

Progressive Brain Changes in the Early Stage of Schizophrenia: A Combined Structural MRI and DTI Study

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Abstract

Purpose: The developmental trajectory of brain structure in the early stage of schizophrenia has not been well defined. In this study, structural MRI and diffusion tensor imaging (DTI) were used to explore the brain gray matter (GM) and white matter (WM) changes in patients with schizophreniform disorder or early schizophrenia.

Methods: Sixteen schizophreniform patients, 19 early schizophrenia patients (duration of illness < 5 years) and 25 healthy controls were enrolled in this study. Structural MRI and DTI images were obtained. GM volumes were examined using voxel-based morphometry (VBM), and fractional anisotropy (FA) was used to measure WM integrity.

Results: Compared with healthy controls, GM volume was smaller in the right hippocampus and larger in the left middle frontal gyrus and right temporal gyrus in schizophreniform patients; there were no significant differences in FA values between the two groups. GM volumes were reduced in the right hippocampus, bilateral parahippocampal gyri, right middle temporal gyrus and precuneus, and left inferior occipital lobe, and increased in the left temporal lobe in schizophrenia patients compared with healthy controls; furthermore, FA values were reduced in the bilateral cingulate, right insular cortex, precuneus and superior frontal gyrus, and increased in the bilateral fusiform gyri, right superior temporal gyrus, right middle frontal lobe of schizophrenia patients compared with healthy controls.

Conclusion: Our study suggests that brain GM and WM abnormalities occur in early stage schizophrenia, with the occurrence of GM changes, particularly those in the right hippocampus, likely preceding changes in WM.

Keywords

Schizophrenia; Early stage; Magnetic resonance imaging (MRI); Diffusion tensor imaging (DTI)

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Introduction:

Schizophrenia is a chronic and disabling disorder characterized by extensive functional impairment [1]. However, the etiology and pathophysiology of schizophrenia remain elusive.

Previous studies have shown grey matter (GM) volume reduction and compromised white matter (WM) integrity in patients with schizophrenia [2,3]. Furthermore, cortical thinning has been reported in corresponding brain areas in individuals at high risk for psychosis and those with schizophrenia, particularly in the frontal and medial temporal cortices, insular and cerebellar, anterior cingulate cortex (ACC), superior temporal gyrus (STG) and hippocampal regions [4-6]. Studies in first-episode psychosis patients have shown reduced whole brain volume and hippocampal volumes, as well as increased lateral ventricular volume [7,8]. Finally, a meta-analysis that included individuals with chronic schizophrenia found that patients also had smaller mean cerebral volumes, greater total ventricular volumes, smaller hippocampus and parahippocampus, amygdala, frontal lobes, and temporal lobes; these changes were largely bilateral [8].

Although previous studies have shed substantial light on the pathophysiological features of the brain associated with schizophrenia, the extent to which factors such as duration of illness, clinical symptom severity, and exposure to antipsychotic treatment have influenced their findings is currently unknown. Importantly, recent studies have indicated that treatment with antipsychotics might give rise to some of the neuroanatomical changes that are commonly attributed to the illness process [9,10].

The majority of studies detailed above have focused on macrostructural indices of volume changes in GM and WM. [9-11]. However, diffusion tensor imaging (DTI) provides a useful method to assess WM integrity and connectivity *in vivo* [12]. Fractional anisotropy (FA), a DTI index, is thought to be a marker of the structural integrity of fibers, the degree of myelination, coherence of fiber tracts, and fiber diameter and packing density [13-15]; changes in FA may indicate changes in any of these characteristics of the WM microstructure or a combination of them. Meta-analyses have reported significant differences in DTI measures in the brains of chronic schizophrenia patients in the fornix, corpus callosum, cingulum bundle, internal capsule, external capsule, superior and inferior

occipito-frontal fasciculus, arcuate fasciculus, and uncinate fasciculus [16]. Combined volumetric MRI and DTI analyses suggest that FA abnormalities precede WM volume loss in schizophrenia [17].

