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

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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 regions4-6) and corpus callosum7,8) 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.
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.\textsuperscript{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, $\lambda_1$, $\lambda_2$, $\lambda_3$) of diffusion in individual voxel. The largest eigenvalue, $\lambda_1$, is the axial (or longitudinal diffusivity), $\lambda_2$, and reflects the axonal integrity, whereas an average of $\lambda_2$ and $\lambda_3$ calculate the radial (or transverse) diffusivity, $\lambda_1$, which reflects myelin integrity.\textsuperscript{19,21} The diffusion tensor can be quantified into different indices such as fractional anisotropy (FA), mean diffusivity (MD), and relative anisotropy (RA).\textsuperscript{22} and the newly proposed indices such as geometric indices\textsuperscript{4,23} and intervoxel coherence (IC).\textsuperscript{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.\textsuperscript{27,28} RA measures the normalized standard deviation that represents the ratio of the anisotropic part of the tensor to its isotropic part.\textsuperscript{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_v) which corresponds to isotropic diffusion.\textsuperscript{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.\textsuperscript{24-26} A high IC value indicates greater coherence of fiber directions in a given and neighbouring voxels.\textsuperscript{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.\textsuperscript{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,\textsuperscript{19} with the assumption that each individual voxel represents the same anatomical location between subjects.\textsuperscript{33} Although voxel based analyses are highly automated and relatively fast,\textsuperscript{32} there are several drawbacks including imperfections in spatial normalization\textsuperscript{19} and false positivity due to multiple statistical comparisons.\textsuperscript{34} A more novel approach to VBA is tract-based spatial statistics (TBSS)\textsuperscript{35} and has been used in a study of recent onset schizophrenia\textsuperscript{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.\textsuperscript{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.\textsuperscript{19} However, ROI method can be time consuming, and dependent on accurate segmentation.\textsuperscript{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.\textsuperscript{36,37} It allow an appreciation of the orientational coherence between voxels as well as three dimensional visual modeling of reconstructed white matter fiber systems.\textsuperscript{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                                                                 |
|-----------------|-------|----------------------------|-------------------|-----------------------|-------------------------------------------------------------------------------|
| Begrè et al.    | 7 FES | 22.6, 6/1                   | 1.5T/SE-EPI, 12 axial slices Slice thickness: 5.0 mm, no gap | ROI of bilateral hippocampi | No difference between FES & HC                                               |
|                 | 7 HC  | 22.8, 6/1                   |                   |                       |                                                                               |
| Chan et al.     | 39 FES| 28.8 (6.8), 30/9            | 3.0T/EPI, 15 directions Slice thickness: 3.0 mm, no gap | VBA & ROI (FA & geometric indices) | ↓ planar anisotropy in right temporal-occipital in FES, corresponding to inferior longitudinal fasciculus |
|                 | 64 HC | 32.3 (10.2), 38/26          |                   |                       |                                                                               |
| Cheung et al.   | 25 FES| 28.5 (9.4), 13/13           | 1.5T/SE-EPI, 25 directions Slice thickness: 5.0 mm with 1.5-mm gap | ROI (FA) | ↓ FA in FES:                                                                      |
|                 | 26 HC | 28.2 (9.2), 11/14           |                   |                       | 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.   | 34 FES| 25.4 (7.5), 17/17           | 1.5T/EPI, 25 directions Slice thickness: 5.0 mm with 1.5-mm gap | VBA (FA) | ↓ IC in FES:                                                                    |
|                 | 32 HC | 27.6 (8.5), 17/15           |                   |                       | Left anterior cingulate gyrus (anterior to fronto-occipital fasciculus)       |
|                 |       |                            |                   |                       | Left superior temporal gyrus (adjacent to inferior longitudinal fasciculus)   |
| Federspiel et al.| 12 FES| 23.4 (3.0), 8/4             | 1.5T/SE-EPI, 6 directions Slice thickness: 5.0 mm, no gap | VBA (IC) | ↓ IC in FES:                                                                    |
|                 | 12 HC | 23.2 (3.1), 8/4             |                   |                       | Right superior transverse fronto-parietal region (near BA10)                 |
|                 |       |                            |                   |                       | Right medial frontal region (near BA10)                                      |
| Friedman et al. | 40 FES| 25.7 (5.8), 30/10           | 3.0T/EPI, 12 directions Slice thickness: 3.0 mm with 1.5-mm gap | ROI (FA) | ↓ FA in left inferior longitudinal fasciculus in FES                         |
|                 | 39 HC | 25.4 (6.0), 28/11           |                   |                       | ↓ FA in bilateral forceps minor, and left inferior longitudinal fasciculus in SCZ. |
|                 | 40 SCZ| 45.2 (17.2), 28/12          |                   |                       | ↓ FA in right forceps minor & left inferior longitudinal fasciculus          |
|                 | 40 HC | 45.2 (17.5), 28/12          |                   |                       |                                                                               |
| Gasparotti et al.| 21 FES| 28.5 (8.8), 11/10           | 1.5T/DW-EPI, 6 directions 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          |
|                 | 21 HC | 27.4 (7.3), 13/8            |                   |                       |                                                                               |

