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Diffusion Tensor Imaging Findings of White Matter Changes in First Episode Schizophrenia: A Systematic Review

Carissa Nadia Kuswanto[1], Irvin Teh[2], Tih-Shih Lee[3], Kang Sim[1]

[1]Institute of Mental Health/Woodbridge Hospital, [2]A*STAR-NUS Clinical Imaging Research Centre, National University of Singapore, [3]Duke-NUS Graduate Medical School, Singapore

Earlier structural magnetic resonance imaging in schizophrenia have noted smaller white matter volumes in diverse brain regions and recent diffusion tensor imaging (DTI) studies have allowed better elucidation of changes in brain white matter integrity within the illness. As white matter abnormalities have been reported to occur early in the course of schizophrenia, we systematically review extant DTI studies of anomalies of white matter integrity in first episode schizophrenia (FES) up till October 2011. Overall, disruptions of white matter integrity were found in the cortical, subcortical brain regions and white matter associative and commissural tracts, suggesting that changes of cortical-subcortical white matter integrity were found at an early stage of the disorder. These changes in white matter integrity were correlated with specific cognitive deficits (verbal and spatial working memory) as well as psychopathology (positive more than negative symptoms) in patients with FES. The correlation of these white matter integrity changes with cognitive and phenomenological factors may shed light on neurobiological substrates underlying these clinical manifestations. Future studies need to validate these findings in larger samples of subjects and in different populations as well as chart the progress of these cerebral white matter changes over time so as to better appreciate their trajectory with illness course, treatment and chronicity.

KEY WORDS: Schizophrenia; Anisotropy; Diffusion tensor imaging; Psychopathology.

INTRODUCTION

Schizophrenia is a complex neuropsychiatric syndrome comprising of psychiatric symptoms (including auditory hallucinations, delusions), cognitive deficits involving domains such as attention, memory and executive function and disruptions in social functioning.[1)] Earlier structural magnetic resonance imaging (MRI) studies in schizophrenia and findings of smaller white matter volumes in diverse white matter regions, including prefrontal,[2,3)] temporal, occipital regions[4-6)] and corpus callosum[7,8)] suggest the involvement of white matter pathology in multiple cerebral regions in the neurobiology of this condition. Since the first use of diffusion tensor imaging (DTI) to elucidate changes of neural substrate in schizophrenia,[9)] various subsequent DTI studies have found evidence of abnormalities in the white matter structure and integrity in different brain regions.[10-12)] Changes in white matter integrity indices in schizophrenia have been correlated with psychotic symptoms such as delusions,[4)] hallucinations,[13)] negative symptoms, impulsiveness and aggressiveness,[14,15)] as well as cognitive deficits such as working memory.[16,17)]

In terms of scanning modality, DTI is a MRI technique that allows *in-vivo* quantification of the characteristics of water diffusion throughout the brain to assess the white matter structure and integrity.[10,18)] The phenomenon of water diffusion is known as Brownian motion, named after the English botanist Robert Brown, which states that the motion of water molecule is affected by the properties of the medium. In the brain, water may diffuse freely in all directions (isotropic diffusion), or restricted along one particular direction of structured tissues such as the cell membranes, myelin sheath, axons, white matter tracts and fibers (anisotropy diffusion). In other words, if the anisotropy is high, then most of the diffusion occurs in the highly ordered directions, indicating a high level of orientation in the structure.[12)] Therefore, decreased anisotropy in white matter regions where anisotropy is expected to be high may predict compromised white matter integrity.

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Address for correspondence: Kang Sim, MD
Institute of Mental Health/Woodbridge Hospital, 10, Buangkok View, Singapore 539747
Tel: +65-63892000, Fax: +65-63855900
E-mail: kang_sim@imh.com.sg

Changes in white matter integrity on DTI may be related to alterations in the density of the fibers, the degree of myelination, the coherence of fiber tracts as well as the number and the diameter of the fibers.[10,12]