In the present study, we sought to examine brain GM and WM abnormalities by comparing groups of patients with schizophreniform disorder and early schizophrenia relative to healthy controls. We hypothesized that both GM and WM abnormalities evolve over time as the illness progresses.

Methods**■ Participants**

This study was conducted at Shanghai Mental Health Center (SMHC), China. Thirty-five patients with a clinical diagnosis of schizophreniform disorder (16 patients) or schizophrenia (19 patients) were recruited for participation. The upper limit for illness duration in the clinical diagnosis of schizophreniform disorder is 6 months, after which a diagnosis of schizophrenia is made if symptoms persist; we confined the disease duration for patients with schizophrenia to 5 years (early schizophrenia). The diagnosis of each patient was confirmed by a research psychiatrist (Y.W.) using the MINI plus v 5.0 [18]. All schizophreniform patients were eventually diagnosed with schizophrenia at post-6 month follow-up. To minimize the potential confounding effects of antipsychotic medication, all schizophreniform patients were drug-naïve, and of the 19 schizophrenia patients, 9 of them were drug-naïve, others had discontinued antipsychotic medications from 8 months to 18 months prior to study participation. All subjects had the capacity to provide informed consent, were in relatively stable clinical condition and were deemed competent for study participation by their treating psychiatrists.

Exclusion criteria for the study included: (1) inability to provide informed consent, (2) acute psychosis or unstable clinical condition (e.g., aggression or uncooperative behavior), (3) current substance abuse, (4) any other psychiatric diagnosis, (5) significant medical conditions including neurological disease, severe cardiovascular, hepatic, or renal diseases, (6) pregnancy or breastfeeding.

Twenty-five healthy controls (HC) were recruited from the local community through advertising. All of them completed a structured

clinical interview conducted by a research psychiatrist using MINI plus v 5.0 [18]. Those with any psychiatric disease, neurological disease, or a positive family history of psychiatric disease were excluded.

Written informed consent was obtained from each participant. The study protocol was approved by the SMHC Ethics Committee in compliance with the Helsinki Declaration. Clinical symptoms were assessed using the Scale for Assessment of Negative Syndrome (SANS) [19] and Scale for Assessment of Positive Syndrome (SAPS) [19]. The severity of illness was also assessed by the Clinical Global Impressions-severity scale (CGI) [20].

■ Image Acquisition

■ Structural imaging

Imaging scans were performed using a SIEMENS Verio 3.0 T scanner at the Shanghai Mental Health Center (SMHC). Scan sequences were identical for all subjects. Head movement was minimized by foam padding across the forehead and chin. A 3-dimensional volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous, 1 mm thick coronal slices. Imaging parameters were: time-to-echo, 2.96msec; time-to-repetition, 2300 msec; flip angle, 90; matrix size, 240×256; field of view, 16 ×16 cm matrix; voxel dimensions, 1mm×1mm×1mm.

■ Diffusion tensor imaging

3 mm thick coronal slices were obtained. Imaging parameters were: time-to-echo, 87 msec; time-to-repetition, 8500 msec; diff directions 32; matrix size, 64×64; field of view, 230; voxel dimensions, 1 mm×1 mm×1 mm.

The scanner was calibrated fortnightly using the same proprietary phantom to ensure stability and accuracy of measurements. A subject code was used to ensure patient confidentiality and blindness of data. A neuroradiologist reviewed all MRI scans.

Image Processing

■ Structural images

We quantitatively characterized GM changes using VBM. All anatomical images were processed in SPM8 and VBM8 toolboxes (<http://dbm.neuro.uni-jena.de/vbm/>) with default parameters under MATLAB 7.0. VBM is a whole-brain, unbiased, semi-automated

technique for characterizing regional cerebral differences in structural magnetic resonance images. First, structural images were segmented to extract GM and then normalized to an asymmetric T1-weighted template in Montreal Neurological Institute (MNI) stereotactic space, in a recursive fashion. Image segmentation incorporated an intensity nonuniformity correction to account for smooth intensity variations caused by gradient distortions and different positions of cranial structures within the MRI coil. The resultant GM images were smoothed with a FWHM kernel of 6 mm in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). Smoothing is required to compensate for the inexact nature of spatial normalization and to maximize the chance that regional effects are expressed at a spatial scale where homologues in structural anatomy exist over subjects. After smoothing, each voxel represents the local average amount of GM in the region, the size of which is defined by the smoothing kernel.

