Neuroanatomical differences between familial and sporadic schizophrenia and their parents: An optimized voxel-based morphometry study

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Abstract

Symptomatic differences have been reported between patients with familial and sporadic schizophrenia. The present study examined neuroanatomical differences between the two subgroups and their parents using voxel-based morphometry. High-resolution T1-weighted images were obtained using 3 Tesla magnetic resonance imaging from 20 patients with schizophrenia (familial subgroup, n = 10; sporadic subgroup, n = 10), 20 of their parents (familial subgroup, n = 10; sporadic subgroup, n = 10) and 20 healthy volunteers. Gray matter density (GMD) was compared between groups on a voxel-by-voxel basis. Compared with the sporadic patients, the familial patients had significantly reduced GMD in the thalamus bilaterally. Reduction of GMD in bilateral thalami was also found in familial parents in comparison with sporadic parents. Compared with controls, both familial and sporadic patients had lower GMD involving bilateral insula, right temporal lobe, right occipital lobe, left lenticular nucleus and right cerebellum. However, only familial patients showed lower GMD than controls in the right thalamus. Compared with controls, only familial parents showed lower GMD in the right insula extending to the right temporal lobe and the right parietal lobule. The present data suggest that familial schizophrenia is associated with more severe structural abnormalities than sporadic schizophrenia, especially in the thalamus.

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Keywords: MRI; Schizophrenia; Gray matter; Familial; Voxel-based morphometry

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1. Introduction

Understanding the pathogenesis of schizophrenia remains one of the greatest challenges in psychiatry, and progress has been made in determining the association of this disease with both genetic and environmental factors. One approach to studying the disorder involves the subdivision of patients with schizophrenia into populations with a presumed high genetic liability (i.e., familial schizophrenia) and those with a low genetic liability (i.e., sporadic schizophrenia) (Murray et al., 1985). The purpose of such a division is to produce populations that are relatively enriched or depleted in terms of a genetic abnormality that might be reflected in phenotypic differences between sporadic and familial patients with schizophrenia.

Over the last decade, family studies of schizophrenia’s phenotypic variability have consistently shown a substantially earlier age of illness onset (Alda et al., 1996; Wickham et al., 2002), a greater severity of negative symptoms (Malaspina et al., 2000; Galderisi et al., 2002), more indicators of dysphoric mood such as anxiety, tension, guilt, depression and somatic concern (Ritsner et al., 2005), poorer outcome and a higher rehospitalization rate (Suvisaari et al., 1998; Feldmann et al., 2000) among familial schizophrenia than sporadic patients. In particular, Malaspina et al. (2000) assessed family history and the deficit syndrome in 99 patients with schizophrenia who were examined during clinical treatment; they found that (1) familial schizophrenia had more and more treatment-resistant negative symptoms than seen in sporadic cases, and (2) the group with a positive family history had a greater severity of negative symptoms related to psychosocial function. Another multicenter study (Galderisi et al., 2002) found that deficit syndromes and negative symptoms were more frequent in familial patients than sporadic ones. A functional neuroimaging study (Malaspina et al., 2004) also showed regional cerebral blood flow (rCBF) differences between the two subtypes of patients when studied in a resting state. In addition, Griffiths et al. (1998) studied the neurological abnormalities in familial and sporadic schizophrenia, and the pattern of neurological abnormality in familial schizophrenia was found to differ from that in sporadic patients. Only the first degree relatives of familial (but not sporadic) schizophrenia patients showed neurological abnormalities. These findings add semiological and functional neuroimaging evidence to support the phenotypic differences between familial and sporadic patients.

