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White matter deficits in first episode schizophrenia: An activation likelihood estimation meta-analysis

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ABSTRACT

Background: Diffusion tensor imaging (DTI) has been widely used in psychiatric research and has provided evidence of white matter abnormalities in first episode schizophrenia (FES). The goal of the present meta-analysis was to identify white matter deficits by DTI in FES.
Methods: A systematic search was conducted to collect DTI studies with voxel-wised analysis of the fractional anisotropy (FA) in FES. The coordinates of regions with FA changes were meta-analyzed using the activation likelihood estimation (ALE) method which weighs each study on the basis of its sample size.
Results: A total of 8 primary studies were selected, including 271 FES patients and 297 healthy controls. Among these studies, 52 regions showed reductions in the FA in FES while 2 regions had increased FA. Consistent FA reductions in the white matter of the right deep frontal and left deep temporal lobes were identified in all FES patients relative to healthy controls. Fiber tracking showed that the main tracts involved were the cingulum bundle, the left inferior longitudinal fasciculus, the left inferior fronto-occipital fasciculus and the interhemispheric fibers running through the corpus callosum.
Conclusions: The current findings provide evidence confirming the lack of connection in the fronto-limbic circuitry at the early stages of the schizophrenia. Because the coordinates reported in the primary literature were highly variable, future investigations with large samples would be required to support the identified white matter changes in FES.

1. Introduction

While gray matter deficits in schizophrenia have been widely reported (Kim et al., 2003; Lui et al., 2009a, 2009b; Whitford et al., 2005), but only a few studies have focused on cerebral white matter (Alexander and Barker, 2005; Allen et al., 2008; Andreasen, 1997), and they have produced inconsistent results (Cheung et al., 2008; Federspiel et al., 2006; Guo et al., 2012; Hao et al., 2006; Kyriakopoulos et al., 2009; Perez-Iglesias et al., 2010; Szeszko et al., 2005; Tang et al., 2010; Q. Wang et al., 2011). However, studying the white matter is crucial to understanding the neurobiological substrate of schizophrenia, because the abnormalities in white matter may play a fundamental role in the neurobehavioral manifestations of schizophrenia (Filley, 2005). Furthermore, one of the debated hypotheses of the etiopathogenesis of schizophrenia is the dysfunction in the neural connectivity (i.e., misconnection) of different cerebral areas or the neural circuitry (Andreasen et al., 1999; McGuire and Frith, 1996).

In recent decades, diffusion tensor imaging (DTI), a magnetic resonance imaging technique sensitive to the orientation of water diffusion restricted within the neuron sheath and myelination, has been widely used in psychiatric research (Stark et al., 2004). One of the commonly used DTI measures is mean diffusivity (MD), which can provide immediate information on changes in the interstitial space (i.e., the empty space between brain structures), such as those that occur following an ischemic incident (Mintorovitch et al., 1991) or inflammation (Tievsky et al., 1999). The apparent diffusion coefficient (ADC) is a similar measure, representing the magnitude of water diffusion. Another commonly used measure is fractional anisotropy (FA), which is thought to reflect the anatomical features of neural fibers, such as the axon caliber, fiber density and myelination (Scholz et al., 2009). Intervoxel coherence (IC) is similar to FA (Klingberg et al., 1999, 2000) and, indicates both the strength of the FA and the agreement between the fiber direction in neighboring voxels (Deutsch et al., 2005).

Abbreviations: DTI, diffusion tensor imaging; FES, first episode schizophrenia; FA, fractional anisotropy; ALE, activation likelihood estimation; IC, intervoxel coherence; SDM, signed differential mapping.

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Using the FA or IC, white matter deficits have been revealed in chronic schizophrenia in the anterior corpus callosum, medial frontal/anterior cingulate cortex, right anterior limb of the internal capsule and left temporal white matter (Ellison-Wright and Bullmore, 2009), although the results are inconsistent due to confounders associated with the illness chronicity and prolonged exposure to antipsychotic medication as well as possible progressive white matter atrophy (Buchanan et al., 1998; Davis et al., 2003; McDonald et al., 2005). Compared to studies with chronic patients, relatively few attempts have been made to investigate in patients with first episode schizophrenia (FES) (Cheung et al., 2008; Federspiel et al., 2006; Guo et al., 2012; Hao et al., 2006; Kyriakopoulos et al., 2009; Lu et al., 2011; Moriya et al., 2010; Perez-Iglesias et al., 2010; Szeszko et al., 2005; Tang et al., 2010; Wang et al., 2011; White et al., 2011) and the results have also been inconclusive in that some studies have identified decreased FA (Cheung et al., 2008; Federspiel et al., 2006; Guo et al., 2012; Hao et al., 2006; Kyriakopoulos et al., 2009; Perez-Iglesias et al., 2010; Szeszko et al., 2005; Tang et al., 2010; Wang et al., 2011), while others have identified increased FA (Federspiel et al., 2006; Kyriakopoulos et al., 2009) and yet more have indentified no changes (Lu et al., 2011; Moriya et al., 2010; White et al., 2011). However, the investigation of FES is important for elucidating the core pathophysiology of schizophrenia (Whitford et al., 2005) and will give significant insight into the nature of the disease. Thus, we sought to verify whether there are white matter deficits in FES and to identify their locations. As a complex statistical method, meta-analysis involves the synthesis of data from relevant studies to identify an effect or draw a conclusion, and this approach can justify and refine hypotheses for various diseases (Mak et al., 2010). Image-based meta-analyses use full image information and well-established statistics, but images are rarely available and this makes image-based meta-analyses highly unfeasible. Peak probability meta-analyses such as ALE and signed differential mapping (SDM), are more feasible because they only require the peak coordinates (Radua et al., 2011). ALE is a quality method extensively used in fMRI, VBM and DTI studies. However, only one meta-analysis with SDM has been conducted for FES, which revealed that the FA was reduced in the left temporal white matter and right posterior limb of the internal capsule in only four DTI studies (Bora et al., 2011).

