Changes in Cerebral Cortex Thickness, Gray Matter Volume and White Matter Integrity in Patients with First-Episode Drug-Naive Schizophrenia and Effects on Cognitive Impairment

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ABSTRACT

Background: The pathogeny of schizophrenia, a severe mental disorder characterized by high prevalence, recurrence and disability rates, insidious onset and complex conditions, remains unclear, and the disease has always been a hotspot of research on mental diseases.

Aim: The study investigated the changes in cerebral cortex thickness, gray matter volume and white matter integrity in patients with first-episode drug-naive schizophrenia and their effects on cognitive impairment.

Methods: Sixty-seven patients diagnosed as first-episode drug-naive schizophrenia from July 2018 to June 2019 and 67 normal subjects were enrolled into patient and control groups, respectively. Their general data and cognitive function evaluation results were compared. The fractional anisotropy (FA), axial diffusivity (AD), radical diffusivity (RD) and mean diffusivity (MD) for cerebral cortex thickness, gray matter volume and white matter structure were compared. The correlations of brain regions showing differences between the two groups with cognitive function in patient group were explored by Pearson's chi-square test.

Results: In the patient group, the cortex thicknesses at left isthmus of cingulate gyrus and lingual gyrus as well as right fusiform gyrus, inferior parietal lobule, isthmus of cingulate gyrus, lateral occipital lobe, lingual gyrus, opercular part of inferior frontal gyrus, precentral gyrus, precuneus, superior parietal lobule, superior temporal gyrus and supramarginal gyrus were lower, but the cortex thickness at inferior part of right anterior cingulate gyrus was higher ($P<0.05$). The gray matter volume at left cuneus and lingual gyrus as well as right fusiform gyrus and lateral occipital lobe decreased ($P<0.05$). The FA values for major forceps, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus in the left brain, and corticospinal tract, minor forceps, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus in the right brain declined ($P<0.05$). The MD values of major forceps, minor forceps, inferior fronto-occipital fasciculus and anterior thalamic radiation in the left brain rose ($P<0.05$). The RD values for left major forceps, minor forceps, anterior thalamic radiation, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus as well as right inferior fronto-occipital fasciculus and inferior longitudinal fasciculus were raised ($P<0.05$). The brain regions with differences were correlated with cognitive impairment ($P<0.05$).

Conclusion: There are significant changes in cerebral cortex thickness, gray matter volume and white matter integrity in patients with schizophrenia, which are associated with cognitive impairment.

**The two authors contributed equally to this study.*

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INTRODUCTION

The pathogeny of schizophrenia, a severe mental disorder characterized by high prevalence, recurrence and disability rates, insidious onset and complex conditions (1), remains unclear, and the disease has always been a hotspot of research on mental diseases. The ability to identify and treat schizophrenia patients in the early stage is unlikely (2). With the development of the disorder, patients' thoughts, emotions, behaviors, languages and social functions are influenced to varying degrees, leading to a gradual decline in interpersonal communication ability and social adaptability and an elevated unemployment rate (3). Long-term administration of antipsychotic drugs and placebo may induce some side effects, which can result in a very heavy economic burden for patients and their families. Besides, the potency of such drugs attenuates gradually with the increases in age of patients and course of disease (4). As a core symptom of schizophrenia, cognitive dysfunction occurs before the onset of schizophrenia and exists in the whole process of the disease (5). With the development of brain imaging techniques such as CT, MRI and PET, the microscopic changes in the structure, function and metabolism of the gray and white matter can be observed from a more subtle perspective (6). Researchers have endeavored to use these techniques to elucidate the pathogenesis of neurological and psychiatric diseases (7). In particular, a non-invasive MRI has high spatial resolution and allows accurate positioning, which is thus suitable for studying the brain structure of patients with psychiatric diseases (8). Until now, the mechanism of structural changes in the brain in patients with schizophrenia remains largely unknown. Thereby motivated, the brain images of first-episode drug-naive schizophrenia patients and normal people were herein collected by MRI, the differences in cerebral cortex thickness, gray matter volume and white matter integrity were compared between the two groups, and the correlations of these differences with cognitive impairment were analyzed, aiming to provide valuable references for further studies on schizophrenia.