Nevertheless, the structural findings associated with familial and sporadic schizophrenia are still unclear. Roy et al. (1994) applied a manually derived region of interest (ROI) method to reveal the increased lenticular nuclei volume and greater lateral ventricular asymmetry in familial patients compared with sporadic cases. These findings could not account for the symptomatic differences between the patients of the two subtypes. Furthermore, manual ROI methods, which are extremely labor-intensive and subject to operator bias, are difficult to apply in the investigation of complex structures such as the cortical gray matter. Voxel-based morphometry (VBM) provides an automated method for the group analysis of tissue distribution (Ashburner and Friston, 2000) and thus facilitates the analysis of brain structures. Gray matter density (GMD), an indicator of the amount of regional gray matter (Ashburner and Friston, 2001), has been used to locate regional gray matter deficits in schizophrenic brains and has been shown to be more sensitive and easily applied than the ROI method (Giuliani et al., 2005). In a recent meta-analysis by Honea et al. (2005), more than 50 regions of GM reduction across the brain were reported in schizophrenia patients, and certain regional gray matter findings seemed to be related to genetic liability, including findings in the thalamus, temporal and frontal lobes (McIntosh et al., 2004, 2006). Studies of unaffected relatives of schizophrenia patients have also shown the presence of similar brain abnormalities in an attenuated form, which are thought to be at least in part due to shared genetic liability (Lawrie et al., 2001; Cannon et al., 2002). Such genetic liability was also supported by VBM studies (Job et al., 2003, 2005; Pantelis et al., 2003) in subjects at high risk for the development of schizophrenia. It was suggested that these structural abnormalities might be associated with clinical symptoms (Antonova et al., 2005). To date, however, no study has yet applied VBM to examining the structural brain differences between familial and sporadic schizophrenic patients, and between their parents.

In the present study, we hypothesized that (1) if familial patients have more genetic liability, they should have more brain structural deficits than sporadic schizophrenia patients, and (2) if these structural differences are the results of genetic make-up, they should also be evident in non-psychotic relatives of the patients. To minimize the heterogeneity of the cohort under investigation, as indicated in a recent VBM study of schizophrenia relatives (Goghari et al., 2007), we specifically opted to use the data from parents rather than to include data from siblings and offspring. We applied an optimized VBM to examining the brain structural differences between familial and sporadic schizophrenia patients and those between their unaffected parents.
2. Methods

2.1. Subjects

All subjects reported here were parts of a large cohort family study of first episode schizophrenia in a Chinese population of Han Nationality in the Mental Health Centre of West China Hospital. This study was performed according to the Declaration of Helsinki (2002) and was approved by the local ethical committee. All patients, relatives, and normal controls give written informed consent to participate. A total of 60 right-handed subjects were recruited in the present study including 20 first-episode, treatment-naïve probands with schizophrenia, 20 of their unaffected parents and 20 normal controls. Table 1 presents demographic information for all subjects. All patients were recruited from the Department of Psychiatry in West China Hospital. Diagnosis and disease duration of schizophrenia were determined by consensus of the attending psychiatrists, who performed a clinical interview, and by a trained interviewer, who used the Structured Interview for DSM-IV (SCID-P). Healthy controls were recruited from the local area by poster advertisement. Unaffected parents and normal controls were also screened using the SCID-Non-patient version to confirm the absence of a history of psychiatric and neurological illness. In addition, control subjects were interviewed to ascertain that there were no family histories of psychiatric illness. All subjects’ clinical variables, i.e., age, sex, handedness (based on the Annett Handedness Scale; Annett, 1970), years of education, duration of illness, Positive and Negative Syndrome Scale (PANSS) total score, and negative and positive PANSS subscale scores, were obtained by two experienced clinical psychiatrists before treatment and magnetic resonance imaging (MRI) examinations. Family history was assessed with a semi-structured interview by an experienced psychiatrist. All affected relatives were assessed directly. Patients with first or second degree family members who had schizophrenia were classified as the familial group, whereas sporadic cases were those who had no first or second degree family members with psychosis. Age, sex, and years of education were matched between the familial and sporadic schizophrenia groups, and also between schizophrenia group and their corresponding normal controls (Table 1). The PANSS total, negative and positive scores did not differ significantly between familial and sporadic patients. The following exclusion criteria applied to all of the above groups: the existence of organic brain disorder, alcohol or drug abuse, pregnancy or any physical illness such as hepatitis, brain tumor, and epilepsy as assessed based on the medical records. No gross abnormalities in brain MRI scans (i.e., T1 weighted and T2 weighted images) were observed for any of the subjects when inspected by an experienced neuroradiologist.

2.2. Data acquisition

High resolution T1-weighted images were acquired using a 3T MRI system (EXCITE, General Electric, Milwaukee, WI, USA) with a volumetric 3D Spoiled Gradient Recall (SPGR) sequence (TR=8.5 ms, TE=3.4 ms, flip angle=12°, slice thickness=1.0 mm) with an eight-channel phase array head coil. A field of view (FOV) of 24 cm² was used with an acquisition matrix comprising 256 readings of 128 phase-encoding steps, producing 156 contiguous coronal slices with slice thickness of 1.0 mm and in-plane resolution of 0.47 mm × 0.47 mm.