■ Diffusion tensor images

The diffusion-tensor images were first corrected for eddy current distortion using a mutual information based registration scheme, and then masked using locally written software plus the Brain Extraction Tool (BET) in the Functional Software Library package (<http://www.fmrib.ox.ac.uk/fsl>). Fractional anisotropy (an index of WM microstructural organisation) was calculated at each voxel to produce a multi-slice fractional anisotropy image in FLRIT. We thus generated a transformation matrix by normalizing each FA image to the Montreal Neurological Institute (MNI)-152 FA brain template [21,22].

■ Statistical analyses

We performed independent samples t-tests in SPM8 to compare GM volumes and FA values between schizophreniform patients and healthy controls (HC) schizophrenia patients and HCs, schizophreniform and schizophrenia patients. Imaging results were considered significant against AlphaSim correction for completeness ($p < 0.001$). The relationships between imaging measures and clinical measures in patients, including hallucinations, bizarre behavior, delusions, positive forms of thought disorder, poverty of thought, emotion dull, lack of will, lack of interest, attention disorder, age, age at onset, duration of illness and education level, were assessed by Spearman rank-order correlation.

Results

Demographic characteristics and clinical variables

Table 1 shows the demographic and clinical characteristics of all the participant groups. One-Way ANOVA showed no significant differences among the three groups in gender and age. However, education level differed among the three groups. Group comparisons between the schizophreniform group and the early schizophrenia group revealed no differences in age of illness onset, SAPS score, SANS score and CGI score. As expected, the illness duration in the early schizophrenia group was significantly longer than in the schizophreniform group ($t=-5.976$, $p <0.001$), and the number of episodes in the early schizophrenia group was significantly higher than in the schizophreniform group ($t=-2.247$, $p=0.031$).

Patients with schizophreniform disorder compared to healthy controls

Compared to HCs, the schizophreniform group exhibited minor variations of brain GM: smaller volume of the right hippocampus, and larger GM volume in the left precentral and right superior temporal gyrus. However, no significant differences were found for any brain WM FA values between the schizophreniform group and HCs (**Figure 1**).

Patients with Early Schizophrenia Compared to Healthy Controls

Both GM and WM abnormalities were found in patients with schizophrenia compared to HCs. The results are shown in **Table 2**.

GM volumes of the right hippocampus, bilateral parahippocampal gyrus, left inferior occipital gyrus, right middle temporal gyrus and precuneus were decreased, and left inferior temporal gyrus were increased in patients. With regard to WM, the FA values of bilateral cingulate gyrus, right precuneus, insula and superior frontal gyrus were decreased, and bilateral fusiform, right superior temporal gyrus, right medial frontal gyrus were increased in patients.

Group differences between the two patient groups

Further comparisons were performed between the two patient groups, and the results are displayed in **Table 3**. Compared to schizophreniform patients, those with schizophrenia showed decreased GM volume of the bilateral middle temporal gyri, right precuneus, left cingulate gyrus and precentral gyrus, and increased GM volume of the posterior cerebellum; FA values of the right superior thalamic radiation were decreased, and those of the bilateral fusiform and left posterior cerebellum were increased (**Table 3**).

Associations between regional gm volumes, fa values and clinical symptoms

In order to further explore associations between regional GM or WM abnormalities with demographic characteristics and clinical variables, schizophreniform patients and schizophrenia patients were combined into one group for correlation analyses. The mean GM volume of the right parahippocampal gyrus correlated negatively with SAPS total score ($r=-$

Table 1: Demographic characteristics and clinical variables of the study groups.

