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White matter reduction in patients with schizophrenia as revealed by voxel-based morphometry: An activation likelihood estimation meta-analysis

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ABSTRACT

Schizophrenia is thought to be a mental disorder caused by the disconnection of brain regions. Cumulative evidence of white matter deficit in patients with schizophrenia has been reported using voxel-based morphometry (VBM), but these studies have not been quantitatively reviewed. In the study reported herein, we used activation likelihood estimation (ALE) analysis to quantitatively estimate focal white matter abnormalities in patients with schizophrenia. Seventeen studies that compared the white matter deficit of patients with schizophrenia and healthy controls were ascertained. The frontal white matter regions and internal capsule revealed consistent white matter reduction in patient groups relative to healthy controls, suggesting a clear focal white matter deficit in patients with schizophrenia. These results support the macro-circuit theory of white matter change in schizophrenia.

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1. Introduction

Schizophrenia has long been considered a disconnection between different cortical areas (Friston and Frith, 1995; Stephan et al., 2006). For example, distinct gray matter networks have been identified to be abnormal in patients with schizophrenia in comparison with healthy controls (Glahn et al., 2008). Given that white matter constitutes the anatomical infrastructure for neural connectivity, it is reasonable to hypothesize the existence of white matter abnormalities in patients with schizophrenia.

Using magnetic resonance imaging (MRI), several studies have shown white matter abnormalities in patients with schizophrenia relative to healthy controls. The whole brain white matter volume was found to be decreased by 1% in schizophrenia patients (Wright et al., 2000). Using region of interest (ROI) analysis, some studies have reported decreases in the white matter volume of the frontal lobes (Buchanan et al., 1998; Hulshoff Pol et al., 2002), but the data on the frontal lobe deficit has not been conclusive. Recently, voxel-based morphometry (VBM) analysis (Ashburner and Friston, 2000) has been used extensively to estimate focal white matter abnormalities in the whole brain volume (e.g. Sigmundsson et al., 2001; Sowell et al., 2000; Paillère-Martinot et al., 2001). However, most VBM studies have not reported consistent white matter deficits in patients with schizophrenia (Hulshoff Pol et al., 2004). Diffusion tensor imaging (DTI) for evaluating the organization and coherence of white matte fiber tracts has also been used extensively to estimate white matter abnormalities in schizophrenia patients. However, the findings were inconclusive (Kanaan et al., 2005), until subjected to meta-analysis (Ellison-Wright and Bullmore, 2008).

VBM analysis is a statistical method extensively used to compare the structural differences of MRI images between two groups of individuals. It registers individual brain volume on a standard template and voxel-wise statistics are used to find voxels across the whole brain volume where there are significant differences between two groups. This kind of mass-univariate statistics has a problem of multiple comparisons. Although several methods for the correction of such comparisons have been used in VBM studies, clusters of false positives cannot be fully excluded, which could explain the inconsistent findings. In addition, several other limitations of the VBM approach such as poor spatial registration (Bookstein, 2001) and sample selection differences can also lead to inconsistencies. Hence, analysis across studies is needed to estimate consistent white matter abnormalities in patients with schizophrenia.

Activation likelihood estimation (ALE, Turkeltaub et al., 2002) is a relatively new method to compensate for the limitations of VBM. It treats a foci reported by a single study as an activation likelihood, and

Abbreviations: ALE, activation likelihood estimation; DTI, Diffusion tensor imaging; FA, fractional anisotropy; FDR, false discovery rate; FES, first-episode schizophrenia; FWHM, full-width half-maximum; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROI, region of interest; VBM, voxel-based morphometry; WMC, white matter concentration; WMV, white matter volume.

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estimates consistent activation clusters among different studies. Although several ALE meta-analyses have investigated structural abnormalities in brain gray matter (Ellison-Wright et al., 2008a; Fornito et al., 2009; Glahn et al., 2008) and diffusion tensor abnormalities in white matter (Ellison-Wright and Bullmore, 2008) of patients with schizophrenia, white matter morphometry abnormalities have not been addressed.

In the present study, we systematically reviewed VBM studies of white matter change in patients with schizophrenia. Although these studies varied from patient samples and VBM processing protocols, we used a quantitative ALE meta-analysis to verify whether there is a consistent focal white matter deficit among schizophrenia patients in the published VBM studies.