2.3. VBM analysis

Optimized VBM was carried out using Statistical Parametric Mapping software (SPM2, Welcome Department

| Table 1 | Demographic summary of the probands, their parents and the normal controls |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|
|         | Probands | Sporadic | Controls | Parents | Sporadic | Controls |
|         | Familial (n=10) | (n=10) | (n=10) | Familial (n=10) | (n=10) | (n=10) |
| Age (S.D.) (years) | 22.0 (8.2) | 21.2 (7.5) | 23.0 (7.9) | 41.4 (3.7) | 45.6 (6.2) | 43.2 (6.3) |
| Male: Female | 5:5 | 5:5 | 5:5 | 3:5 | 5:7 | 4:6 |
| Years of education (S.D.) | 9.7 (4.1) | 12.4 (2.3) | 10.8 (2.5) | 6.7 (2.8) | 8.2 (3.4) | 7.8 (3.8) |
| Months of disease duration (S.D.) | 4.1 (3.1) | 4.8 (3.2) | | | | |
| PANSS score | Total (S.D.) | 101.7 (15.5) | 93.6 (15.4) | | | |
|           | Negative (S.D.) | 24.4 (5.4) | 22.6 (6.6) | | | |
|           | Positive (S.D.) | 18.6 (4.1) | 20.1 (7.2) | | | |

Note: all subjects are right-handed, and there were no statistically significant differences between the matched groups (P>0.05); PANSS: Positive and Negative Syndrome Scale.
of Imaging Neuroscience, London; available at [http://www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm). The analytic procedure has been described in detail elsewhere (Good et al., 2001).

Optimized VBM involves spatial transformation of all data into a common stereotactic space by registering each image in native space to the same template image before voxel-wise statistical analysis. Gray matter was automatically segmented from the raw MR images using tissue signal intensity values and *a priori* information about the distribution of brain tissue type (the 148-normal dataset of the Montreal Neurological Institute). An automated brain extraction step was included to eliminate voxels from non-gray matter structures, such as the dural venous sinuses, scalp, cranial marrow and diplopic space. Non-brain voxels with similar intensities as gray matter are inherently included as brain tissue during standard segmentation. Gray matter partitions were spatially normalized (using a 12-parameter affine transformation and 7×8×7 non-linear basis functions, which are the default normalization parameters in SPM2) to a customized gray matter template, which was constructed from the normalized, segmented and smoothed gray matter datasets of all 60 subjects. The deformation parameters obtained from the normalization process were applied to the original raw images (in native space) of all participants to create optimally normalized whole-brain images, which were recursively segmented and brain-tissue-extracted. The optimally processed images were smoothed with an isotropic Gaussian kernel with full width-half maximum of 8 mm.

The multiplication of the spatially normalized gray matter (or other tissue class) by its relative volume before and after warping has critical implications for the interpretation of what VBM is actually testing for. Without modulation, VBM can be thought of as comparing the relative concentration of gray or white matter structures in the spatially normalized images. With modulation, VBM can be thought of as comparing the absolute volume of gray or white matter structures. The two approaches are known as “non-modulated” and “modulated” VBM, respectively, and they usually show similar results (Good et al., 2001). Each of these methods has been frequently used to study brain morphometry in schizophrenia (Honea et al., 2005). In the present study, we adopted the “non-modulated” approach based on our experience with this method (Gong et al., 2005), and its use in more recent patient studies (Bonilha et al., 2006; Spencer et al., 2006; Agosta et al., 2007; Hornyak et al., 2008). Furthermore, it has been suggested that in patients with gross neuroanatomical abnormalities (Borgwardt et al., 2006), modulation may not be desired because it could have widespread effects on voxel signal intensities (Eckert et al., 2006).