DTI detects and measures the degree of anisotropy by quantifying the diffusion tensor. Diffusion tensor is a mathematical description of a three-dimensional ellipsoidal shape that depicts the magnitude (eigenvalue) and orientation (eigenvectors, λ_1, λ_2, λ_3) of diffusion in individual voxel. The largest eigenvalue, λ_1, is the axial (or longitudinal diffusivity, λ_L, and reflects the axonal integrity, whereas an average of λ_2 and λ_3 calculate the radial (or transverse) diffusivity, λ_T, which reflects myelin integrity.[19-21] The diffusion tensor can be quantified into different indices such as fractional anisotropy (FA), mean diffusivity (MD), and relative anisotropy (RA),[22] and the newly proposed indices such as geometric indices[4,23] and intervoxel coherence (IC).[24-26] The most commonly used index of diffusion is FA, which measures the directional preference of water diffusion to indicate the organization of fiber tracts, using an index ranging from 0 (isotropic) to 1 (maximally anisotropic). MD calculates the average diffusivity independently from directions of diffusion, hence increased MD may denote demyelination, axon loss or oedema.[27,28] RA measures the normalized standard deviation that represents the ratio of the anisotropic part of the tensor to its isotropic part.[10] Meanwhile, geometric indices categorize diffusion measures into three parts: linear diffusion (c_l) which corresponds to regions of fiber bundles in the same direction, planar diffusion (c_p) which corresponds to fiber crossing and twisting on a plane, or to tissues arranged in sheets; and spherical diffusion (c_s) which corresponds to isotropic diffusion.[4,23] Lastly, IC uses the average of the angle between the eigenvector of the largest eigenvalue in a given voxel and its neighbors to represent the extent to which the vectors point in the same directions and are coherent.[24-26] A high IC value indicates greater coherence of fiber directions in a given and neighbouring voxels.[23,29]

Two main approaches are adopted to analyse DTI data, namely voxel-based approach and region of interest (ROI) methods. Voxel based approach (VBA) is a hypothesis free, exploratory approach that is suitable for identifying white matter regions that differ between groups when researchers without a priori hypothesis regarding specific differences.[10,19,30-33] It is achieved by spatially normalizing all the structural images onto a stereotaxic brain atlas. Then, a voxel-by-voxel statistical comparison is made to detect regional differences between populations or to find areas that have correlations with a covariate of interest,[19] with the assumption that each individual voxel represents the same anatomical location between subjects.[33] Although voxel based analyses are highly automated and relatively fast,[32] there are several drawbacks including imperfections in spatial normalization[19] and false positivity due to multiple statistical comparisons.[34] A more novel approach to VBA is tract-based spatial statistics (TBSS)[35] and has been used in a study of recent onset schizophrenia[16] whereby the mean FA image was created and narrowed to generate a mean FA skeleton. This FA skeleton has the locally highest FA value and represents the center of all tracts common to the entire group.

On the other hand, the ROI method is often hypothesis-based, whereby one or a few specific regions of interest were specified a priori and defined by either manually placed ROIs, or extracted through quantitative fiber tracking or tractography, where it depicts selective white matter fiber tracts, commissures and fasciculi.[19,32] ROIs can be manually outlined or automatically segmented according to a fixed size (square or circle) or to the shape of the structure. Findings from ROI studies can help to validate and complement findings based on VBA analyses.[19] However, ROI method can be time consuming, and dependent on accurate segmentation.[10] A more advanced ROI method is called tractography or fiber tracking, which allows examination of white matter tracts themselves. It is done by measuring the degree to which the diffusion orientation of an initial voxel (seed point) is similar to its neighbors, which is moved along to the next voxel along the anisotropic direction to trace each fiber bundle until a stopping criterion is met.[36,37] It allow an appreciation of the orientational coherence between voxels[38,39] as well as three dimensional visual modeling of reconstructed white matter fiber systems.[19]

As white matter abnormalities have been reported to occur in early onset cases of schizophrenia, we seek to systematically review extant findings of white matter integrity disruptions in first episode schizophrenia (FES). First, we summarise the main DTI findings involving the different brain regions (cortical, subcortical white matter and white matter tracts) in FES. Second, we discuss clinical implications of these white matter disruptions and the limitations of current studies. Third, we suggest potential future research directions using DTI in FES.