2. Methods

2.1. Paper selection

We used the key words "voxel based morphometry," "schizophrenia" and "white matter" to search for appropriate studies in the MEDLINE and PubMed databases. Studies were selected according to the following inclusion criteria: 1) they had to be research articles published in international journals; 2) they had to use VBM analysis to investigate white matter density change in the MRI dataset; 3) they had include a control group and a direct comparison of patients with schizophrenia and healthy controls; and 4) the results had to be normalized to a stereotaxic standardized space such as the Montreal Neurological Institute (MNI) space or the Talairach space (Talairach and Tournoux, 1988), and the coordinates of the activation areas had to be explicitly reported. In addition, we searched the reference lists of the studies identified for potential inclusion.

Table 1 shows that 17 articles met the inclusion criteria for the ALE meta-analysis (twelve studies of chronic schizophrenia, four studies of first-episode schizophrenia (FES), and one study that pooled chronic and FES patients to compare them to healthy controls). A total of 712 patients and 639 healthy controls were included in the meta-analysis. All of the studies reported white matter reduction, but two articles also reported white matter increases. Because two papers were not sufficient for us to run an ALE meta-analysis, we only conducted it for white matter reduction.

2.2. Activation likelihood estimation

The analyses were conducted in the Talairach space, with activation coordinates that were originally reported in MNI space converted using Lancaster's transform (Lancaster et al., 2007). Some of the papers used Brett's formulation to convert from MNI to Talairach (Brett, 1999), so the results were first converted back to MNI coordination, and then transformed into the Talairach space using Lancaster's transform.

The meta-analysis was carried out using GingerALE software (Laird et al., 2005). The idea behind ALE analysis is that the peak coordinates reported in VBM studies should be viewed as probability distributions around themselves (Turkeltaub et al., 2002). In practical terms, an ALE map was constructed based on 65 foci from seventeen studies (see Table 1), and then convolved with a 3D Gaussian kernel. Because the smoothing kernels used in the reviewed VBM studies ranged from 4 mm to 12 mm full-width half-maximum (FWHM) for an average of 9.04 mm, we used a smoothing kernel with 10 mm FWHM to construct the ALE map. Then we simulated activation maps with randomly distributed foci equal to the number of foci in the ALE analysis using a permutation test with 5000 iterations. The clusters identified in the meta-analysis were obtained after controlling the false discovery rate (FDR) at $p<0.05$ and applying a cluster extent threshold of 100 voxels. Given the activated clusters, we further examined which studies reported foci located in specific clusters. Because four out of the eleven identified clusters were contributed by a single study under $p<0.05$, a more stringent threshold FDR of $p<0.01$ was used to present the results. The label of the white matter structure was identified according to the white matter atlas (Wakana et al., 2004).

3. Results

Four clusters were identified in the ALE analysis under FDR $p<0.01$ and $k>100$. As illustrated in Fig. 1 and Table 2, several regions, including the frontal white matter regions and the bilateral internal capsule, show consistent white matter deficit in patients with schizophrenia compared to healthy controls.

Two clusters were activated in the frontal white matter regions (peak Talairach coordinates at 20, 46, 26 and −8, 48, −2). Four out of the seventeen studies reported white matter reduction in these two

Table 1
Summary of articles included in the meta-analysis (FES, first-episodic schizophrenia; FWHM, full-width half-maximum; WMC = white matter concentration; WMV = white matter volume).

No.	Study	Patients/ male		Mean age of patients	Controls/ male		Duration of illness	Percentage taking antipsychotic medication	Type	Smoothing FWHM (mm)	White matter measure
1	Ananth et al. (2002)	20	10	37.8	20	10	15.8	All	Chronic	12	WMV
2	Antonova et al. (2005)	45	27	40.5	43	25	16.9	78%	Chronic	12	WMV
3	Bassitt et al. (2007)	50	38	31.7	30	21	11.4	All	Chronic	12	WMV
4	Chua et al. (2007)	26	12	32	38	18	0.33	No	FES	4.4	WMC
5	Hulshoff Pol et al. (2004)	159	112	35.6	158	106	12.3	98%	Chronic	8	WMC
6	Pagsberg et al. (2007)	29	11	15.7	29	11	2.1	62%	FES	12	WMV
7	Paillère-Martinot et al. (2001)	20	20	29	20	20	10	90%	Chronic	10	WMC
8	Price et al. (2006)	16	12	26.3	12	4	<1 month	All	FES and chronic	6	WMV
9	Seok et al. (2007)	30	15	30	22	11	7.5	All	Chronic	6	WMC
10	Shapleske et al. (2002)	72	72	34.1	32	32	11.5	All	Chronic	2D 4.2	WMC
11	Sigmundsson et al. (2001)	27	26	34.9	27	25	13.9	N/A	Chronic	2D 4.2	WMC
12	Spalletta et al. (2003)	28	14	34.6	28	14	11	All	Chronic	10	WMC
13	Suzuki et al. (2002)	45	23	26.4	42	22	5.2	All	Chronic	12	WMC
14	Whitford et al. (2007)	41	26	19.8	47	33	0.69	All	FES	12	WMV
15	Witthaus et al. (2008)	23	16	26.4	29	17	N/A	26%	FES	12	WMV
16	Wolf et al. (2008)	28	20	33.1	14	9	5.82	96%	Chronic	8	WMC
17	Zhou et al. (2003)	53	27	26.5	48	26	3.88	98%	Chronic	12	WMC