	Patients with schizophreniform disorder (n=16)	Patients with Schizophrenia (n=19)	Healthy controls (n=25)	Group comparisons	
				Fort	p
	Mean(SD)	Mean (SD)	Mean (SD)		
Age (years)	27.19(7.43)	29.26(4.34)	27.08(4.86)	0.979	0.382
Education (years)	13.63(2.06)	15.00(2.08)	16.24(1.05)	11.40	<0.001
Age of onset (years)	27.56(7.25)	26.68(4.15)		0.449	0.657
Duration of illness (months)	2.38(1.98)	32.11(19.77)		-5.976	<0.001
Episode	1.0(0.00)	1.47(0.84)		-2.247	0.031
SAPS	41.00 (13.43)	40.84 (12.58)		0.036	0.972
SANS	33.88 (21.39)	37.16 (18.56)		-0.486	0.630
CGI-severity	5.33(0.49)	5.21(0.63)	/	0.642	0.525
	N%	N (%)	N (%)	χ^2	p
Gender				0.059	0.971
Male	7(43.8)	8(42.1)	10(40)		
Female	9(56.3)	11(57.9)	15(60)		

Notes: SANS: Scale for Assessment of Negative Syndrome, SAPS: Scale for Assessment of Positive Syndrome, CGI-S: Clinical Global Impression-Ser-
vity.