### 2.4. Statistical analysis

Voxel-by-voxel based comparisons of GMD were performed between groups using two-sample *t*-tests, i.e., familial versus sporadic schizophrenia; familial versus sporadic parents; familial or sporadic schizophrenia versus controls and their respective parents versus controls. The whole brain voxel-by-voxel analysis was supplemented with a small-volume correction (SVC) for the amygdala–hippocampus and the thalamus, as these structures have been suggested to play a key role in the pathogenesis of schizophrenia (Preuss et al., 2005). The extent and location of inter-group differences were illustrated with statistical parametric maps. Many approaches can be used to correct for multiple comparisons (Moorhead et al., 2005), and we used random field theory, which is the most widely used method in previous VBM studies. The SPM{t} values were transformed to the normal distribution [SPM{z}] and with a threshold at *P*<0.005. The significance of each region was estimated by distributional approximations from the theory of random Gaussian fields, and significance levels were set at corrected *P*<0.05. For the amygdala–hippocampus and thalamus, a *P*<0.05 with SVC was deemed significant. The MNI coordinates of our results were transformed to Talairach coordinates using mni2tal [http://imaging.mrc-cbu.cam.ac.uk/down load /MNI2tal](http://imaging.mrc-cbu.cam.ac.uk/download/MNI2tal).

### 3. Results

#### 3.1. Proband study

Firstly, to examine whether the patterns of gray matter abnormalities differed between familial and sporadic probands, each patient group was compared with the same individually matched control group. Compared with controls, both familial and sporadic probands showed significantly reduced GMD in the bilateral insula, right temporal lobe, right occipital lobe, left lenticular nucleus, right cerebellum and left rectal gyrus extending to the anterior cingulate gyrus (Table 2, Fig. 1A and B, respectively). However, the familial probands presented additional significantly reduced GMD in the right thalamus, left parahippocampal gyrus extending to the left inferior temporal lobe, left cerebellum, left inferior frontal gyrus and right parahippocampal gyrus (Table 2, Fig. 1A), whereas reductions in the left parietal lobe and the left medial temporal lobe were observed in sporadic patients (Table 2, Fig. 1B). No significant increases in GMD were found in either patient group compared with normal controls.
After application of the SVC for bilateral thalami and amygdala–hippocampus, patients with familial schizophrenia had significant reduction in GMD only in bilateral thalami (Talairach: −14, −28, 12; 13, −24, 13) relative to the sporadic group (Table 2, Fig. 1C). However, no significant increases in GMD were found in familial patients compared with the sporadic group.

3.2. Parents study

Compared with controls, only parents in the familial group showed lower GMD in areas including the right insula extending to the right temporal lobe and the right parietal lobule (Table 3, Fig. 2A), most of which were consistent with the findings in the familial probands. No significant difference in GMD was observed between controls and parents in the sporadic group.

To examine the difference between familial and sporadic parents, a direct comparison between the two groups was also performed. Similar to the findings in probands, familial parents showed significantly reduced GMD in bilateral thalami (Talairach: −8, −15, 4; 10, −20, 5) relative to sporadic parents after correction at the whole brain level (Table 3, Fig. 2B). Other brain regions including right middle temporal gyrus and bilateral occipital lobe also showed significantly lower GMD in familial parents compared with sporadic parents (Table 3, Fig. 2B). After application of the SVC for bilateral amygdala–hippocampus, familial parents showed lower GMD than sporadic parents in the right amygdala–hippocampus. No significant increases in GMD were observed in familial versus sporadic parents.

4. Discussion

The present study presents the first VBM results of neuroanatomical differences between subgroups of familial and sporadic patients, and between parents in the corresponding subgroups, from a cohort of first episode, treatment-naive schizophrenia patients and their unaffected biological parents. In both comparisons of the probands and their parents, we observed more brain structural abnormalities in the familial group than in the sporadic group. These findings are consistent with our hypothesis that the familial group would have a greater genetic liability than the sporadic group and consequently more severe gray matter abnormalities.

It is interesting to note that GMD in bilateral thalami was significantly reduced in both familial probands and their non-psychotic parents when compared with findings in the sporadic group (Tables 2 and 3, Figs. 1C and 2B), implicating the crucial role of the thalamus.
as a structural manifestation of greater genetic liability. In fact, McIntosh et al. (2004) reported that the reduction of GMD in the thalamus was the main correlate of genetic risk for psychosis in individuals at high risk for the development of schizophrenia. In addition, one recent study of twins with schizophrenia also revealed that the volumetric thalamus abnormalities were suggestive of the substantial genetic contribution to schizophrenia (Ettinger et al., 2007). Genetic abnormalities of the thalamus have been reported including the increases in ERK2, c-fos and c-jun protein and mRNA levels in schizophrenia (Kyosseva, 2004), and it is likely that these may be more severe in the familial group than in the sporadic group. By comparing the structural difference between the familial and the sporadic group, the present study adds structural imaging evidence to support the relationship between thalamic GMD reduction and genetic liability.