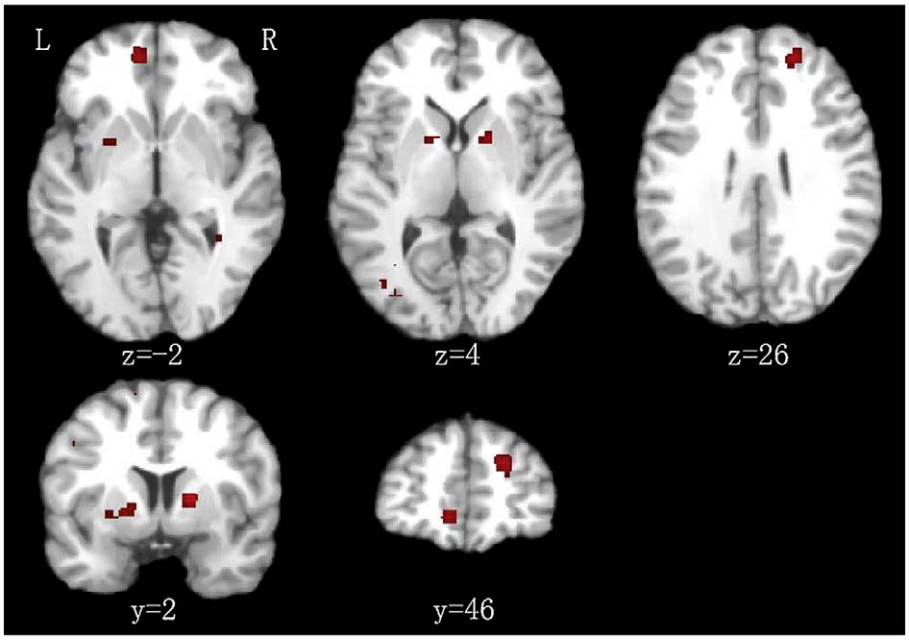

Fig. 1. White matter reduction in patients with schizophrenia compared to healthy controls, displayed on a three-dimensional rendered brain with the anterior part of the left hemisphere removed. Significance threshold with a false discovery rate at $p < 0.01$.

regions (Bassitt et al., 2007; Paillère-Martinot et al., 2001; Spalletta et al., 2003; Witthaus et al., 2008). The remaining two clusters were in the bilateral internal capsule (peak Talairach coordinates at 16, 4, 8 and −16, 2, 2). Three out of the seventeen studies reported white matter reduction in these two regions (Chua et al., 2007; Suzuki et al., 2002; Zhou et al., 2003).

4. Discussion

Using the quantitative ALE method, we evaluated the consistent focal white matter deficit of patients with schizophrenia in VBM studies. Multiple white matter fasciculi reductions were found in patients with schizophrenia, including in the frontal white matter regions and the bilateral internal capsule. The current ALE results were consistent with evidence from other techniques. Frontal lobe white matter reductions in patients with schizophrenia have been widely reported in region-of-interest white matter volumetry studies (Breier et al., 1992; Buchsbaum et al., 2006; Hulshoff Pol et al., 2002; Mathalon et al., 2003; Sanfilipo et al., 2000; Wible et al., 2001) and fractional anisotropy (FA) studies using diffusion tenser imaging (Hao et al., 2006; Hoptman et al., 2002; Kitamura et al., 2005; Kumra et al., 2004; Lim et al., 1999; Minami et al., 2003; Steel et al., 2001; Wolkin et al., 2003). Our results demonstrated white matter abnormities in the right and medial frontal white matter regions, which is in line with these studies. The deficit in the internal capsule was consistent with the findings of many diffusion tensor imaging studies (Buchsbaum et al., 2006; Kubicki et al., 2005, 2007; Szeszko et al., 2005). The white matter reductions in the frontal white matter and deep temporal white matter regions were also in line with the findings of a recently published ALE analysis of diffusion tensor FA studies (Ellison-Wright and Bullmore, 2008).