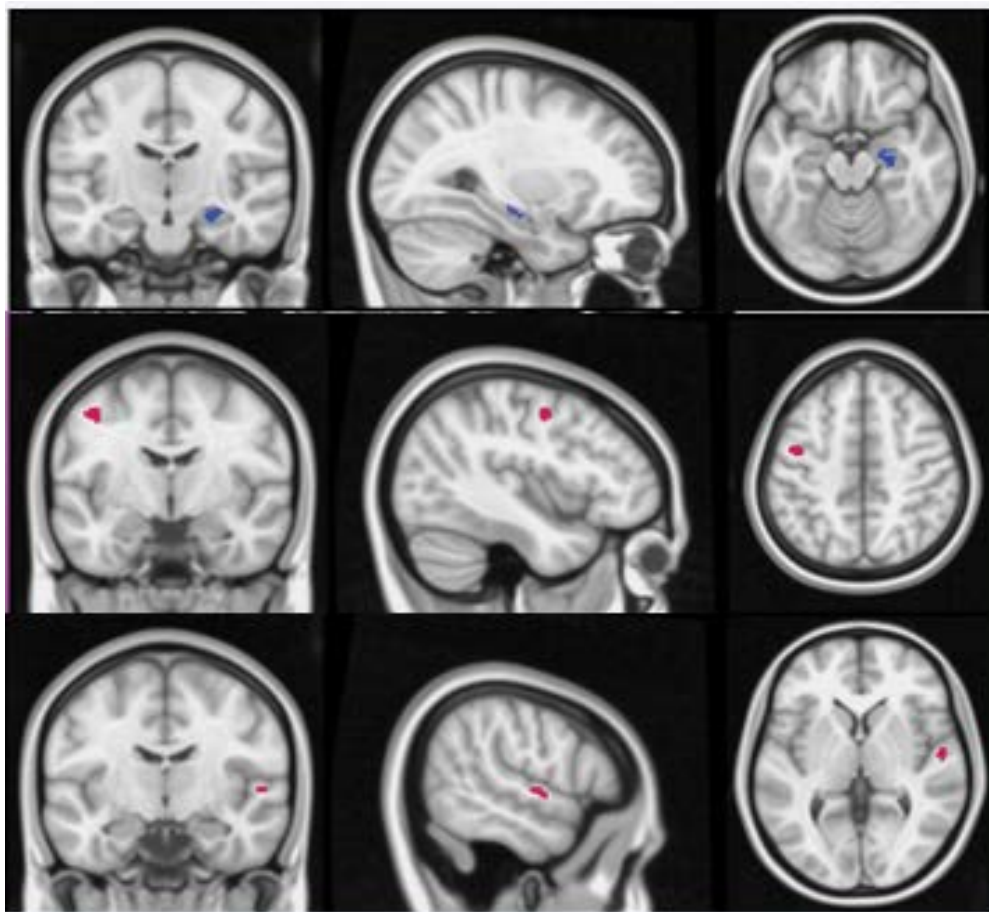


Figure 1: Grey matter volume changes in schizophreniform patients. Grey matter volume reduction is indexed in blue, and gray matter volume increase is shown in red. Statistical threshold is set at $p < 0.001$ (AlphaSim correction), and a minimum cluster extent of 50 voxels.

0.355, $p=0.039$), bizarre behavior score ($r=-0.369$, $p=0.032$), and SANS avolition apathy score ($r=-0.418$, $p=0.014$). The mean WM FA value of the right superior temporal gyrus correlated positively with age at illness onset ($r=0.388$, $p=0.023$), and negatively with alogia score in SANS ($r=-0.347$, $p=0.044$).

Discussion

To our knowledge, this is the first study to investigate differences in brain structure among individuals diagnosed with schizophrenia, those with schizophreniform disorder, and healthy controls. Our main findings show that GM and WM abnormalities in schizophrenia appear to advance as the stage of illness progresses. The right hippocampus was the only structure showing volume reduction in schizophreniform patients, indicating the potential utility of this finding as a biomarker for the early identification of schizophrenia. As the disease progresses, changes in terms of volume reduction of the bilateral

parahippocampus, right middle temporal gyrus and precuneus may gradually emerge. In addition, schizophreniform patients showed no significant abnormalities in WM microstructure. However, our results indicate that FA values of some brain regions decrease, while those of other brain regions increase at later stages of the disease. All of the above findings are consistent with the notion that GM abnormalities precede WM changes in schizophrenia.

The majority of previous studies comparing first-episode patients to those with chronic schizophrenia do not explicitly report illness duration or stage [23-25]. An advantage of the present study is the clear distinction between patients with schizophreniform disorder and early schizophrenia at defined stages of illness. More widespread brain changes in early schizophrenia patients than in schizophreniform disorder may imply the progression of brain anatomical changes after illness onset. Meanwhile such abnormalities can be used as

Table 2: The changes of regional gray matter volume and white matter FA value in patients with Schizophrenia.

Cerebrum	Anatomical region	Cluster size	MNI Coordinates			Peak intensity
			x	y	z	
Grey matter						
Schizophrenia patients < Healthy controls						
L	parahippocampal gyrus	118	-25.5	-19.5	-12	-4.5431
L	Inferior occipital gyrus	399	-36	-90	-13.5	-4.3192
R	parahippocampal gyrus	82	33	-28.5	-18	-4.1679
R	Hippocampus	59	27	-16.5	-13.5	-4.5419
R	Middle temporal gyrus	56	64.5	-30	-6	-4.0477
R	Precuneus	135	4.5	-66	31.5	-3.9406
Schizophrenia patients > Healthy controls						
L	Inferior temporal gyrus	59	-48	-9	-42	4.1878
L	Inferior temporal gyrus	55	-40.5	-31.5	-18	3.7725
White matter						
Schizophrenia patients < Healthy controls						
L	Cingulate gyrus	656	-4	-26	43	-4.4675
R	Cingulate gyrus	390	12	-29	41	-4.127
R	precuneus	631	7	-67	31	-5.6586
R	Insula	374	43	-21	14	-4.4877
R	Superior frontal gyrus	408	22	51	-19	-3.82
Schizophrenia patients > Healthy controls						
L	Fusiform	2260	-21	4	-43	5.1562
R	Fusiform	848	26	3	-46	3.9692
R	Superior temporal gyrus	1128	52	-23	2	5.094
R	Medial frontal gyrus	299	6	-1	66	4.8427

Notes: MNI=Montreal Neurological Institute, R/L=right/left.