The lower GMD in bilateral thalami in familial probands than sporadic ones was also consistent with the symptom differences between the two subgroups. In contrast to sporadic patients, the familial probands were found to have more deficit syndromes (Galderisi et al., 2002), greater and more treatment-resistant negative symptoms (Malaspina et al., 2000; Galderisi et al., 2002), poorer outcome and a higher rehospitalization rate (Suvisaari et al., 1998; Feldmann et al., 2000), and these characteristics were thought to be related to the abnormality of bilateral thalami. The reduction in neuronal density and metabolism in bilateral thalamus has been reported in postmortem (Pakkenberg, 1992) and imaging studies (McIntosh et al., 2004) of schizophrenia. The latter studies examined the relationship between thalamus and psychotic symptoms. Andreasen et al. (1999) found that the dysfunction of the thalamo-cortico-thalamic loop was related to the deficit syndrome in patients with schizophrenia and the thalamus was thought to be the core of the loop. Other studies (Strungas et al., 2003; Brickman et al., 2004) showed a relationship of volumetric reduction in the thalamus, especially the left thalamus, with poor outcome of schizophrenia. More recently, Preuss et al. (2005) found that the thalamus, especially the left thalamus, was negatively correlated with PANSS negative symptoms in first episode schizophrenia. The lower GMD in bilateral thalami in familial probands than sporadic ones most likely reflects reduced neuronal (Ashburner and Friston, 2001) and/or glial tissue (Apkarian et al., 2004) of the thalamus in these patients, and thus provides neuroanatomical imaging evidence to support symptomatic differences such as more symptoms of the deficit syndrome, greater and more treatment-resistant negative symptoms and poorer outcome in familial patients compared with sporadic ones.

Compared with normal controls, both familial and sporadic probands showed lower GMD in many areas including the bilateral insula, right temporal lobe, right occipital lobe, left lenticula, right cerebellum and left occipital lobe, left lenticular, right cerebellum and left rectal gyrus extending to anterior cingulate gyrus. Familial patients showed additional area of lower gray matter density in the right thalamus. In subsequent comparison with the sporadic patients (C), familial patients showed significant reduction in gray matter density in bilateral thalami.

Table 3
VBM analysis of parents

<table>
<thead>
<tr>
<th>Correction</th>
<th>Talairach(mm)</th>
<th>Voxel size</th>
<th>t-score</th>
<th>Point of maximal change</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X  Y  Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial parents&lt; control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.011</td>
<td>34  4  41</td>
<td>12135</td>
<td>4.0</td>
<td>Insula extending to right temporal lobe</td>
<td>R</td>
</tr>
<tr>
<td>0.017</td>
<td>46  66 41</td>
<td>11385</td>
<td>3.9</td>
<td>Inferior parietal lobe</td>
<td>R</td>
</tr>
<tr>
<td>Familial parents&lt; sporadic parents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.002*</td>
<td>−8  −15 4</td>
<td>4031</td>
<td>4.6</td>
<td>Thalamus</td>
<td>L</td>
</tr>
<tr>
<td>0.038*</td>
<td>10  −20 5</td>
<td>4221</td>
<td>3.5</td>
<td>Thalamus</td>
<td>R</td>
</tr>
<tr>
<td>0.008**</td>
<td>30  −34 −3</td>
<td>605</td>
<td>3.9</td>
<td>Amygdala–hippocampus</td>
<td>R</td>
</tr>
<tr>
<td>0.049*</td>
<td>44  4  −35</td>
<td>1564</td>
<td>3.4</td>
<td>Middle temporal gyrus</td>
<td>R</td>
</tr>
<tr>
<td>0.015*</td>
<td>−20  −94 10</td>
<td>5635</td>
<td>3.8</td>
<td>Occipital lobe</td>
<td>L</td>
</tr>
<tr>
<td>0.012*</td>
<td>31  −92  −5</td>
<td>5742</td>
<td>3.9</td>
<td>Occipital lobe</td>
<td>R</td>
</tr>
</tbody>
</table>