METHODS

A literature search of published DTI studies in FES up

Table 1. Main findings of DTI studies in FES

Authors	N	Mean age (SD), gender (M/F)	Imaging parameters	Analysis method	Main findings
Begré *et al.*[50]	7 FES 7 HC	22.6, 6/1 22.8, 6/1	1.5T/SE-EPI 12 axial slices Slice thickness: 5.0 mm, no gap	ROI of bilateral hippocampi (FA)	No difference between FES & HC
Chan *et al.*[4]	39 FES 64 HC	28.8 (6.8), 30/9 32.3 (10.2), 38/26	3.0T/EPI 15 directions 42 axial slices Slice thickness: 3.0 mm, no gap	VBA & ROI (FA & geometric indices)	↓ planar anisotrpy in right temporal-occipital in FES, corresponding to inferior longitudinal fasciculus
Cheung *et al.* [42]	25 FES 26 HC	28.5 (9.4), 13/13 28.2 (9.2), 11/14	1.5T/SE-EPI 25 directions Slice thickness: 5.0 mm with 1.5-mm gap	VBA (FA)	↓ FA in FES: Left fronto-occipital fasciculus Left inferior longitudinal fasciculus Parietal lobe, WM adjacent to right precuneus Subcortical regions: right splenium of CC, right posterior limb of internal capsule, WM adjacent to right substantia nigra Left cerebral peduncle
Cheung *et al.*[44]	34 FES 32 HC	25.4 (7.5), 17/17 27.6 (8.5), 17/15	1.5T/EPI 25 directions Slice thickness: 5.0 mm with 1.5-mm gap	VBA (FA)	↓ FA in FES: Left anterior cingulate gyrus (anterior to fronto-occipital fasciculus) Left superior temporal gyrus (adjacent to inferior longitudinal fasciculus)
Federspiel *et al.*[24]	12 FES 12 HC	23.4 (3.0), 8/4 23.2 (3.1), 8/4	1.5T/SE-EPI 6 directions 12 axial slices Slice thickness: 5.0 mm, no gap	VBA (IC)	↓ IC in FES: Right superior transverse frontopol reg (near BA10) Right medial frontal region (near BA10) Right superior temporal region (near BA42) Right anterior transverse temp reg (near BA22) Right anterior part external capsule Right anterior superior longitudinal fascicle Right anterior occipito-frontal fascicle Left inferior transv frontopol region (near BA10) Left posterior cingulate (BA23) Left anterior crus internal capsule Left posterior radiation CC ↑ IC in FES: Right anterior thalamic peduncle Right optic radiation Left posterior part external capsule
Friedman *et al.*[53]	40 FES 39 HC 40 SCZ 40 HC	25.7 (5.8), 30/10 25.4 (6.0), 28/11 45.2 (17.2), 28/12 45.2 (17.5), 28/12	3.0T/EPI 12 directions 28 axial slices Slice thickness: 3.0 mm with 1 mm gap	ROI (FA)	↓ FA in left inferior longitudinal fasciculus in FES ↓ FA in bilateral forceps minor, and left inferior longitudinal fasciculus in SCZ. ↓ FA in right forceps minor & left inferior longitudinal fasciculus
Gasparotti *et al.*[51]	21 FES 21 HC	28.5 (8.8), 11/10 27.4 (7.3), 13/8	1.5T/DW-EPI 6 directions 29 axial slices Slice thickness: 5.0 mm, no gap	ROI in genu & splenium of CC (FA)	↓ FA in the splenium of CC and not in the genu, more evident in males

till October 2011 was conducted using two major databases: National Centre for Biotechnology Information (NCBI) PubMed (MEDLINE) and ScienceDirect Online. The focus of the search was defined by the key words ‘schizophrenia’, ‘first episode’ and ‘diffusion tensor imaging’. Studies were included if they satisfied the following criteria: (1) the patient population had a diagnosis of FES and (2) diffusion tensor imaging was an imaging technique used and (3) the article was published in English. Additionally, references from the selected papers were evaluated and included if they were found to be relevant to the focus of this systematic review.

Table 1. Continued

Authors	N	Mean age (SD), gender (M/F)	Imaging parameters	Analysis method	Main findings
Hao *et al.*[40]	21 FES 21 HC	23.7 (5.5), 12/9 25.1 (4.6), 10/11	1.5T/SE-EPI 13 directions 30 axial slices Slice thickness: 4.0 mm, no gap	VBA (FA)	↓ FA in FES: Bilateral cerebral peduncle Bilateral hippocampus gyrus Right corona radiate Bilateral precuneus Bilateral cuneus Left fronto-orbital area Right middle frontal lobe Bilateral inferior temporal gyrus Right superior cerebellar peduncle Bilateral insular Right anterior cingulum
Karlsgodt *et al.*[16]	12 EOS 17 HC	20.9 (3.5), 7/5 20.6 (2.0), 9/8	1.5T 6 directions 75 interleaved slices Slice thickness: 2.0 mm, no gap	TBSS (FA) ROI in bilateral SLF	↓ FA in the bilateral superior longitudinal fasciculus in EOS
Kong *et al.*[67]	15 FES 15 Chronic SCZ 15 HC	24.3 (6.4), 10/5 24.3 (6.4), 10/5 24.2 (6.2), 10/5	1.5T/SE-EPI 13 directions 30 axial slices Slice thickness: 4.0 mm, no gap 2×2×2 mm^3	VBA & Fibertracking (FA)	Significant ↓ FA in genu CC when chronic group was compared with FES and HC. No other regions showed significant differences among the 3 groups No significant difference between FES and HC FA and mean FA in genu CC: Chronic group<FES<HC
Luck *et al.*[49]	32 FES 25 HC	23.6 (0.7), 22/10 24.2 (0.8), 13/12	1.5T/SE-EPI 60 directions Slice thickness: 4.4 mm, no gap	Tractography of the fornix	↓ FA in the bilateral fornices in FES
Luck *et al.*[52]	44 FEP patients consisting of: 20 FEP with good outcome 24 FEP with poor outcome 30 HC	23.2 (0.5), 31/13 24.2 (0.6), 12/8 22.8 (0.8), 19/5 24.5 (0.5), 18/12	1.5T/SE-EPI 60 directions 60 axial slices Slice thickness: 2.2 mm, no gap	Tractography (FA) of SLF, uncinate fasciculus and cingulum	↓ FA in FEP compared to HC: Uncinate fasciculus Superior longitudinal fasciculus ↓ FA in FEP with poor outcome compared to FEP with good outcome: Uncinate fasciculus Superior longitudinal fasciculus No significant difference in cingulum cingulate gyrus part and cingulum hippocampal part
Moriya *et al.*[45]	19 FES 19 HC	29.9 (12), 9/10 29.7 (11.3), 9/10	3.0T/SE-EPI 25 directions Slice thickness: 4.0 mm, no gap	VBA (FA & MD)	↑ MD in the left parahippocampal gyrus, left insula, and right anterior cingulate gyrus in FES No significant difference in FA and brain volume between FES and HC groups
Pérez-Iglesias *et al.*[48]	62 FEP 54 HC	30.8 (9.5), 31/31 29.9 (7.7), 33/21	1.5T/SE-EPI 25 directions 27 axial slices Slice thickness: 5.0 mm, no gap	VBA (FA)	↓ FA in FEP in four clusters, bilaterally to WM regions of: Superior longitudinal fasciculus Inferior longitudinal fasciculus Forceps major Superior and anterior thalamic radiation Corpus callosum
Peters *et al.*[37]	10 FES 10 UHR 10 HC	21.2 (3.0) 21.6 (2.8) 21.1 (2.8) All males	3.0T/SE-EPI 16 directions	Tractography (FA)	No significant difference in FA values for uncinate & arcuate fasciculus, anterior & dorsal cingulum, and CC