Table 3: Comparison of regional grey matter volume and white matter FA value between two patients groups.

Cerebrum	Anatomical region	Cluster size	MNI Coordinates			Peak intensity
			x	y	z	
Grey matter						
Schizophrenia patients < schizophreniform patients						
R	Middle temporal gyrus	159	63	-28.5	-7.5	-4.9056
R	Precuneus	391	4.5	-69	33	-6.391
L	Middle temporal gyrus	86	-49.5	-64.5	19.5	-3.942
L	Cingulate gyrus	116	-1.5	-43.5	37.5	-4.2024
L	Precentral gyrus	139	-42	-15	51	-4.4863
Schizophrenia patients > schizophreniform patients						
L	Posterior cerebellum lobe	69	-18	-66	-31.5	4.4649
White matter						
Schizophrenia patients < schizophreniform patients						
R	Superior thalamic radiation	401	22	-18	30	-4.2767
Schizophrenia patients > schizophreniform patients						
L	Fusiform	2723	-27	-2	-23	5.988
R	Fusiform	2340	21	6	-45	4.6838
L	Posterior cerebellum lobe	3114	-2	-80	-24	4.7008

Notes: MNI=Montreal Neurological Institute, R/L=right/left.

biomarkers. Continuing changes may evolve as illness duration increases [26].

Past studies have found reductions in hippocampal volume in first episode patients with schizophrenia [27,28]. This indicates with relative certainty that a loss of tissue in the hippocampus occurs in the period near disease

onset. In addition, studies in high risk individuals who later developed schizophrenia found decreased hippocampal volume compared with healthy controls [27,29]. The first VBM study to examine GM volumes in high-risk individuals found reductions in right hippocampal and parahippocampal areas. Our finding of GM

volume reductions of right hippocampus in schizophreniform patients is in line with these past findings.

Temporolimbic structures including the hippocampus, parahippocampus and amygdala, are part of a network that integrates external and internal information [30]. Volume reduction in these brain regions has been reported in previous VBM investigations of schizophrenia [26,31,32]. Here, we did not find abnormalities of the amygdala. This discrepancy might be due to different imaging methods used here and in other studies [28]. Moreover, it could be related to different spatial normalization and image processing procedures [33,34]. Furthermore, previous studies either did not consider sex differences, or included a preponderance of patients. This is particularly relevant since divergent abnormalities of the amygdala have been shown in men and women with schizophrenia. Specifically, men show decreased volume while women show increased volume [35]. Investigations in patients with treatment-naïve, first-episode schizophrenia have revealed significant GM volume abnormalities in bilateral hippocampal gyri, right middle temporal gyrus, left fusiform gyrus and left orbital inferior frontal gyrus, shown to be related to cognitive deficits [36]. In cortical regions, the superior temporal gyrus (STG) of schizophrenia patients is often reported to be smaller than that of HCs [37,38]. The superior temporal gyrus is involved in auditory processing as well as language functions and auditory memory; GM abnormalities of the superior temporal gyrus in patients with schizophrenia may be related to auditory and higher cognitive functioning deficits that often manifest in this disorder. However, we did not find a generalized reduction in STG volume, possibly because most schizophreniform patients included here were experiencing auditory hallucinations at illness onset. STG volume may have increased as an early compensatory effect.

The present study shows that GM abnormalities, including those in the middle temporal gyrus, parahippocampal gyrus, hippocampus, and precuneus, are more extensive in early schizophrenia. Activity in the middle temporal gyrus is related to semantic memory processing and language processes, which suggest that structural abnormalities in this region may play a role in the cognitive deficits in semantic function that have been found among Han Chinese family members with schizophrenia. And the above

results consistent with a systematic meta-review reported that the GM reductions of temporal lobe and hippocampus were magnified over time in psychotic phases.