METHODS

SUBJECTS

A total of 67 patients definitely diagnosed with first-episode drug-naive schizophrenia in our hospital from July 2018 to June 2019 were selected as the patient group. Meanwhile, 67 healthy volunteers recruited by the hospital in the same time period were assigned to the control group. The age, sex, body mass index (BMI), family history and educational level were not significantly different between the two groups ($P>0.05$). This study was approved by the Ethics Committee of the hospital, and all the subjects and their families agreed and signed an informed consent form.

Inclusion criteria for patient group: (1) patients meeting the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (9), (2) those suffering from first episode and never treated with drugs, (3) those aged 18-50 years old, and (4) those with right handedness.

Exclusion criteria for patient group: (1) patients complicated with other mental diseases, (2) those with serious somatic diseases or organic brain diseases, (3) those unable to receive MRI scanning, (4) those who underwent brain surgery previously, or (5) those with drug or alcohol addiction.

Inclusion criteria for control group: (1) people without medical history and family history of cerebral and neurological diseases, (2) those who had not taken hormone drugs and psychoactive substances recently, and (3) those with right handedness.

Exclusion criteria for control group: (1) people with an unstable mental status, (2) those with somatic diseases, or (3) those with drug or alcohol addiction.

GENERAL DATA, COGNITIVE FUNCTION AND POSITIVE AND NEGATIVE SYMPTOM SCALE (PANSS) EVALUATION

The general data of the 134 subjects were collected, including age, BMI, family history and educational level. MATRICS Consensus Cognitive Battery (MCCB) tests (10) were conducted, which consisted of Trail Making Test, Brief Assessment of Cognition, Verbal Learning Test, Spatial Span Test, Maze Test, Visual Memory Test, Category Fluency Test, Emotional Intelligence Test and Identical Pairs Test. The final results of the MCCB tests included the scores of speed of information processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition of the subjects. In this study, the MCCB tests on subjects were performed by three psychiatrists trained in testing, among which the Brief Assessment of Cognition, Verbal Learning Test and Visual Memory Test were employed to evaluate the working memory, verbal learning and visual learning of the subjects, respectively. Finally, the severity of schizophrenia of the subjects was assessed using the PANSS (11).

MRI COLLECTION

The heads of subjects were scanned using Verio 3.0 Tesla high-field MRI scanner (Siemens, Germany), with a

32-channel radiofrequency coil. Specifically, the subjects lay in the supine position with cervical gear, and sponge cushions were placed on both sides of the head to restrict head movement. Professional physicians were responsible for controlling the image results and scanning the whole brain. The sagittal brain section of the subjects was scanned layer-by-layer for 8 min. through 3D-T1 spoiled gradient recalled echo sequence, and the axial brain section was scanned layer-by-layer via T2-weighted echo-planar imaging sequence for 6 min. to obtain diffusion tensor images. By 3D-T1 and T2-weighted scanning, the subjects with obvious organic brain diseases were excluded.

3D phase acquisition: The whole brain was scanned. The subject was scanned slice by slice in the sagittal plane of the brain using 3D magnetization-prepared rapid gradient-echo imaging sequence. T1-weighted phase scan parameters are as follows: TR=2300 ms, TE=2.96 ms, FOV=256×256 mm^2, FOV phase=93.8%, matrix=256×256, voxel size=0.93×0.93×1 mm^3, slice thickness=1 mm, slice spacing=0, number of scanned slices=192, and scanning time=8 minutes.