Table 1. Continued

Authors	N	Mean age (SD), gender (M/F)	Imaging parameters	Analysis method	Main findings
Price *et al.*[27]	20 FES 29 HC	24.95, 14/6 28.06, 11/18	1.5T/DW-EPI 7 directions 21 axial interleaved slices Slice thickness: 5 mm	ROI of CC (FA and MD)	No significant difference in FA and MD in both genu and splenium of CC between FES and HC, after adjusting for gender, age, and handedness
Qiu *et al.*[17]	32 FES 49 HC	28.0 (6.4), 8/32 31.1 (9.6), 16/49	3.0T/SE-EPI 16 directions 42 axial slices Slice thickness: 3.0 mm	ROI for thalamus (FA & MD) - using a thalamus mask	No significant difference in FA and MD in both left and right thalamus between FES and HC
Schneiderman *et al.*[46]	35 adults with SCZ 23 adolescents with FEP 33 HC adults matched with adults with SCZ 15 HC matched adolescents with FEP	43.1 (10.8), 25/10 16.1 (2.1), 15/8 42.2 (11.5), 20/13 17.1 (2.1), 8/7	1.5T 6 directions 14 axial slices Slice thickness: 7.5 mm	ROI (RA)	↑ FA in: 2 anterior internal capsule in right hemisphere adolescents with FEP Right anterior thalamic radiations in female patients Left anterior fasciculus in female patients Frontal superior longitudinal fasciculus in female patients Right CC: body in male patients, genu and anterior portion of splenium in female patients Left CC: genu in female patients ↓ FA in: Posterior, genu and posterior limb of internal capsule, more pronounced in adolescent males with FEP in left hemisphere Right anterior thalamic radiations in male patients Left inferior level of fronto-occipital fasciculus in male patients Superior level of fronto-occipital fasciculus in female patients Bilateral frontal anterior fasciculus for male patients and right frontal anterior fasciculus for female patients Frontal superior longitudinal fasciculus extending superiorly to the temporal lobe in male patients, prominently in male adolescents with FEP Right cingulum bundle in male patients, left cingulum bundle in female patients Temporal-occipital region, more prominently in posterior temporal region in female adolescent with FEP Right CC: genu and splenium in male patients, body and posterior portion of splenium in female patients Left CC: body and splenium in female patients, left CC in male patients with the exception of the anterior portion of the genu
Szeszko *et al.*[41]	10 FES 13 HC	26.9 (4.6), 6/4 28.9 (6.0), 7/6	1.5 T/SE-EPI 7 directions 18 axial slices Slice thickness: 5.0 mm	VBA (FA)	↓ FA in FES: Left middle frontal gyrus region Left posterior temporal gyrus region Left internal capsule extending into the globus pallidus

RESULTS

Overall, we reviewed twenty-two studies that have adopted DTI to study white matter abnormalities in FES (Table 1). The findings are grouped into white matter pathology affecting cortical, subcortical and white matter tracts (Table 2) and further summarised into a figure (Fig. 1).