Thus, the present study aims to investigate whether there are consistent white matter deficits in FES and to identify their locations using ALE meta-analysis of voxel-based DTI studies in FES.

2. Materials and methods

2.1. Inclusion of studies

Literature searches were accomplished using PubMed/Medline and EMBASE with the following keywords: ("diffusion tensor" or "DTI"), ("voxel*" or "whole brain"), ("schizophrenia" or "schizoaffective disorder"), ("first episode schizophrenia" or "FES") and ("white matter"). Additional studies were identified by manually searching the references of each article found in the initial online search. Studies published before November 2012 were selected if they met the following inclusion criteria: 1) voxel-based analysis was used to investigate changes in the entire brain or entire white matter in first episode schizophrenia patients; 2) the study compared the group of patients with healthy controls; 3) the study normalized the data of the abnormal region(s) using the Talairach space or the Montreal Neurological Institute (MNI) space and reported the three-dimensional coordinates explicitly; and 4) the study was reported in English. We also contacted authors for additional information when necessary.

Three studies were excluded due to their unclear description of whether the patients were first episode or not. One TBSS study was excluded to avoid potential confounds caused by statistical methods (Guo et al., 2012). Finally, the studies written in Chinese were excluded (Wei et al., 2011). Our initial literature search yielded 11 original articles, but 3 of them reported no FA difference between FE schizophrenia patients and the control group (Lu et al., 2011; Moriya et al., 2010; White et al., 2011), which couldn't be taken into the analysis. Finally, a total of 8 studies with 271 patients, 297 controls and 52 coordinates were included in our meta-analysis (Table 1).

Only 3 studies reported MD measures of FES, so we did not conduct an ALE meta-analysis on these limited studies which may have produced unreliable results.

2.2. Data extraction

The coordinates reported with MNI space were converted to Talairach coordinates using the Lancaster transform carried out by GingerALE 2.1.1 (Laird et al., 2005). According to the ALE manual, several coordinates (Cheung et al., 2008) that had been transformed to Talairach space using the Brett transformation, were first "un-Brett" then converted to Talairach space by the Lancaster transform.

2.3. Activation likelihood estimation

The meta-analysis was conducted by applying the GingerALE software (www.brainmap.org). The analysis was conducted in the Talairach space. The ALE technique treated the reported foci as spatial probability distributions centered on the given coordinates instead of points (Turkeltaub et al., 2002). GingerALE 2.1.1 provided a random-effects model that considered the spatial relationship between the individual foci for each study instead of a fixed-effects model. The algorithm weighted the studies included in the meta-analysis on the basis of their sample size, thereby giving more weight to the spatial conjunction of different foci from different studies than to different foci from a single study (Eickhoff et al., 2009). In practical terms, a total of 55 coordinates extracted from the studies listed in Table 1 were used to construct the ALE map. The clusters identified in the meta-analysis were obtained after calculating the ALE values of each voxel and controlling the false discovery rate (FDR) at $p < 0.01$ while applying a cluster extent threshold of 100 voxels (Chan et al., 2011).

The most probable white matter tracts crossing the clusters of voxels had significantly decreased FA values that were identified using an atlas of human white matter anatomy (Wakana et al., 2004) and DTI query software. We used the sample data supplied with the software on a normal 35-year-old male and then filtered the results with the center coordinates and volume of the region of interest as well as the tract length.

3. Results

3.1. FA decrease in FES

A total of 8 studies reported FA reductions in 52 foci in 271 FES patients compared with 297 healthy controls (Table 1). ALE analysis identified two regions with significantly decreased FA in FES patients.

Cluster 1 was activated in the white matter of the right frontal lobe (right anterior cingulum) with a maximum probability at $x = 12, y = 36$ and $z = 12$ (cluster size = 328 mm^3) (Fig. 1). Two of eight studies contributed to this cluster (Hao et al., 2006; Tang et al., 2010). White matter tracts traversing through these voxels were displayed in a bounding box size of $6.9 \times 6.9 \times 6.9$ mm^3 with DTI query software. We identified three white matter tracts traversing through the cluster namely, the inter-hemispheric fibers (via anterior corpus callosum), the cingulum bundle and the uncinate fasciculus (Fig. 2).

Cluster 2 was located in the left temporal deep white matter, with a maximum probability at $x = -40, y = -16$ and $z = -16$ (cluster size = 296 m^3) (Fig. 1). Two of eight studies contributed to this cluster (Kyriakopoulos et al., 2009; Wang et al., 2011). White matter tracts traversing this region were visualized using a $6.7 \times 6.7 \times 6.7$ mm^3 bounding box. The main tracts were the left inferior longitudinal

Table 1
VBA[a] studies of FES[b] included in the present meta-analysis.