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.
| Authors          | N       | Mean age (SD), gender (M/F) | Imaging parameters | Analysis method | Main findings                                                                                                                                                                                                 |
|------------------|---------|-----------------------------|--------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hao et al<sup>40</sup> | 21 FES  | 23.7 (5.5), 12/9            | 1.5T/SE-EPI        | 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 |
|                  | 21 HC   | 25.1 (4.4), 10/11           | 13 directions, 30 axial slices, Slice thickness: 4.0 mm, no gap |
| Karlsgodt et al<sup>16</sup> | 12 EOS  | 20.9 (3.5), 7/5             | 1.5T               | TBSS (FA)       | ↓ FA in the bilateral superior longitudinal fasciculus in EOS                                                                                                                                             |
|                  | 17 HC   | 20.6 (2.0), 9/8             | 6 directions, 75 interleaved slices, Slice thickness: 2.0 mm, no gap |
| Kong et al<sup>67</sup> | 15 FES  | 24.3 (6.4), 10/5            | 1.5T/SE-EPI        | VBA & Fibertracting (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                                                                                                                                             |
|                  | 15 Chronic SCZ | 24.3 (6.4), 10/5 | 13 directions, 30 axial slices, Slice thickness: 4.0 mm, no gap |
|                  | 15 HC   | 24.2 (6.2), 10/5            | 30 axial slices, Slice thickness: 4.0 mm, no gap |
| Luck et al<sup>49</sup> | 32 FES  | 23.6 (0.7), 22/10           | 1.5T/SE-EPI        | Tractography of the fornix | ↓ FA in the bilateral fornices in FES                                                                                                                                                                      |
|                  | 25 HC   | 24.2 (0.8), 13/12           | 60 directions, Slice thickness: 4.4 mm, no gap |
| Luck et al<sup>52</sup> | 44 FEP patients consisting of: 20 FEP with good outcome 24 FEP with poor outcome | 23.2 (0.5), 31/13 | 1.5T/SE-EPI | Tractography (FA) of SLF, uncinate fasciculus and cingulum | ↓ FA in FEP compared to HC: Uncinate fasciculus, Superior longitudinal fasciculus, Superior longitudinal fasciculus, Uncinate fasciculus, Superior longitudinal fasciculus |
|                  | 30 HC   | 24.5 (0.5), 18/12           | 60 directions, Slice thickness: 2.2 mm, no gap |
| Moriya et al<sup>45</sup> | 19 FES  | 29.9 (12), 9/10             | 3.0T/SE-EPI        | VBA (FA & MD)   | ↑ MD in the left parahippocampal gyrus, left insula, and right anterior cingulate gyrus in FES                                                                                                                |
|                  | 19 HC   | 29.7 (11.3), 9/10           | 25 directions, Slice thickness: 4.0 mm, no gap |
| Pérez-Iglesias et al<sup>66</sup> | 62 FEP | 30.8 (9.5), 31/31          | 1.5T/SE-EPI        | 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 No significant difference in FA values for uncinate & arcuate fasciculus, anterior & dorsal cingulum, and CC |
|                  | 54 HC   | 29.9 (7.7), 33/21           | 25 directions, 27 axial slices, Slice thickness: 5.0 mm, no gap |
| Peters et al<sup>37</sup> | 10 FES  | 21.2 (3.0)                 | 3.0T/SE-EPI        | Tractography (FA) | No significant difference in FA values for uncinate & arcuate fasciculus, anterior & dorsal cingulum, and CC                                                                                               |
|                  | 10 UHR  | 21.6 (2.8)                 | 16 directions |
|                  | 10 HC   | 21.1 (2.8)                 | All males |
### Table 1. Continued