Table 1. Continued

Authors	N	Mean age (SD), gender (M/F)	Imaging parameters	Analysis method	Main findings
Tang et al.[56]	38 EOS 38 HC	16.3 (1.0), 20/18 16.5 (0.9), 20/18	1.5 T/SE-EPI 13 directions 30 axial slices Slice thickness: 4.0 mm, no gap	VBA & ROI (FA)	↓ FA in the right anterior cingulum region in EOS
Wang et al.[43]	68 FES, consisting of: 22 FES with PFH 46 FES with NFH 100 HC	24.1 (8.0), 32/36 24.0 (8.9), 7/15 24.2 (7.7), 25/21 25.6 (8.1), 52/48	3.0T/SE-EPI 15 directions 42 axial slices Slice thickness: 3.0 mm, no gap	VBA (FA)	↓ FA in FES compared to HC: Right CC Left CC Left temporal lobe ↓ FA in both FES with PFH and with NFH compared to HC: Right CC Left temporal lobe Right parietal lobe precuneus Left occipital lobe precuneus
White et al.[47]	31 FES 83 Chronic SCZ 43 HC matched with FES 95 HC matched chronic	25.2 (6.7), 22/9 36.4 (11.0), 62/21 25.2 (6.6), 24/19 34.0 (11.3), 57/38	Different image acquisition and parameters on 4 sites	VBA (FA)	When comparison between HC and combined FES and chronic patients, patients had ↓ FA in the whole brain, frontal, parietal, occipital and temporal lobes. None of the regions were significant in a comparison between FES vs HC matched FES, nor between FES vs chronic group although chronic patients had lower FA than FES.

BA, Brodmann Area; CC, corpus callosum; DTI, diffusion tensor imaging; EOS, early onset psychosis; EPI, echo planar protocol; FA, fractional anisotropy; FEP, first episode psychosis; FES, first episode schizophrenia; HC, healthy control; IC, intervoxel coherence; MD, mean diffusivity; NFH, negative family history; RA, relative anisotropy; PFH, positive family history; ROI, region of interest; SCZ, schizophrenia; SLF, superior longitudinal fasciculus; TBSS, tract-based spatial statistics; UHR, ultra high risk; VBA, voxel-based approach; WM, white matter.

Cortical Regions

Several DTI studies reported a decrease of FA in medial and middle frontal lobe,[24,40,41] precuneus and parietal lobe,[40,42,43] anterior and posterior cingulate cortex[24,44,45] but predominantly in the temporal lobe such as the superior temporal gyrus,[24,44] inferior temporal gyrus,[40] temporal-occipital region,[4] and posterior temporal regions.[41,43,46] The majority of the findings were generated in studies that employed VBA method and some of these studies also detected white matter abnormalities in subcortical regions within the FES group, suggesting evidence of disconnectivity between brain regions early in the illness. However, a large collaborative and multisite study by the MIND Clinical Imaging Consortium which studied 31 patients with FES, 83 patients with chronic schizophrenia found significant FA differences only in patients with chronic schizophrenia but not in the FES group, although FA was significantly lower in entire patient group (chronic schizophrenia and FES) across the frontal, parietal, occipital and temporal lobes.[47] Two DTI studies which included ROI methods reported anisotropy changes in temporo-occipital region in FES compared to the healthy controls (HCs).[4,46] Female adolescents with first episode of psychosis showed more prominent FA reduction in posterior temporal region[46] whilst planar anisotropy reduction was found within right temporal- occipital region in FES.[4]

Subcortical Regions

Overall, DTI findings in subcortical regions are relatively more scant. FA reductions were found in the anterior and poster internal capsule using both VBA and ROI.[41,42,46,48] White matter abnormalities were also observed in external capsule, where patients with FES exhibited lower IC in anterior part and higher IC in posterior portion[24] and tractography revealed FA reductions in the fornix.[49] With regard to the hippocampus, VBA studies found lower FA in bilateral hippocampal gyri[40] and increase of MD in the left parahippocampal gyrus,[45] in contrast to negative finding of a ROI study.[50]