No.	Study	Number of		Matching	Diagnosis details	Medication	Duration of illness	No. of coordinates
		Patients (male)	Controls (male)					
1	Cheung et al. (2008)	26(13)	25(11)	Age, gender, handedness, ethnicity, parental social class	DSM-IV for schizophrenia	Naive	6 months	7
2	Tang et al. (2010)	38(20)	38(20)	Age, gender, handedness, education	DSM-IV for schizophrenia or schizophreniform disorder	Naive	9.1 months	1
3	Wang et al. (2011)	68(32)	100(52)	Age, gender, handedness, education	DSM-IV for schizophreniform psychosis	Not stated	9.15/8.73 months	3
4	Federspiel et al. (2006)	12(8)	12(Not stated)	Age,gender,handedness	ICD-10 for schizophrenia	10.5 days	115.7 days	11
5	Szeszko et al. (2005)	10(6)	13(7)	Age,gender,race,handedness, parental social class	DSM-IV for schizophrenia or schizoaffective disorder	15 days	Not stated	3
6	Perez-Iglesias et al. (2010)	62(31)	54(33)	Age,gender,education, laterality index	DSM-IV for brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder	Naive or less than 6 weeks lifetime exposure	9.4 months	4
7	Hao et al. (2006)	21(12)	21(10)	Age, gender, handedness	DSM-IV for schizophrenia	Less than 2 weeks in the year or 6 weeks lifetime exposure	10.33 months	17
8	Kyriakopoulos et al. (2009)	34(26)	34(23)	Age, gender, handedness	DSM-IV for schizophrenia	21.76/20.42/naive	Not stated	6

[a] VBA, voxel based analysis.
[b] FES, first episode schizophrenia.

fasciculus, the left inferior fronto-occipital fasciculus, the inter-hemispheric fibers (via posterior corpus callosum) and the fornix (Fig. 2).

3.2. FA increases in FES

Only two studies reported FA or intervoxel coherence increases in FES compared to controls. Researchers found three clusters that yielded higher intervoxel coherence values, which included the right anterior thalamic peduncle, the right optic radiation and the left posterior part external capsule (Federspiel et al., 2006) and one frontal region including the genu of the corpus callosum and the anterior cingulum showed higher FA values (Kyriakopoulos et al., 2009). Two studies with increased FA were insufficient to conduct a meta-analysis.

4. Discussion

Using ALE meta-analysis of voxel-based DTI studies in FES, the present study confirmed two regions (the white matter of right frontal lobe and the left temporal lobe) with decreased FA in patients at the early stages of schizophrenia. These two regions involved four white matter tracts, namely, the inter-hemispheric fibers (via the anterior corpus callosum), the cingulum bundle, the left inferior longitudinal fasciculus and the left inferior fronto-occipital fasciculus. With fewer confounders, including illness chronicity, antipsychotic medication and possible progressive white matter atrophy, the current findings support the assertion that white matter deficits can be observed at the early stage of schizophrenia and may be associated with the disrupted neural circuit in FES (Wang et al., 2004).

We indentified the decreased FA in the anterior cingulate region; this region contains two main bundles, the right anterior cingulum bundle and inter-hemispheric fibers traversing through the anterior corpus callosum. The anterior cingulum is one of the regions that have been most frequently reported to be abnormal in schizophrenia patients. Evidence from histopathology, postmortem and functional imaging studies supports the involvement of white matter in the anterior cingulum in schizophrenia patients. Functional studies have found reduced metabolism of the anterior cingulate cortex in schizophrenia

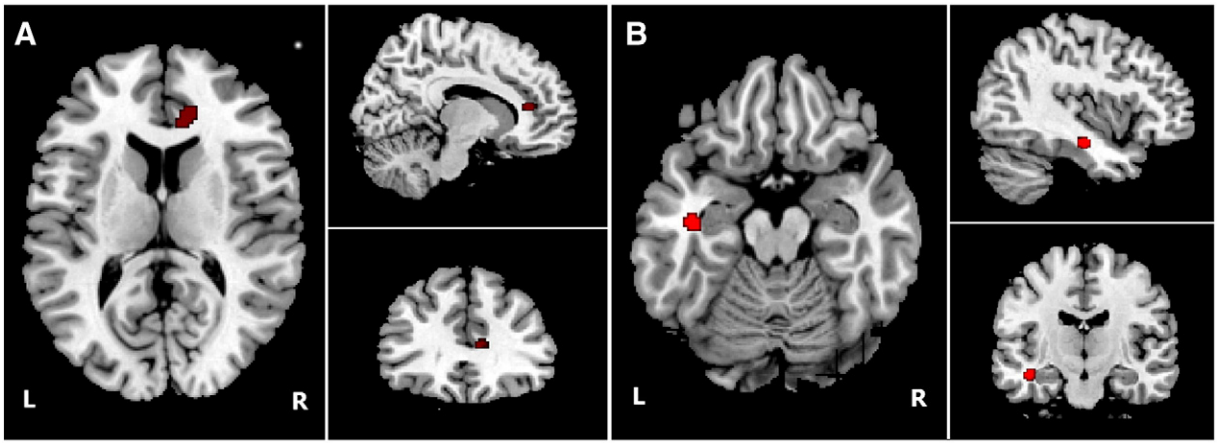

Fig. 1. Meta-analysis revealed the regions that have a reduction in fractional anisotropy in the deep white matter of the right frontal lobe (A) and left temporal lobe (B) in FES patients compared to healthy controls.