The precuneus is a brain area that occupies the posterior region of the medial parietal cortex, and is involved in numerous complex functions, including recollection and memory, integration of information relating to perception of the environment, cue reactivity, mental imagery strategies, episodic memory retrieval, and affective responses to pain [39]. Schizophrenia patients typically display cognitive deficits, which may be related to GM reduction in the precuneus. Our finding of extensive GM abnormalities in early schizophrenia patients is consistent with the results of previous studies comparing groups of first-episode and chronic schizophrenia patients [11,26,31,32,]. Our findings are also in agreement with a meta-analysis that found extensive GM deficits involving the frontal cortices, cingulate cortex, temporolimbic region and temporal gyrus in schizophrenia [32].

WM is usually assessed using the FA index of water diffusion, which is calculated from diffusion tensor imaging data [40]. Schizophrenia was one of the first psychiatric disorders in which FA methods were applied. Reduced FA at the onset and chronic states of schizophrenia has been reported in a number of studies [3,16,41]. However, the regions in which abnormalities have been detected are not consistent between them. Commonly reported regions of significant FA reduction in schizophrenia are the frontal and temporal WM tracks, including the uncinate fasciculus, cingulum bundle, arcuate fasciculus, corpus callosum that connect the bilateral frontal lobes. Our results showed no differences between schizophreniform patients and HCs. In patients with early schizophrenia, reduced FA was found in the cingulate gyrus, WM regions in occipital lobe, precuneus, WM regions in insula, and WM regions in the superior frontal gyrus, compared to HCs. Higher FA values were also found in a number of regions. The fusiform area, known as the (discontinuous) occipitotemporal gyrus, is part of the temporal lobe and occipital lobe in Brodmann area 37. [42]. Anatomically, the fusiform gyrus is the largest macro-anatomical structure within the ventral temporal cortex, and mainly includes structures involved in high-level vision [42,43]. Though the functionality of the fusiform gyrus is not fully understood, it has

been linked with various neural pathways related to recognition, such as face hallucinations, dyslexia, and synaesthesia [44]. We found that FA values in WM regions of the fusiform are increased in schizophrenia compared to HCs, which may be related to the regularly experienced hallucinations of most patients in this study. We think that is because the compensatory increase in these regions in schizophrenia patients.

The neurodevelopmental and neurodegenerative theories of schizophrenia are two competing hypotheses on the etiology and clinical course of this disease [45]. The neurodevelopment model proposes that schizophrenia is caused by environmental or genetic insults that occur during prenatal, perinatal, or early childhood, leading to changes of brain structure and function in schizophrenia [46-48]. This model is supported by studies reporting significant changes in cerebral structures undergone prior to the onset of psychosis in individuals at high risk for developing schizophrenia [49,50]. However, it fails to address the heterogeneous and sometimes deteriorating clinical course of schizophrenia after illness onset. The role of progressive neurodegeneration in schizophrenia was first proposed by Kraepelin who observed mental decline in schizophrenia patients [51,52]. Patients with schizophrenia often follow a progressive, neurodegenerative clinical course, an observation that has been repeatedly been upheld [51]. However, studies focused on this model have yielded controversial results, with some researchers finding no changes in brain volume over time [53]. Neither of these two models can independently or accurately explain the etiology and clinical course of schizophrenia. Our findings can be taken to lend partial support to each of these two models, indicating that the schizophrenic brain begins to change at disease onset and progressively worsens throughout the course of the disease.

Several limitations of the present study should be taken into account. First, the patient sample size is relatively small. Second, groups were not matched for education level, and education level was therefore controlled for in the following analyses. Third, the data here is cross-sectional rather than longitudinal, and longitudinal researches are needed to further corroborate the present findings. Last, since many studies had mentioned that antipsychotics had an effect on the brain volumes, and the drugs ever taken by schizophrenia patients in the present study might be a potential confounding factor.

Conclusion

Abnormalities of brain GM and WM in schizophrenia seem to evolve as the stage of illness progresses, lending support to the neurodegenerative hypothesis of schizophrenia. Decreased volume in the right hippocampus may be a potential biomarker for early diagnosis of schizophrenia.

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