Table 2. Summary of DTI findings in FES

WM regions	VBA			ROI/Tractography		
	↓ FA/ ↑MD in FES	↑ FA in FES	No difference	↓ FA in FES	↑ FA in FES	No difference
Cortical regions						
Frontal lobe	Szeszko *et al.*[41] Federspiel *et al.*[24] Hao *et al.*[40]		White *et al.*[47]			
Temporal lobe & temporal-occipital regions	Szeszko *et al.*[41] Federspiel *et al.*[24] Hao *et al.*[40] Chan *et al.*[4] Moriya *et al.*[45] Cheung *et al.*[44] Wang *et al.*[43]		White *et al.*[47]	Schneiderman *et al.*[46]		
Parietal lobe	Hao *et al.*[40] Cheung *et al.*[42] Wang *et al.*[43]		White *et al.*[47]			
Cingulate gyrus						Luck *et al.*[52]
Anterior	Moriya *et al.*[45] Cheung *et al.*[44]					
Posterior	Federspiel *et al.*[24]					
Subcortical regions						
Hippocampus	Hao *et al.*[40] Moriya *et al.*[45]					Begré *et al.*[50] Luck *et al.*[52]
Internal capsule						
Anterior	Szeszko *et al.*[41] Federspiel *et al.*[24] Pérez-Iglesias *et al.*[48]				Schneiderman *et al.*[46]	
Posterior	Cheung *et al.*[42]			Schneiderman *et al.*[46]		
External capsule						
Anterior	Federspiel *et al.*[24]					
Posterior		Federspiel *et al.*[24]				
Fornix				Luck *et al.*[49]		
WM tracts						
Corpus callosum	Wang *et al.*[43]		Kong *et al.*[67]			
Genu	Pérez-Iglesias *et al.*[48]			Schneiderman *et al.*[46]	Schneiderman *et al.*[46]	Price *et al.*[27]
Splenium	Federspiel *et al.*[24]			Cheung *et al.*[42] Gasparotti *et al.*, 2009 Schneiderman *et al.*[46]	Schneiderman *et al.*[46]	Price *et al.*[27] Peters *et al.*[37]
Cingulum				Schneiderman *et al.*[46]		Peters *et al.*[37] Luck *et al.*[52]
Anterior	Hao *et al.*[40] Tang *et al.*[56]			Tang *et al.*[56]		
Posterior						
Superior longitudinal fasciculus	Federspiel *et al.*[24] Pérez-Iglesias *et al.*[48]			Karlsgodt *et al.*[16] Luck *et al.*[52]	Schneiderman *et al.*[46]	
Inferior longitudinal fasciculus	Cheung *et al.*[42] Chan *et al.*[4] Pérez-Iglesias *et al.*[48] Cheung *et al.*[44]			Friedman *et al.*[53]		
Arcuate fasciculus						Peters *et al.*[37]
Uncinate fasciculus				Luck *et al.*[52]		Peters *et al.*[37]
Thalamic radiation (thalamocortical fiber)	Pérez-Iglesias *et al.*[48]			Schneiderman *et al.*[46]	Schneiderman *et al.*[46]	
Occipital-frontal asciculus	Federspiel *et al.*[24] Cheung *et al.*[42] Pérez-Iglesias *et al.*[48] Cheung *et al.*[44]				Schneiderman *et al.*[46]	

DTI, diffusion tensor imaging; FA, fractional anisotropy; FES, first episode schizophrenia; MD, mean diffusivity; ROI, region of interest; VBA, voxel-based approach; WM, white matter.

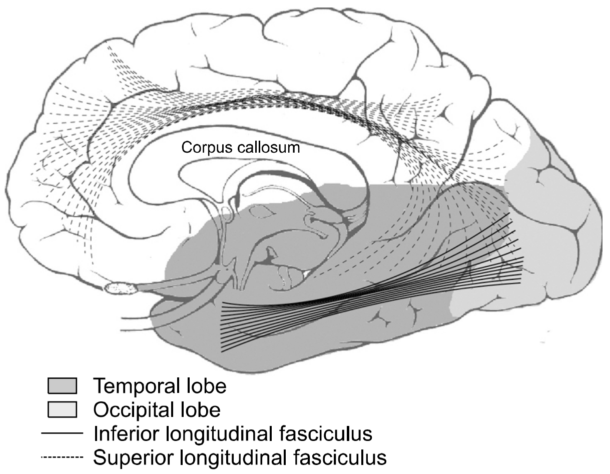

Fig. 1. Major brain regions implicated in first episode schizophrenia (FES) based on diffusion tensor imaging studies. A parasagittal section of the cerebrum shows the major brain regions and white matter tracts, i.e., temporal lobe (highlighted dark grey), occipital lobe (highlighted light grey), corpus callosum, inferior (straight lines) and superior longitudinal fasciculi (dotted lines) that have been shown to exhibit white matter abnormalities in FES.

White Matter Tracts

Corpus callosum

Changes in white matter integrity within corpus callosum (CC), a commissural tract comprising the largest bundle of fibers connecting the two brain hemispheres, have been reported in studies employing both VBA and ROI methods.[24,42,43,46,48,51] FA reductions are observed in the splenium[24,42,51] as well as genu of CC.[48] Gasparotti *et al*.[51] found that drug naïve FES patients exhibited a significant decrease of mean FA in the splenium but not genu of CC especially in males suggesting possible gender effects on CC white matter integrity. In addition, decrease of FA values was seen in the left genu and splenium of female patients, and right genu and splenium of male patients.[46] There were two negative studies. Peters *et al*.,[37] employing a tractography method in 10 male patients with FES and 10 subjects with ultra high risk, found no difference in FA and trace and an earlier ROI study by Price *et al*.[27] with a bigger sample size also found no significant difference in MD and FA between FES patients and HC.