| Authors              | N   | Mean age (SD), gender (M/F) | Imaging parameters | Analysis method | Main findings                                                                 |
|----------------------|-----|-----------------------------|--------------------|-----------------|-------------------------------------------------------------------------------|
| Price et al.²⁷       | 20  | FES 24.95, 14/6             | 1.5T/DW-EPI 7 directions | 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 28.0 (6.4), 8/32        | 3.0T/SE-EPI 16 directions | 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 43.1 (10.8), 25/10 | 1.5T 6 directions | 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 |
|                     | 23  | adolescents with FEP 16.1 (2.1), 15/8 | 14 axial slices | Slice thickness: 7.5 mm | ↓ 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 superiority 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 |
| 33 HC adults matched with SCZ | 42.2 (11.5), 20/13 | 18 axial slices | 1.5T/SE-EPI 14 axial slices | Slice thickness: 7.5 mm | ↓ FA in FES:  
Left middle frontal gyrus region  
Left posterior temporal gyrus region  
Left internal capsule extending into the globus pallidus |
| 15 HC matched adolescents with FEP | 17.1 (2.1), 8/7 | 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.         | 38 EOS| 16.3 (1.0), 20/18           | 1.5 T/SE-EPI       | VBA & ROI (FA) | ↓ FA in the right anterior cingulum region in EOS |
|                     | 38 HC | 16.5 (0.9), 20/18           | 13 directions     |                |                                                   |
|                     |       |                            | 30 axial slices    |                |                                                   |
|                     |       |                            | 4.0 mm, no gap    |                |                                                   |
| Wang et al.         | 68 FES| 24.1 (8.0), 32/36           | 3.0 T/SE-EPI       | VBA (FA)       | ↓ FA in FES compared to HC:                       |
|                     |       |                            | 15 directions     |                | Right CC                                          |
|                     |       |                            | 42 axial slices    |                | Left temporal lobe                                |
|                     |       |                            | 3.0 mm, no gap    |                |                                                   |
|                     | 22 FES| 24.0 (8.9), 7/15            |                   |                |                                                   |
|                     |       |                            |                   |                |                                                   |
|                     | 46 FES| 24.2 (7.7), 25/21          |                   |                |                                                   |
|                     |       |                            |                   |                |                                                   |
|                     | 100 HC| 25.6 (8.1), 52/48          |                   |                |                                                   |
| White et al.        | 31 FES| 25.2 (6.7), 22/9            | Different image    | VBA (FA)       | When comparison between HC and combined FES      |
|                     |       |                            | acquisition and   |                | and chronic patients, patients had ↓ FA in the   |
|                     | 83 SCZ| 36.4 (11.0), 62/21         | parameters on     |                | whole brain, frontal, parietal, occipital and     |
|                     | 43 HC | 25.2 (6.6), 24/19          | 4 sites           |                | temporal lobes.                                   |
|                     | 95 HC | 34.0 (11.3), 57/38         |                   |                |                                                   |

Cortical Regions

Several DTI studies reported a decrease of FA in medial and middle frontal lobe, anterior and posterior cingulate cortex, but predominantly in the temporal lobe such as the superior temporal gyrus, inferior temporal gyrus, temporal-occipital region, and posterior temporal regions. 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 disconnection 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. Two DTI studies which included ROI methods reported anisotropy changes in temporal-occipital region in FES compared to the healthy controls (HCs). Female adolescents with first episode of psychosis showed more prominent FA reduction in posterior temporal region whilst planar anisotropy reduction was found within right temporal-occipital region in FES.

