a positive correlation with each other. It was suggested that extensive structural white matter disconnectivity gets into the subcortical regions and those disorders existed prior to emergence of the disease in the first episode schizophrenia patients[26]. As a result of white matter studies, particularly axonal atrophy and distensions in periaxonal oligodendrocyte were observed in prefrontal cortex of schizophrenia patients[27]. This finding was consistent with increased radial permeability and decreased FA values in white matter of schizophrenia patients. This also suggests that decreased FA values are comprised of changes in axon skeletal structure or demyelization rather than a big degeneration in axons[28]. In a study on schizophrenia patients by Hakak and others[29], it was reported that a disorder in oligodendroglia function depends on a disorders in the expression of the genes encoding myelin and not related with treatment and duration of disease. It means that, the existence of white matter changes even in the first episode drug naive schizophrenia patients supports the view that these problems occurs in a developmental stage.

These findings show that CC which is the main conduit of interhemispheric connection has been affected distinctly in patients with schizophrenia. When all these findings are considered, these probably would result in a neuro-developmental defect and create a shortage in neurons' modulator capacity paving the way to changes in cellular morphology than abnormal synaptic circuits.

It has been suggested that the pathophysiology of schizophrenia may involve the cortico-cortical and cortico-subcortical conduits or networks of brain regions' disconnectivity through a distributed network in whole brain especially in prefrontal cortex associated with working memory[3,4,25]. Also, in schizophrenia patients, Andreasen et al.[30] reported that drug naive schizophrenia patients were impaired on the Tower of London task (well-known test used for assessment of executive functioning-working memory) and show hypofrontal blood flow while performing it.

Moreover, working memory deficits may be a core feature of the schizophrenia that influence cognitive processing, symptomatology, and functional outcomes[3]. Hence, entirely, understanding of the neural circuitry underlying cognitive process is crucial. Furthermore, abnormal connectivity in schizophrenia have been proposed to particular different models. For example, Friston and Frith[4] postulate that schizophrenia is a result of disturbed communication between multiple regions, and that this functional disconnectivity is based on alterations

in synaptic connection. Otherwise, Bullmore et al.[31] set forth the "dysplastic net" hypothesis, signifying that schizophrenia involves a disturbance of anatomical connectivity that appears at least in part of during prenatal development.

So, probability of combining fMRI (functional MRI) and DTI data sets may also open new opportunities for therapy and prevention by examining the structure–function relationship of the brain.

In the present study, the probability of findings due to design artefacts are unlikely. Because, it was paid attention to similarity of prognostic demographic factors such as age, gender, education, and substance use between two experimental groups. Besides, artefacts, which might be come from imaging data acquisition error was prevented by using 3D correction (Eddy Current Correction) and non-positive tensor filtration. To minimize CSF and gray matter contamination that might affect these results during the measurement[32], standard size circular ROI probes were used that would fit in corpus callosum by utilizing tractography. Also the implementations of ROIs' were in maximal thickness and brightness and also in a way ROI's circular edges were within red weighted color on color-coded maps. Also in order to control probable changes that might originate from psychotic disorder and present developmental side of neuropathology or treatment itself, first episode antipsychotic drug-naive schizophrenia patients were selected as a study group. Additionally, when frequency of schizophrenia among ambidexters is considered[33]; it is clear that this might be a significant confounding factor in studies from the point of hand reference related with cerebral lateralization. Therefore, in our study, we preferred the same handedness both in patients and control groups.

In studies, although callosal FA differences were in tendency appear to be present predominantly in men[9], use of only male subjects can be considered as a limitation. In some studies it is reported that women have less diffusion inhibitor barriers and that is related with decreased FA values[34]. Therefore, it is important to pay attention to the choice of same gender in study patients and healthy controls rather than choosing different genders.

Further, we know that thickness of the CC is affected by peripheral white matter loss. So, CC's volume may be a potential surrogate marker of brain volume[35]. Therefore, firstly, an important limitation of the study is that we have not compared CC volumes between the two study groups. Secondly, small sample size might be one of the limitations of the study. Thirdly, four week follow-up period of the study might be insufficient to point out the probability of a brain's permanent structural changes in white matter integrity. And finally, serum concentrations of antipsychotics were not measured with any assays.

In conclusion, we report FA reductions in especially posterior region of CC, also insufficient FA increase in white matter after antipsychotic treatment in patients experiencing a first episode of a psychotic spectrum disorder. However, forthcoming collaborative and using a combination of different neuroimaging techniques, e.g., functional diffusion tensor imaging (fDTI) that measuring task- related changes in FA along white matter tracts, are needed to clarify the potential long-term effects of antipsychotics on white matter microstructure and also its reversibility.

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