Association Fibers

Abnormalities in the white matter association fibers, such as the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF) and fronto-occipital fasciculus (FOF) have been observed in patients with FES. Reductions of FA in the SLF, which connects the frontal lobe with occipital and temporal areas, have been reported,[16,24,46,48,52] especially on right and verbal working memory was correlated with the left SLF.[16] Patients with FES were found with lower FA in the ILF bilaterally,[4,42,44,48,53] and FA in the left ILF was correlated with PANSS positive symptom subscale scores.[44] Reductions of FA were also found in the UF which are anterior temporo-frontal fiber tracts connecting orbito-frontal and anterior and medial temporal lobes[52] and FOF, which extends backward from the frontal lobe and spreading into the temporal and occipital lobes in VBA and ROI studies.[24,42,44,46,48] In contrast, findings on arcuate fasciculus (AF), a fiber tract that stems from the caudal part of the superior temporal gyrus that arches around the Sylvian fissure, sweeps around insula and extends to the lateral prefrontal cortex, the superior and middle frontal regions,[54] have been negative,[37] suggesting sparing of AF in the early stage of schizophrenia.

Limbic system fibers and other fibers

The cingulum fibers project both posteriorly from the cingulate gyrus to the entorhinal cortex, temporal lobe (posterior cingulum) and anteriorly to the premotor, prefrontal regions and the striatum (anterior cingulum). The fornix connects the hippocampus to the mamillary bodies, nucleus accumbens, medial prefrontal cortex and septal regions, thus this fiber serves as the main output and input pathway for hippocampus.[49] While the cingulum tracks along the ventral surface of the hippocampus, the fornix projects along its dorsal surface.[55] Reductions of FA values were found in the cingulum especially anteriorly,[40,46,56] but not in tractography studies.[37,52] One study found lower FA in the fornix bilaterally.[49] Thalamic radiation, or thalamocortical fiber, is a bundle of projection fibers that provides a functional loop between the cerebral cortex and the thalamus. All thalamic radiations converged into the internal capsule, located between the putamen and the thalamus-caudate nucleus regions.[55] This bundle has been reported to be affected in patients with early episode of psychosis,[46,48] with FA reduction in male patients and FA increase in female patients compared to the HC.[46]

Clinical Correlations between White Matter and Clinical Symptoms and Cognitive Measures

Positive syndrome subscale scores of the Positive and Negative Syndrome Scale (PANSS) were correlated with right ILF,[4,44] left FOF,[44] and white matter adjacent to right lateral ventricle.[45] Correlations involving negative symptoms are inconsistent with positive correlations involving SLF and UF,[52] white matter adjacent to lateral ventricles[45] and absence of correlation with the fornix.[49] To date, only two studies have used various cognitive tasks to examine the correlation between deficits in cognitive functioning with white matter abnormalities in FES.[16,17] Using TBSS, Karlsgodt *et al.*[16] found that lower FA values in the left SLF correlated with verbal working memory assessed using a modified Sternberg item recognition task in FES. Qiu *et al.* [17] found no difference in thalamic MD and FA between FES and HC groups, but noted that the left thalamic FA was correlated with spatial working memory in FES.

DISCUSSION

There are several notable findings. First, extant DTI studies in patients with FES have revealed evidence of white matter abnormalities early in the course of illness involving cortical and subcortical regions as well as white matter tracts. Second, these cerebral white matter changes have been correlated with specific cognitive deficits (such as working memory) as well as clinical symptoms (such as positive more than negative symptoms), suggesting that biological changes may underlie these clinical factors in FES. However, these findings have to be carefully interpreted, as most studies have small sample sizes, and need to take into account gender and laterality effects as well as the effects of antipsychotic medications on the findings especially if the subjects have been started on such treatment at the time of recruitment and prospectively.