Subcortical Regions

Overall, DTI findings in subcortical regions are relatively more scant. FA reductions were found in the anterior and posterior internal capsule using both VBA and ROI. 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 and tractography revealed FA reductions in the fornix. With regard to the hippocampus, VBA studies found lower FA in bilateral hippocampal gyrus and increase of MD in the left parahippocampal gyrus, in contrast to negative finding of a ROI study.
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. (2011)                     | White et al. (2017) |
|                          | Federspiel et al. (2016)                  |                  |               |
|                          | Hao et al. (2011)                         |                  |               |
| Temporal lobe &         | Szeszko et al. (2011)                     | White et al. (2017) |
| temporal-occipital regions | Federspiel et al. (2016)                  | Schneiderman et al. (2016) |
|                          | Hao et al. (2011)                         |                  |               |
|                          | Chan et al. (2016)                       |                  |               |
|                          | Moriya et al. (2016)                     |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |
|                          | Wang et al. (2016)                       |                  |               |
| Parietal lobe            | Hao et al. (2011)                         | White et al. (2017) |
|                          | Cheung et al. (2016)                     |                  |               |
|                          | Wang et al. (2016)                       |                  |               |
| Cingulate gyrus          |                                          |                  |               |
| Anterior                 | Moriya et al. (2016)                     |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |
|                          | Federspiel et al. (2016)                  |                  |               |
| Posterior                |                                          |                  |               |
| Hippocampus              | Hao et al. (2011)                         |                  |               |
|                          | Moriya et al. (2011)                     |                  |               |
| Internal capsule         | Szeszko et al. (2011)                     |                  |               |
| Anterior                 | Federspiel et al. (2016)                  | Schneiderman et al. (2016) |
|                          | Pérez-Iglesias et al. (2016)             |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |
| Posterior                |                                          |                  |               |
| External capsule         |                                          |                  |               |
| Anterior                 | Federspiel et al. (2016)                  |                  |               |
| Posterior                |                                          |                  |               |
| Fornix                   |                                          |                  |               |
| WM tracts                |                                          |                  |               |
| Corpus callosum          | Wang et al. (2013)                        | Kong et al. (2017) |
| Genu                     | Pérez-Iglesias et al. (2016)             | Schneiderman et al. (2016) |
|                          | Federspiel et al. (2017)                 | Schneiderman et al. (2016) |
|                          | Cheung et al. (2017)                     | Price et al. (2017) |
|                          | Gasparotti et al., 2009                  | Schneiderman et al. (2016) |
|                          | Pérez-Iglesias et al. (2016)             | Price et al. (2017) |
|                          | Cheung et al. (2017)                     | Peters et al. (2017) |
|                          | Pérez-Iglesias et al. (2016)             | Schneiderman et al. (2016) |
|                          | Cheung et al. (2017)                     | Schneiderman et al. (2016) |
| Cingulum                 | Hao et al. (2016)                         | Tang et al. (2016) |
| AnTERIOR                 | Federspiel et al. (2016)                 | Karlgodt et al. (2016) |
|                          | Pérez-Iglesias et al. (2016)             | Luck et al. (2017) |
|                          | Cheung et al. (2016)                     | Friedmann et al. (2016) |
| Posterior                | Superior longitudinal fasciculus         |                  |               |
|                          | Federspiel et al. (2016)                 |                  |               |
|                          | Pérez-Iglesias et al. (2016)             |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |
|                          | Pérez-Iglesias et al. (2016)             |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |
| Arcuate fasciculus       |                                          |                  |               |
| Uncinate fasciculus      | Pérez-Iglesias et al. (2016)             |                  |               |
| Thalamic radiation       |                                          |                  |               |
| (thalamocortical fiber)  | Pérez-Iglesias et al. (2016)             |                  |               |
| Occipito-frontal fasciculus | Federspiel et al. (2016)               |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |
|                          | Pérez-Iglesias et al. (2016)             |                  |               |
|                          | Cheung et al. (2016)                     |                  |               |