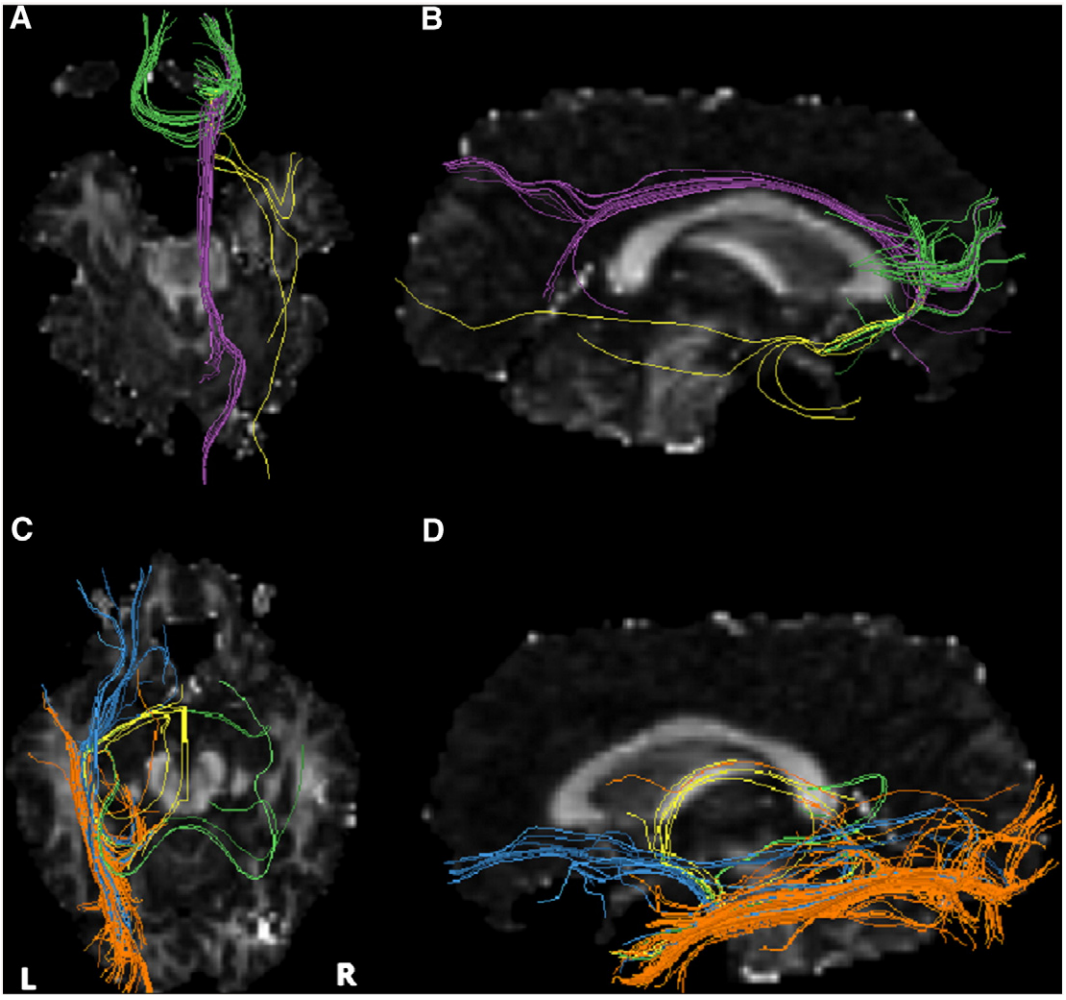

Fig. 2. White matter tracts crossing the right frontal lobe region. Three-dimensional images showing decreased FA centered on x = 12, y = 36 and z = 12 (Talairach coordinates, cluster size: 328 mm^3) and x = −10, y = −16 and z = −16 (Talairach coordinates, cluster size:296 mm^3) in the first and second rows respectively. Left image viewed from above (A, C), right image viewed from the right (B) and left (D) sides of the brain. The tracts include the cingulum bundle tracts (purple), the interhemispheric fibers running through the corpus callosum (green), the left inferior longitudinal fasciculus (orange) and the left inferior fronto-occipital fasciculus (blue). The remaining tracts are yellow (white matter tracts extracted with DTI query from the data for a single normal individual, projected on a view of an FA map).

patients when performing cognitive tasks (Carter et al., 2001; Nordahl et al., 2001). The abnormalities of the connectivity between the anterior cingulate cortex and adjoining regions were also observed in many postmortem studies of schizophrenia patients (Cohen et al., 2000). In fact, the cingulum bundle was essential to the limbic circuitry (Tamminga et al., 2000) for connections between the cingulate cortex and the other components of Broca's "grand limbic lobe" (Knochel et al., 2012b; Kubicki et al., 2003), which integrates external and internal information and mediates physiological, behavioral, and psychological responses.

A range of neurocognitive impairments are associated with the cingulate gyrus or the cingulum bundle especially for attention and working memory (Cabeza and Nyberg, 1997; Cohen et al., 1998; Kubicki et al., 2003, 2009). The cingulum bundle traverses through the thalamus and the frontal and parietal regions, which are thought to support cognitive processes including central executive functions of working memory as well as attention functions (Cabeza and Nyberg, 1997; Cohen et al., 1998; Kubicki et al., 2003, 2009), all of which support the above-mentioned viewpoint. Findings from patients with cingulotomy also supported the premise that lesions in the anterior cingulate gyrus are related to deficits of attention and sustained attention as well as executive dysfunction, which are prominent features of schizophrenia (Benes, 1993; Cohen et al., 1999; Dollfus et al., 2002).