Note: no differences were found between sporadic parents and controls; *: P<0.05, corrected at whole brain level; **: P<0.05 after small volume correction (SVC).
rectal gyrus extending to the anterior cingulate gyrus (Table 2, Fig. 1) that were consistent with previous VBM findings (Pantelis et al., 2003; Honea et al., 2005; Borgwardt et al., 2007). However, there were additional regions of lower GMD between the two subgroups. For instance, when compared with controls, familial probands showed more abnormal areas including right thalamus, left parahippocampal gyrus extending to left inferior temporal lobe, left cerebellum, and left inferior frontal gyrus. This suggests that the patterns of neuroanatomical abnormalities differ in the two subgroups, which may contribute to the heterogeneity of the VBM findings in previous research (Honea et al., 2005). Although we did not observe significantly lower GMD in the left thalamus in our patients as observed in a previous study with a larger sample size (Job et al., 2003; McIntosh et al., 2004), it is important to note that only familial patients showed lower GMD in the anterior frontal gyrus.
part of the right thalamus, and this again supports the possibility of a greater thalamus deficit in familial patients.

To our knowledge, the present study provides the first structural imaging evidence that familial parents have more neuroanatomical abnormalities than sporadic parents. In comparison with sporadic parents, the familial parents showed lower GMD in the right middle temporal gyrus, right amygdala–hippocampus and bilateral occipital lobes, in addition to the bilateral thalami (Fig. 2B). Furthermore, compared with normal controls, only familial parents showed lower GMD in several areas including the right temporal lobe and the right parietal lobule (Table 3, Fig. 2A). It seems that more extensive deficits were found in the comparison between familial parents and sporadic parents than when comparing familial parents directly with controls. However, when significance was set to $P<0.005$ uncorrected, deficits in the bilateral occipital lobes, the bilateral thalami in addition to the right temporal lobe and the right parietal lobule were observed only in familial parents in comparison to controls. In fact, results from previous VBM studies also indicated that individuals at high risk for the development of schizophrenia may have genetically associated reductions in cortical volumes in the temporal lobe (Job et al., 2005), occipital lobe (Campbell et al., 2006) and amygdala– hippocampus (Lawrie et al., 2001; Job et al., 2002) compared with healthy controls, and the abnormalities of the temporal lobe and amygdala–hippocampus have been suggested to be related to their memory and recognition deficits (Antonova et al., 2005). Though both familial and sporadic parents are at increased genetic liability, our results add to previous imaging research by supporting the concept that the familial parents have a higher risk of schizophrenia in relation to the sporadic group.

The present study examined brain structure in a cohort of first episode, treatment-naive schizophrenia patients and their unaffected biological parents. All the comparisons between the groups were controlled for age, sex and disease duration, largely minimizing the effect of possible confounds as reported in a previous study (Good et al., 2001; Lieberman et al., 2005). Moreover, VBM is an established technique for studying GMD (Gong et al., 2005). In contrast to ROI analysis, VBM provides an automated assessment of GMD in an objective manner and enables quantification of group differences in neuroanatomy without any a priori ROIs. When ROI and VBM approaches were compared, their results were generally consistent (Job et al., 2002), as suggested in a recent study of the prefrontal cortex by Gong et al. (2005). Though the ventricular enlargement in schizophrenia has potential impact on thalamic density, such an influence did not differ between the familial and sporadic patients as noted in a recent morphometric study (McDonald et al., 2006). Nevertheless, the larger ventricular volumes in familial than sporadic relatives may affect the thalamic density (McDonald et al., 2006), and a future study using ventricular volume as a covariate in a larger group of subjects would help to clarify this point. Although the optimized method of VBM was employed in the current study, and this has largely minimized the contamination of the non-brain voxels that were inherently included as brain tissue using traditional methods (Good et al., 2001; Huang et al., 2007), there is a possible issue of brain normalization for specific ethnic groups. The optimized templates generated here were based on the generic MNI template, and the MNI template is known to differ structurally from the brains of non-Caucasian populations (Sato et al., 2003). For further analyses, it is therefore necessary to create an ethnic-specific brain template (i.e., Chinese brain template). Furthermore, although possible confounds such as age, sex and disease duration were all matched between groups to minimize any false-positive or -negative findings, we recognize the modest group size in the present study; it is necessary to carry out a large cohort study to verify current findings.

In summary, by studying a cohort of first episode, treatment-naive schizophrenia patients and their unaffected biological parents, the present study firstly revealed that the familial group has more severe neuroanatomical abnormalities than the sporadic group, especially in bilateral thalamus. The differences in these regions may be attributable to a greater influence of genetic factors in the familial group. Further studies involving genotyping are needed to identify the particular genes that account for these differences.

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