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.
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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 splenium24,42,51] 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.,47 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.46] 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.46] Reductions of FA were also found in the UF which are anterior temporo-frontal fiber tracts connecting orbito-frontal and anterior and medial temporal lobes52] and FOIf, 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,55 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 mammillary 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.59] 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 nuclei 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]
toms are inconsistent with positive correlations involving SLF and UF, white matter adjacent to lateral ventricles and absence of correlation with the fornix. 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. Using TBSS, Karlsgodt et al. 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. 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. Dysmyelination and cellular changes in density and size of the oligodendrocytes may be the results of glutamatergic excitotoxicity during critical periods of myelination. Glutamatergic excitotoxicity is related to hypofunction of N-methyl-D-aspartic acid receptors, as well as impact of environmental agents or metabolic insults at other points of neurodevelopment. 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.

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 misinterpretation 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. The correlation between negative symptoms and specific white matter changes is less consistent which may suggest that neural factors underling 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, 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 suggest 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. 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, differences in matching of subjects between groups, and duration of prior treatment. A ROI study by Schneiderman et al. 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. 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 myeli-
nation and coherence of cortico-cortical axonal projections. 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.

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 or MD in the whole brain and cortical regions. 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. Bartzokis and colleagues reported higher white matter volumes in patients treated with atypical antipsychotics compared to 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, 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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REFERENCES

1. Picchioni MM, Murray RM. Schizophrenia. BMJ 2007;335:91-95.
2. Hulshoff Pol HE, Schnack HG, Bertens MG, Van Haren NE, Van der Tweel I, Staal WG, et al. Volume changes in gray matter in patients with schizophrenia. Am J Psychiatry 2002;159:244-250.
3. Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 2001;58:148-157.
4. Chan WY, Yang GL, Chia MY, Lau IY, Sitoh YY, Nowinski WL, et al. White matter abnormalities in first-episode schizophrenia: a combined structural MRI and DTI study. Schizophr Res 2010;119:52-60.
5. Mielman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS. MRI assessment of gray and white matter distribution in Brodmann’s areas of the cortex in patients with schizophrenia with good and poor outcomes. Am J Psychiatry 2003;160:2154-2168.
6. Takahashi T, Suzuki M, Kawasaki Y, Hayato H, Yamashita I, Nohara S, et al. Perigenual cingulate gyrus volume in patients with schizophrenia: a magnetic resonance imaging study. Biol Psychiatry 2003;53:593-600.
7. Keshavan MS, Diwadkar VA, Harrenski K, Rosenberg DR, Sweeney JA, Pettegrew JW. Abnormalities of the corpus callosum in first episode, treatment naive schizophrenia. J Neurol Neurosurg Psychiatry 2002;72:757-760.
8. McDonald C, Bullmore E, Sham P, Chinnis X, Suckling J, MacCabe J, et al. Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder: computational morphometry study. Br J Psychiatry 2005;186:369-377.
9. Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, et al. MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. Neureport 1998;9:425-430.
10. Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R, et al. A review of diffusion tensor imaging studies in schizophrenia. J Psychiatric Res 2007;41:15-30.

11. Kyriakopoulos M, Frangou S. Recent diffusion tensor imaging findings in early stages of schizophrenia. Curr Opin Psychiatry 2009;22:168-176.

12. Peters BD, Blas J, de Haan L. Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? J Psychiatr Res 2010;44:993-1004.

13. Hubl D, Koenig T, Strik W, Federspiel A, Kreis R, Boesch C, et al. Pathways that make voices: white matter changes in auditory hallucinations. Arch Gen Psychiatry 2004;61:658-668.

14. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. Biol Psychiatry 2002;52:9-14.

15. Wolkin A, Choi SJ, Szilagyi S, Sanfilipo M, Rotrosen JP, Lim KO. Inferior frontal white matter anisotropy and negative symptoms of schizophrenia: a diffusion tensor imaging study. Am J Psychiatry 2003;160:572-574.

16. Karlsgodt KH, van Eer TG, Poldrack RA, Bearden CE, Nuechterlein KH, Cannon TD. Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. Biol Psychiatry 2008;63:512-518.

17. Qin A, Zhong J, Graham S, Chia MY, Sim K. Combined analyses of thalamic volume, shape and white matter integrity in first-episode schizophrenia. Neuroimage 2009;47:1163-1171.

18. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J 1994;66:259-267.

19. Chanraud S, Zahr N, Sullivan EV, Pfefferbaum A. MR diffusion tensor imaging: a window into white matter integrity of the working brain. Neuropsychol Rev 2010;20:209-225.

20. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination found through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 2002;17:1429-1436.

21. Sun SW, Liang HF, Le TQ, Armstrong RC, Cross AH, Song SK. Differential sensitivity of in vivo and ex vivo diffusion tensor imaging to evolving optic nerve injury in mice with retinal ischemia. Neuroimage 2006;32:1195-1204.

22. Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed 1995;8:333-344.

23. Westin CF, Maier SE, Mamata H, Nabavi A, Jolesz FA, Kikinis R. Processing and visualization for diffusion tensor MRI. Med Image Anal 2002;6:93-108.

24. Federspiel A, Begré S, Kiefer C, Schroth G, Strik WK, Dierks T. Alterations of white matter connectivity in first episode schizophrenia. Neurobiol Dis 2006;22:702-709.

25. Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. Magn Reson Med 1996;36:893-906.

26. Pfefferbaum A, Sullivan EV, Hedehus M, Adalsteinsson E, Lim KO, Moseley M. In vivo detection and functional correlates of white matter microstructural disruption in chronic alcoholism. Alcohol Clin Exp Res 2000;24:214-221.

27. Price G, Bagary MS, Cercignani M, Altman DR, Ron MA. The corpus callosum in first episode schizophrenia: a diffusion tensor imaging study. J Neurol Neurosurg Psychiatry 2005;76:585-587.

28. Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology 1999;52:1626-1632.

29. Deutsch GK, Dougherty RF, Bammer R, Siok WT, Gabrieli JD, Wandell B. Children’s reading performance is correlated with white matter structure measured by diffusion tensor imaging. Cortex 2005;41:354-363.

30. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage 2000;11:805-821.

31. Mechelli A, Friston KJ, Frackowiak RS, Price CJ. Structural covariance in the human cortex. J Neurosci 2005;25:303-8310.

32. Melonakis ED, Shenton ME, Rathi Y, Terry DP, Bouix S, Kubicki M. Voxel-based morphometry (VBM) studies in schizophrenia-can white matter changes be reliably detected with VBM? Psychiatry Res 2011;193:65-70.

33. Snook L, Plewes C, Beaulieu C. Voxel based versus region of interest analysis in diffusion tensor imaging of neurodevelopment. Neuroimage 2007;34:243-252.

34. Loring DW, Meador KD, Allison JD, Pilail JJ, Lavin T, Lee GP, et al. Now you see it, now you don’t: statistical and methodological considerations in fMRI. Epilepsy Behav 2002;3:539-547.

35. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487-1505.

36. Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S. DiStudio: resource program for diffusion tensor computation and fiber bundle tracking. Comput Methods Programs Biomed 2006;81:106-116.

37. Peters BD, de Haan L, Dekker N, Blaas J, Becker HE, Dingemans PM, et al. White matter fibertracking in first-episode schizophrenia, schizoaffective patients and subjects at ultra-high risk of psychosis. Neuropsychobiology 2008;58:19-28.