Our analysis also revealed another region with aberrant FA in the left temporal lobe. Several structural brain imaging studies and postmortem studies have demonstrated abnormalities of temporal lobe in both chronic and first episode schizophrenia (Lawrie and Abukmeil, 1998; Wright et al., 2000). The pathologic changes in temporal lobe and constituent parts may be an important step in the development of several symptoms in schizophrenia, such as auditory hallucinations and thought disorder (Seok et al., 2007; Shenton et al., 1992). The main white matter tracts traversing through the region we identified in the left temporal lobe were the left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus and inter-hemispheric fibers traversing through the posterior corpus callosum. The inferior longitudinal fasciculus is defined as the bundle of long association fibers running the length of the occipital and temporal lobes, which connect the visual areas to the main components of the limbic system, the amygdala and hippocampus (Catani et al., 2003) and are related to emotional behavior. The inferior longitudinal fasciculus is also involved in visual perception and memory (Ffytche, 2008; Ross, 2008), face recognition (Fox et al., 2008), reading (Epelbaum et al., 2008) and functions related to language (Catani and Mesulam, 2008). The inferior fronto-occipital fasciculus is a large white matter tract that connects the orbitofrontal cortex and the temporal and occipital lobes; its functions are poorly understood but it may be involved in reading, attention and visual processing.

The bundle with decreased FA that is involved in both of the regions is the bundle of inter-hemispheric fibers traversing through the corpus callosum. The corpus callosum is a midline brain structure composed of white matter fiber tracts that interconnect the left and right hemispheres to facilitate the proper functioning of the nervous system as a whole. Researchers believe that the corpus callosum is involved in a wide range of normal inter-hemispheric functions including relaying sensory, motor and cognitive information from homologous brain regions (de Lacoste et al., 1985). In the present study, we found FA reductions in the inter-hemispheric fibers traversing through the anterior portion of the corpus callosum which carries fibers linking the prefrontal and orbitofrontal regions and the posterior portion connecting the temporal lobes. This finding supports the notion that inter-hemispheric information transfer is impaired in schizophrenia patients at an early stage (Kubicki et al., 2008; Schmahmann and Pandya, 2009). Although the correlation between the corpus callosum and the clinical symptoms in FES is not clear, studies have found that the corpus callosum is involved in the pathogenesis of both negative (Foong et al., 2001; Woodruff et al., 1997) and positive symptoms of schizophrenia, especially the hallucinations (Brambilla et al., 2005; Hubl et al., 2004; Rotarska-Jagiela et al., 2009).

The decreased FA in both the anterior cingulate gyrus and temporal lobe has also been confirmed by numerous DTI and tractography studies that have included chronic schizophrenia patients (Ellison-Wright and Bullmore, 2009; Phillips et al., 2009; Rosenberger et al., 2008; Sun et al., 2003; Tang et al., 2007), and the disruptions may contribute to the abnormal functional connectivity. In contrast, few studies have reported volumetric deficits in the white matter in the cingulum and temporal lobes of schizophrenia patients, and the results have been inconsistent. Two meta-analyses suggested that the evidence supporting the white matter deficits in schizophrenia is inadequate (Olabi et al., 2011; Shepherd et al., 2012). The fact may suggest that, as the abnormal volume of the white matter is a macrostructural measure, the DTI measures reveal the microstructural changes, which appear to be more sensitive to white matter abnormalities in schizophrenia. DTI studies have also investigated the white matter connectivity of non-affected relatives, and multiple white matter tracts including the anterior cingulum and inferior longitudinal fasciculus were found to be altered; the reduced integrity might be associated with the genetic liability of schizophrenia (Camchong et al., 2009; Knochel et al., 2012a).

Our findings provide evidence that there is disruption in the brain connectivity for the frontal lobe and limbic system in first episode schizophrenia. Previous neuroimaging studies have demonstrated dysfunction in frontal lobe regions including the prefrontal cortex and the anterior cingulated cortex, which are critical for cognitive control, planning, and working memory (JL and MS, 2003). Furthermore, limbic function abnormalities have been demonstrated in schizophrenia with affective interference paradigms (Mohanty et al., 2005); the deficits emerged early and declined further with illness progression (Das et al., 2007; Gur et al., 2007; Takahashi et al., 2006). Although the frontal lobe and limbic lobe abnormalities may account for different core symptoms of schizophrenia, they are not independent. The frontal lobe and limbic system are highly interconnected, integrated frontal–limbic networks that mediate many important language, memory and emotional processes. Functional neuroimaging studies have shown that the propensity to auditory hallucinations is associated with disrupted frontal–limbic functional and structural integrity (Hubl et al., 2004; Mechelli et al., 2007). Additional studies have suggested that the relationship between prefrontal cognitive control decision making regions and limbic affective processing areas subserves a critical function in the regulation of attention and response selection in the presence of emotionally arousing information and vice versa (Bunge et al., 2001; Ochsner, 2008; Ochsner and Phelps, 2007; Ochsner et al., 2002). Considering that the present meta-analysis results revealed white matter impairment in multiple fascicules of this network, we suggest that the dysfunction of the fronto-limbic circuitry may emerge at the early stage of schizophrenia.