Although there is clear evidence to support the disconnection theory in schizophrenia, the evidence for aberrant long-range anatomical connections is still less convincing (Stephan et al., 2006, 2009). The present results, together with an ALE analysis of diffusion tensor FA studies (Ellison-Wright and Bullmore, 2008), provide clear evidence of macro-circuit white matter changes in patients with schizophrenia (Konrad and Winterer, 2008). The macro-circuit theory proposes that specific white matter tracts are disrupted in schizophrenia, rather than the uniform reduction of white matter throughout the brain.

The current results suggest that the VBM approach can be a useful method in estimating white matter abnormalities in schizophrenia. However, there are some technical points we should consider in future studies. First, depending on whether or not modulation was performed, VBM measured either white matter concentration (WMC) or white matter volume (WMV). These measures assessed different aspects of white matter deficit, and may therefore reflect different pathological processes (Fornito et al., 2009). Second, the smoothing kernel could also have affected the VBM results. For example, Honea et al. (2005) illustrated that a smaller smoothing kernel led to the detection of a greater number of regions implicated in schizophrenia. As shown in Tables 1 and 2, the activated clusters in the present study were contributed by studies using both WMC measure and WMV

Table 2
Activation likelihood estimation results of white matter reduction in patients with schizophrenia.

Cluster #	Volume (mm^3)	Peak ALE value	Talairach coordinates			Label	# of studies contributed to the cluster
			x	*y*	*z*		
1	544	0.010283	20	46	26	R. frontal white matter	3, 7, 15
2	352	0.011932	16	4	8	R. internal capsule	4, 17
3	336	0.010507	−8	48	−2	L. frontal white matter	12, 15
4	248	0.008271	−16	2	2	L. internal capsule	13, 17

The peak coordinates were in Talairach system. (L. left; R. right).

measure, and studies using both larger kernel (10–12 mm) and small kernel (4–8 mm). There was no evidence for an influence of WMC/WMV measure or smoothing kernel on WM changes. Given the limited number of studies in the present meta-analysis, further study using a larger sample size should be conducted to clarify these issues.

However, the present results revealed only a small number of studies contributing to the positive results, which is in contrast to another DTI meta-analysis (Ellison-Wright and Bullmore, 2008). This may suggest that the regional white matter reduction in schizophrenia could not be measured robustly by VBM technique. The reason may be that the real effect of white matter deficit is shape change, which cannot be measured properly by univariate measurement. It will be appropriate to use multivariate statistics for VBM analysis (e.g. Kawasaki et al., 2007), and the FA or tractography technique for DTI data (Kanaan et al., 2006; Kubicki et al., 2007; Kyriakopoulos et al., 2008; Nestor et al., 2008) in the future to describe white matter abnormalities more accurately.

Each significant cluster in the present results was only contributed by 2–3 studies. This suggests that the current ALE algorithm has high sensitivity but low robustness. One possible shortcoming of the conventional ALE analysis is that it uses a fixed effect analysis estimating consistency across individual foci rather than individual studies. This may be problematic in some condition (Eickhoff et al., 2009), and cannot weight studies by factors such as sample size. Some algorithm considering random effect analysis should be considered in the future, such as Genome Scan Meta-Analysis (Ellison-Wright et al., 2008b), and random effect ALE analysis (Eickhoff et al., 2009).

A number of factors can affect brain structure changes in schizophrenia, such as the stage of illness (Glahn et al., 2008), antipsychotic use, and age effects (Jones et al., 2006). The heterogeneity of the reviewed studies could thus have led us to underestimate the results of white matter reduction. These factors should be further explored in a study using a larger sample size.

In conclusion, we indentified consistent white matter reduction in schizophrenia patients in the frontal white matter regions and the bilateral internal capsule. These findings, taken in conjunction with a meta-analysis of diffusion tenor studies (Ellison-Wright and Bullmore, 2008), provide evidence for macro-circuit white matter changes in schizophrenia.

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