38. Jones DK, Simmons A, Williams SC, Horsfield MA. Non-normative assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn Reson Med 1999;42:37-41.

39. Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M. Age-related decline in white matter anisotropy measured with spatially corrected echoplanar diffusion tensor imaging. Magn Reson Med 2000;44:259-268.

40. Hao Y, Liu Z, Jiang T, Gong G, Liu H, Tan L, et al. White matter integrity of the whole brain is disrupted in first-episode schizophrenia. Neuroreport 2006;17:23-26.

41. Szczesko PR, Ardekani BA, Asharti M, Kumra S, Robinson DG, Sevy S, et al. White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. Am J Psychiatry 2005;162:602-605.

42. Cheung V, Cheung C, McLonan GM, Deng Y, Wong JG, Yip L, et al. A diffusion tensor imaging study of structural connectivity in never-medicated, first-episode schizophrenia. Psychol Med 2008;38:877-885.

43. Wang Q, Deng W, Huang C, Li M, Ma X, Wang Y, et al. Abnormalities in connectivity of white-matter tracts in patients with familial and non-familial schizophrenia. Psychiatr Med 2011;41:1691-1700.

44. Cheung V, Chiu CP, Law CW, Cheung C, Hui CL, Chan KK, et al. Positive symptoms and white matter microstructure in never-medicated first episode schizophrenia. Psychiatr Med 2011;41:1709-1719.

45. Moriya I, Kakuda S, Abe O, Goto N, Yoshimura R, Hori H, et al. Gray and white matter volumetric and diffusion tensor imaging (DTI) analyses in the early stage of first-
episode schizophrenia. Schizophr Res 2010;116:196-203.

46. Schneiderman JS, Buchsbaum MS, Haznedar MM, Hazlett EA, Brickman AM, Shihabuddin L, et al. Age and diffusion tensor anisotropy in adolescent and adult patients with schizophrenia. Neuroimage 2009;45:662-671.

47. White T, Magnotta VA, Bockholt HJ, Williams S, Wallace S, Ehrlich S, et al. Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. Schizophr Bull 2011;37:222-232.

48. Pórez-Iglesias R, Tordesillas-Güiteres D, Barker GJ, McGuire PK, Roiz-Santínez R, Mata I, et al. White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging. Neuroimage 2010;49:199-204.

49. Luck D, Malla AK, Joober R, Lepage M. Disrupted integrity of the fornix in first-episode schizophrenia. Schizophr Res 2010;119:61-64.

50. Begré S, Federspiel A, Kiefer C, Schrot G, Dierks T, Strik WK. Reduced hippocampal anisotropy related to anteriorization of alpha EEG in schizophrenia. Neuroreport 2003;14:739-742.

51. Gasparotti R, Valsecchi P, Carletti F, Galluzzo A, Liserre M. MRI find-ings in first-episode and chronic schizophrenia patients. Am J Psychiatry 2011;168:739-742.

52. Bartzokis G, Lu PH, Nuechterlein KH, Gitlin M, Doi C, Lucas AJ, et al. Does antipsychotic medication affect white matter in schizophrenia and bipolar disorder? A review of diffusion tensor imaging literature. Eur Psychiatry 2011;26:1280.

53. Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. Harv Rev Psychiatry 1996;3:241-253.

54. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995;52:998-1007.

55. Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A 2001;98:4746-4751.

56. Karantzou G, ErmicBold, Dietrich DE. The myelination-athogenesis puzzle in schizophrenia: a literature review. Mol Psychiatry 2008;13:245-260.

57. Allen P, Amaro E, Fu CH, Williams SC, Brammer MJ, Johns LC, et al. Neural correlates of the misattribution of speech in schizophrenia. Br J Psychiatry 2007;190:162-169.

58. Allen PP, Johns LC, Fu CH, Broome MR, Vythilingum GN, McGuire PK. Misattribution of external speech in patients with hallucinations and delusions. Schizophr Res 2004;69:277-287.