Several issues should be addressed when explaining the current findings. First, the results of the 8 primary studies showed low consistency, although we still identified two consistent regions. A variety of factors, including the differences in the populations studied and the DTI data, may have contributed to the inconsistencies between the studies. The studies we selected included schizophrenia patients with heterogeneous symptoms even though white matter changes may be specific to certain symptoms (Melonakos et al., 2011). In addition to the clinical characteristics, factors such as medication, genetic background and sample size may also account for the inconsistent findings across the studies. Among the studies, 5 primary studies included patients with a short course of antipsychiatric treatment. Although no study has addressed the issue of the effects of medication on white matter integrity, several studies have demonstrated that antipsychotic treatment may affect the brain structure (Koutsouleris et al., 2010; Li et al., 2011; Moncrieff and Leo, 2010). Additionally, schizophrenia is strongly influenced by genetic factors (Maier et al., 2005). Another complicating factor was the number of studies and their sample size, several primary studies included fewer than 20 subjects, which may be insufficient to eliminate individual variations. Meta-analyses with larger patient sample sizes should be performed in the future. In addition to clinical variation, different parameters for DTI data such as diffusion weighting, different B values and data resolution can also influence the results (Alexander and Barker, 2005; Ben Bashat et al., 2005; Oouchi et al., 2007). Furthermore, 3 studies (75 patients in total) with negative findings that did not report any coordinates were not taken into the meta-analysis because of the limitation of the technique. Finally, the results need to be confirmed as the 2 clusters were only contributed by 2 studies each.

5. Conclusion

The present meta-analysis of DTI studies identified white matter deficits in the right frontal lobe and left temporal lobe in first episode schizophrenia, providing a strong evidence of a structural basis for the involvement of the fronto-limbic neural circuit. Because the coordinates reported by the primary literature were varied, future investigations with larger sample sizes are warranted to provide further evidence for the white matter changes in FES. Furthermore, whether the white matter changes are affected by the illness duration remains to be established in longitudinal, prospective studies of people at-risk of schizophrenia or FES.

Authorship contributions

Su Lui and Qi-Yong Gong contributed to the conception of the study. Li Yao and Su Lui performed the data analyses and wrote the manuscript. Yi Liao and Ming-Ying Du helped perform the analysis with constructive discussions. Na Hu and Joy A. Thomas contributed to the design and data analysis and provided language help.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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References

Alexander DC, Barker GJ. Optimal imaging parameters for fiber-orientation estimation in diffusion MRI. Neuroimage 2005;27:357–67.

Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. Neurosci Biobehav Rev 2008;32:175–91.

Andreasen NC. The role of the thalamus in schizophrenia. Can J Psychiatry 1997;42:27–33.

Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol Psychiatry 1999;46:908–20.

Ben Bashat D, Ben Sira L, Graif M, Pianka P, Hendler T, Cohen Y, et al. Normal white matter development from infancy to adulthood: comparing diffusion tensor and high b value diffusion weighted MR images. J Magn Reson Imaging 2005;21:503–11.

Benes FM. Neurobiological investigations in cingulate cortex of schizophrenic brain. Schizophr Bull 1993;19:537–49.

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res 2011;127:46–57.

Brambilla P, Cerini R, Gasparini A, Versace A, Andreone N, Vittorini E, et al. Investigation of corpus callosum in schizophrenia with diffusion imaging. Schizophr Res 2005;79:201–10.

Buchanan RW, Vladar K, Barta PE, Pearlson GD. Structural evaluation of the prefrontal cortex in schizophrenia. Am J Psychiatry 1998;155:1049–55.

Bunge SA, Ochsner KN, Desmond JE, Glover GH, Gabrieli JD. Prefrontal regions involved in keeping information in and out of mind. Brain 2001;124:2074–86.

Cabeza R, Nyberg L. Imaging cognition: an empirical review of PET studies with normal subjects. J Cogn Neurosci 1997;9:1-26.

Camchong J, Lim KO, Sponheim SR, Macdonald AW. Frontal white matter integrity as an endophenotype for schizophrenia: diffusion tensor imaging in monozygotic twins and patients' nonpsychotic relatives. Front Hum Neurosci 2009;3:35.

Carter CS, MacDonald III AW, Ross LL, Stenger VA. Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. Am J Psychiatry 2001;158:1423–8.

Catani M, Jones DK, Donato R, Ffytche DH. Occipito-temporal connections in the human brain. Brain 2003;126:2093–107.

Catani M, Mesulam M. The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. Cortex 2008;44:953–61.

Chan RC, Di X, McAlonan GM, Gong QY. Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. Schizophr Bull 2011;37:177–88.

Cheung V, Cheung C, McAlonan GM, Deng Y, Wong JG, Yip L, et al. A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. Psychol Med 2008;38:877–85.

Cohen JD, Botvinick M, Carter CS. Anterior cingulate and prefrontal cortex: who's in control? Nat Neurosci 2000;3:421–3.

Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H. Impairments of attention after cingulotomy. Neurology 1999;53:819–24.

Cohen RM, Nordahl TE, Semple WE, Andreason P, Pickar D. Abnormalities in the distributed network of sustained attention predict neuroleptic treatment response in schizophrenia. Neuropsychopharmacology 1998;19:36–47.

Das P, Kemp AH, Flynn G, Harris AW, Liddell BJ, Whitford TJ, et al. Functional disconnections in the direct and indirect amygdala pathways for fear processing in schizophrenia. Schizophr Res 2007;90:284–94.

Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, et al. White matter changes in schizophrenia: evidence for myelin-related dysfunction. Arch Gen Psychiatry 2003;60:443–56.

de Lacoste MC, Kirkpatrick JB, Ross ED. Topography of the human corpus callosum. J Neuropathol Exp Neurol 1985;44:578–91.

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;41:354–63.

Dollfus S, Lombardo C, Benali K, Halbecq I, Abadie P, Marie RM, et al. Executive/attentional cognitive functions in schizophrenic patients and their parents: a preliminary study. Schizophr Res 2002;53:93–9.

Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 2009;30:2907–26.

Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res 2009;108:3-10.