Changes in white matter integrity may be the result of different pathology including that involving the oligodendrocytes and myelin.[57] Dysmyelination and cellular changes in density and size of the oligodendrocytes may be the results of glutamatergic excitotoxicity[58,59] during critical periods of myelination. Glutamatergic excitotoxicty is related to hypofunction of N-methyl-D-aspartic (NMDA) acid receptors,[60,61] as well as impact of environmental agents or metabolic insults at other points of neurodevelopment.[57] The levels of myelin associated proteins expressions, such as Nogo, myelin-associated glycoprotein (MAG), myelin/oligodendrocyte protein (MOG), proteolipid protein (PLP1) and 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP) have also been found to be dysregulated in schizophrenia, which may reflect compromised oligodendrocyte function and myelin maintenance.[57,62,63]

The observed white matter integrity changes in the cingulate gyrus and correlation between positive symptoms in patients with FES and white matter changes in associative tracts, suggest that white matter dysconnectivity between the limbic system and the cortical regions such as frontal, temporal and occipital lobes may underlie the clinical symptoms. The white matter dysconnectivity occurring at an early stage of the illness may be neural pathways behind misinterpretion and misattribution of internally self-generated thoughts as externally generated sensory stimulus which can contribute towards the onset of psychotic symptoms including auditory hallucination as well as delusion.[64-66] The correlation between negative symptoms and specific white matter changes is less consistent which may suggest that neural factors underlying such symptoms are not yet evident at this stage of the illness but may appear with chronicity of illness. Associated cognitive deficits with white matter changes in patients with FES include verbal and spatial working memory,[16,17] highlighting that memory may be involved at an incipient phase of the illness or that the biological substrates target such cognitive function early on the course of illness. Such working memory deficits may interact and affect executive functioning which can have considerable impact on the level of psychosocial functioning of the sufferer with FES.

Decreases of FA in different cortical regions, subcortical regions as well as white matter tracts support notion of early dysconnectivity between brain regions. However, as these findings were derived from studies mostly with small sample sizes, they need to be replicated in larger studies. In some cases, inconsistency of findings may have been caused by lack of power attributed to the small sample sizes.[37,50,67] Furthermore, the inclusion criteria may vary in details such as period of evaluation during episode of illness varying from one month to one year after presentation of symptoms to the clinic or ward,[27,50] differences in matching of subjects between groups, and duration of prior treatment. A ROI study by Schneiderman *et al.*[46] pointed out the effect of gender and age of onset on changes of white matter integrity as well as the hemispheric laterality of FA in FES. Sexual dimorphism in white matter structures and anisotropy have been investigated and evident in other DTI studies of healthy subjects, which involves the CC, thalamus, cingulum, superior corona radiate, corticospinal tracts, ILF and SLF.[68-70] In such studies, higher FA in the CC, thalamus and cingulum was found in males more than females which suggest possible underlying gender differences in the degree of myelination and coherence of cortico-cortical axonal projections.[69,70] On the other hand, adolescent females were found to have higher FA in the corona radiata, corticospinal tract, and ILF, pointing towards possible differences in and specificity of white matter neurodevelopment, organization and differentiation.[68,71,72]

The impact of medications on white matter integrity is far from well understood. One DTI study found no correlation between the dose of antipsychotic medication and FA of the whole brain and cortical regions.[47] A recent extensive literature review on 40 schizophrenia and 8 bipolar cross-sectional studies indicated no relationship between antipsychotic medication (dose, cumulative exposure) and FA or MD in 80% of the studies.[73] Bartzokis and colleagues[74,75] reported higher white matter volumes in patients treated with atypical antipsychotics compared with typical antipsychotics. Conversely, it was found that patients treated with typical antipsychotics had a decrease of white matter volume compared to HC. A longitudinal MRI study of patients with FES reported that patients in the treatment group had longitudinal white matter volume reductions,[76] highlighting the importance of tracking such white matter changes from the onset in FES and then following up over time and course of illness. The observation of such progressive changes may allow better understanding of relationship between brain white matter integrity and illness and treatment factors.

What are the implications and future directions for research? First, in light of the findings of extensive involvement of cortical and subcortical white matter regions in FES, there is a need to better understand the relationship between these neural changes with clinical manifestations, cognitive and social functioning and outcomes. Second, replication of the existing findings in larger samples from diverse populations is needed. Third, understanding the progression of these changes over the span of the illness is important whilst taking into account the possible confounding effects of age, age of onset, duration of illness, sex, and treatment. This will potentially allow better staging of the illness, identification of biomarkers for monitoring course of the illness as well as response to treatment. Fourth, network analysis of future findings may allow better appreciation of anatomical connectivity between the implicated brain white matter regions. Fifth, combination of DTI findings with genetic factors may enhance understanding of the neurobiology of FES and how these factors may affect the white matter neuroplasticity.

In conclusion, despite heterogeneity of DTI findings in FES, there is mounting evidence of disruptions of white matter integrity in cortical-subcortical brain regions, as well as associative and commissural tracts in FES, highlighting neural changes early in the course of schizophrenia. The correlation of these white matter integrity changes with cognitive and phenomenological factors may shed light on biological substrates underlying these clinical manifestations. Future studies need to validate these findings in larger samples of subjects and in different populations as well as chart the progress of these cerebral white matter changes over time so as to better appreciate the trajectory with illness course, treatment and chronicity.

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