Epelbaum S, Pinel P, Gaillard R, Delmaire C, Perrin M, Dupont S, et al. Pure alexia as a disconnection syndrome: new diffusion imaging evidence for an old concept. Cortex 2008;44:962–74.

Federspiel A, Begre S, Kiefer C, Schroth G, Strik WK, Dierks T. Alterations of white matter connectivity in first episode schizophrenia. Neurobiol Dis 2006;22:702–9.

Ffytche DH. The hodology of hallucinations. Cortex 2008;44:1067–83.

Filley CM. White matter and behavioral neurology. Ann N Y Acad Sci 2005;1064:162–83.

Foong J, Symms MR, Barker GJ, Maier M, Woermann FG, Miller DH, et al. Neuropathological abnormalities in schizophrenia: evidence from magnetization transfer imaging. Brain 2001;124:882–92.

Fox CJ, Iaria G, Barton JJ. Disconnection in prosopagnosia and face processing. Cortex 2008;44:996-1009.

Guo W, Liu F, Liu Z, Gao K, Xiao C, Chen H, et al. Right lateralized white matter abnormalities in first-episode, drug-naive paranoid schizophrenia. Neurosci Lett 2012;531:5–9.

Gur RE, Loughead J, Kohler CG, Elliott MA, Lesko K, Ruparel K, et al. Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. Arch Gen Psychiatry 2007;64:1356–66.

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;17:23–6.

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;61:658–68.

JL C, MS M. Neuropsychiatry and behavioural neuroscience. New York: Oxford Univ. Press; 2003.

Kim JJ, Crespo-Facorro B, Andreasen NC, O'Leary DS, Magnotta V, Nopoulos P. Morphology of the lateral superior temporal gyrus in neuroleptic nai;ve patients with schizophrenia: relationship to symptoms. Schizophr Res 2003;60:173–81.

Klingberg T, Hedehus M, Temple E, Salz T, Gabrieli JD, Moseley ME, et al. Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. Neuron 2000;25:493–500.

Klingberg T, Vaidya CJ, Gabrieli JD, Moseley ME, Hedehus M. Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. Neuroreport 1999;10:2817–21.

Knochel C, O'Dwyer L, Alves G, Reinke B, Magerkurth J, Rotarska-Jagiela A, et al. Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives. Schizophr Res 2012a;140:129–35.

Knochel C, Oertel-Knochel V, Schonmeyer R, Rotarska-Jagiela A, van de Ven V, Prvulovic D, et al. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. Neuroimage 2012b;59:926–34.

Koutsouleris N, Gaser C, Bottlender R, Davatzikos C, Decker P, Jager M, et al. Use of neuroanatomical pattern regression to predict the structural brain dynamics of vulnerability and transition to psychosis. Schizophr Res 2010;123:175–87.

Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, et al. Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. Biol Psychiatry 2003;54:1171–80.

Kubicki M, Styner M, Bouix S, Gerig G, Markant D, Smith K, et al. Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. Schizophr Res 2008;106:125–31.

Kubicki M, Niznikiewicz M, Connor E, Nestor P, Bouix S, Dreusicke M, et al. Relationship between white matter integrity, attention, and memory in schizophrenia: a diffusion tensor imaging study. Brain Imaging Behav 2009;3:191–201.

Kyriakopoulos M, Perez-Iglesias R, Woolley JB, Kanaan RA, Vyas NS, Barker GJ, et al. Effect of age at onset of schizophrenia on white matter abnormalities. Br J Psychiatry 2009;195:346–53.

Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, et al. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 2005;25:155–64.

Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 1998;172:110–20.

Li M, Chen Z, Deng W, He Z, Wang Q, Jiang L, et al. Volume increases in putamen associated with positive symptom reduction in previously drug-naive schizophrenia after 6 weeks antipsychotic treatment. Psychol Med 2011:1–9.

Lu LH, Zhou XJ, Keedy SK, Reilly JL, Sweeney JA. White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. Bipolar Disord 2011;13:604–13.

Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H, et al. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am J Psychiatry 2009a;166:196–205.

Lui S, Deng W, Huang X, Jiang L, Ouyang L, Borgwardt SJ, et al. Neuroanatomical differences between familial and sporadic schizophrenia and their parents: an optimized voxel-based morphometry study. Psychiatry Res 2009b;171:71–81.

Maier W, Hofgen B, Zobel A, Rietschel M. Genetic models of schizophrenia and bipolar disorder: overlapping inheritance or discrete genotypes? Eur Arch Psychiatry Clin Neurosci 2005;255:159–66.

Mak A, Cheung MWL, Fu EHY, Ho RCM. Meta-analysis in medicine: an introduction. Int J Rheum Dis 2010;13:101–4.

McDonald C, Bullmore E, Sham P, Chitnis 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;186:369–77.

McGuire PK, Frith CD. Disordered functional connectivity in schizophrenia. Psychol Med 1996;26:663–7.

Mechelli A, Allen P, Amaro Jr E, Fu CH, Williams SC, Brammer MJ, et al. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. Hum Brain Mapp 2007;28:1213–22.

Melonakos 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.

Mintorovitch J, Moseley ME, Chileuitt L, Shimizu H, Cohen Y, Weinstein PR. Comparison of diffusion- and T2-weighted MRI for the early detection of cerebral ischemia and reperfusion in rats. Magn Reson Med 1991;18:39–50.

Mohanty A, Herrington JD, Koven NS, Fisher JE, Wenzel EA, Webb AG, et al. Neural mechanisms of affective interference in schizotypy. J Abnorm Psychol 2005;114:16–27.

Moncrieff J, Leo J. A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 2010;40:1409–22.
Moriya J, Kakeda 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.
Nordahl TE, Carter CS, Salo RE, Kraft L, Baldo J, Salamat S, et al. Anterior cingulate metabolism correlates with stroop errors in paranoid schizophrenia patients. Neuropsychopharmacology 2001;25:139–48.
Ochsner KN. The social-emotional processing stream: five core constructs and their translational potential for schizophrenia and beyond. Biol Psychiatry 2008;64:48–61.
Ochsner KN, Phelps E. Emerging perspectives on emotion–cognition interactions. Trends Cogn Sci 2007;11:317–8.
Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci 2002;14:1215–29.
Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiatry 2011;70:88–96.
Oouchi H, Yamada K, Sakai K, Kizu O, Kubota T, Ito H, et al. Diffusion anisotropy measurement of brain white matter is affected by voxel size: underestimation occurs in areas with crossing fibers. AJNR Am J Neuroradiol 2007;28:1102–6.
Perez-Iglesias R, Tordesillas-Gutierrez D, Barker GJ, McGuire PK, Roiz-Santianez 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.
Phillips OR, Nuechterlein KH, Clark KA, Hamilton LS, Asarnow RF, Hageman NS, et al. Fiber tractography reveals disruption of temporal lobe white matter tracts in schizophrenia. Schizophr Res 2009;107:30–8.
Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, et al. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur Psychiatry 2011;27:605–11.
Rosenberger G, Kubicki M, Nestor PG, Connor E, Bushell GB, Markant D, et al. Age-related deficits in fronto-temporal connections in schizophrenia: a diffusion tensor imaging study. Schizophr Res 2008;102:181–8.
Ross ED. Sensory-specific amnesia and hypoemotionality in humans and monkeys: gateway for developing a hodology of memory. Cortex 2008;44:1010–22.
Rotarska-Jagiela A, Oertel-Knoechel V, DeMartino F, van de Ven V, Formisano E, Roebroeck A, et al. Anatomical brain connectivity and positive symptoms of schizophrenia: a diffusion tensor imaging study. Psychiatry Res 2009;174:9-16.
Schmahmann JD, Pandya DN. Fiber Pathways of the Brain. Oxford University Press; 2009.
Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white-matter architecture. Nat Neurosci 2009;12:1370–1.
Seok JH, Park HJ, Chun JW, Lee SK, Cho HS, Kwon JS, et al. White matter abnormalities associated with auditory hallucinations in schizophrenia: a combined study of voxel-based analyses of diffusion tensor imaging and structural magnetic resonance imaging. Psychiatry Res 2007;156:93-104.
Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, et al. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N Eng J Med 1992;327:604–12.
Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev 2012;36:1342–56.
Stark AK, Uylings HB, Sanz-Arigita E, Pakkenberg B. Glial cell loss in the anterior cingulate cortex, a subregion of the prefrontal cortex, in subjects with schizophrenia. Am J Psychiatry 2004;161:882–8.
Sun Z, Wang F, Cui L, Breeze J, Du X, Wang X, et al. Abnormal anterior cingulum in patients with schizophrenia: a diffusion tensor imaging study. Neuroreport 2003;14:1833–6.
Szeszko PR, Ardekani BA, Ashtari 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;162:602–5.
Takahashi T, Suzuki M, Zhou SY, Tanino R, Hagino H, Niu L, et al. Temporal lobe gray matter in schizophrenia spectrum: a volumetric MRI study of the fusiform gyrus, parahippocampal gyrus, and middle and inferior temporal gyri. Schizophr Res 2006;87:116–26.
Tamminga CA, Vogel M, Gao X-M, Lahti AC, Holcomb HH. The limbic cortex in schizophrenia: focus on the anterior cingulate. Brain Res Rev 2000;31:364–70.
Tang CY, Friedman J, Shungu D, Chang L, Ernst T, Stewart D, et al. Correlations between Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (1H MRS) in schizophrenic patients and normal controls. BMC Psychiatry 2007;7:25.
Tang J, Liao Y, Zhou B, Tan C, Liu T, Hao W, et al. Abnormal anterior cingulum integrity in first episode, early-onset schizophrenia: a diffusion tensor imaging study. Brain Res 2010;1343:199–205.
Tievsky AL, Ptak T, Farkas J. Investigation of apparent diffusion coefficient and diffusion tensor anisotrophy in acute and chronic multiple sclerosis lesions. AJNR Am J Neuroradiol 1999;20:1491–9.
Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 2002;16:765–80.
Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology 2004;230:77–87.
Wang F, Sun Z, Cui L, Du X, Wang X, Zhang H, et al. Anterior cingulum abnormalities in male patients with schizophrenia determined through diffusion tensor imaging. Am J Psychiatry 2004;161:573–5.
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. Psychol Med 2011;41:1691–700.
Wei QL, Kang Z, Wu XL, Zhang JB, Li LJ, Zheng LR, et al. Diffusion tensor imaging findings in first-episode and chronic schizophrenics. Zhonghua Yi Xue Za Zhi 2011;91:2186–9.
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;37:222–32.
Whitford TJ, Farrow TF, Gomes L, Brennan J, Harris AW, Williams LM. Grey matter deficits and symptom profile in first episode schizophrenia. Psychiatry Res 2005;139:229–38.
Woodruff PW, Wright IC, Shuriquie N, Russouw H, Rushe T, Howard RJ, et al. Structural brain abnormalities in male schizophrenics reflect fronto-temporal dissociation. Psychol Med 1997;27:1257–66.
Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 2000;157:16–25.