Diffusion tensor image acquisition: Axial slice-by-slice scan was performed using echoplanar imaging. Scanning parameters are as follows: TR=7900 ms, TE=97 ms, FOV=230×230 mm^2, matrix=122×122, voxel size=1.9×1.9×2.3 mm^3, slice thickness=2.3 mm, slice spacing=0 mm, number of slices=55, number of gradient directions=64, and B=1000 s/mm^2, including one B0 image.

T2 phase acquisition: T2-weighted phase scan parameters are as follows: TR=3200 ms, TE=422 ms, FOV=256×256 mm^2, FOV phase=93.8%, acquisition matrix=256×256, voxel size=0.93×0.93×1 mm^3, slice thickness=1 mm, slice spacing=0, number of scanned slices=192, and scanning time=6 minutes.

Next, the cerebral cortical and subcortical structures were divided using Freesurfer 6.0, the non-brain structures were removed, the white matter was segmented, and white matter surface and gray matter surface were generated. Later, a high-accuracy cortical surface calculation model of Athiniola A. Martinos and Desikan-Killiany atlas segmentation were applied to acquire the numerical values of fractional anisotropy (FA), axial diffusivity (AD), radical diffusivity (RD) and mean diffusivity (MD) for cortex thickness, gray matter volume and white matter structure of the subjects (12, 13).

STATISTICAL ANALYSIS

SPSS 21.0 software was used for statistical analysis. The numerical data were represented as % and examined by chi-square test. The normally distributed measurement data were expressed as ($\bar{\chi} \pm s$) and subjected to *t*-test. Pearson's coefficient was utilized to analyze the correlations of brain regions with P<0.05 between the two groups with cognitive function evaluation results in patient group. P<0.05 suggested that a difference was statistically significant.

RESULTS

GENERAL DATA, COGNITIVE FUNCTION EVALUATION AND PANSS EVALUATION RESULTS

A total of 134 subjects were enrolled into the patient group (n=67) and the control group (n=67) in this study. The differences in the age, sex, BMI, family history and educational level were not significant between the two groups (P>0.05), while there were significant differences in the scores of Brief Assessment of Cognition, Verbal Learning Test and Visual Memory Test (P<0.05) (Table 1).

Table 1. *General data, cognitive function evaluation and PANSS evaluation results*

Item	Patient group (n=67)	Control group (n=67)	t/χ2	P
Age (year)	29.68±8.02	28.94±7.54	0.526	0.600
Sex [n (%)]				
Male	36 (53.73)	30 (49.12)	0.262	0.609
Female	31 (46.27)	37 (50.88)		
BMI (kg/m2)	25.14±2.58	24.97±2.26	0.387	0.699
Family history [n (%)]				
Yes	10 (14.93)	13 (22.81)	1.266	0.260
No	57 (85.07)	44 (77.19)		
Educational level [n (%)]				
Junior high school and below	28 (41.79)	21 (31.34)	1.596	0.450
Special secondary school or senior high school	26 (38.81)	30 (44.78)		
College or university and above	13 (19.40)	16 (23.88)		
Cognitive function evaluation (point)				
Brief Assessment of Cognition	36.27±10.53	47.02±6.38	7.147	0.000
Verbal Learning Test	34.78±8.44	40.52±10.81	3.426	0.001
Visual Memory Test	37.56±12.80	45.37±10.10	3.921	0.000
PANSS evaluation (point)				
Positive symptom	22.14±4.81	-	-	-
Negative symptom	25.49±4.30	-	-	-
General psychopathology	44.51±7.67	-	-	-
Total PANSS score	92.14±13.25	-	-	-

CEREBRAL CORTEX THICKNESS

Compared with those in the control group, the cortex thicknesses at left isthmus of cingulate gyrus and lingual gyrus as well as right fusiform gyrus, inferior parietal lobule, isthmus of cingulate gyrus, lateral occipital lobe, lingual gyrus, opercular part of inferior frontal gyrus, precentral gyrus, precuneus, superior parietal lobule, superior temporal gyrus and supramarginal gyrus were lower in the patient group [P<0.05, threshold-free cluster enhancement (TFCE) correction]. However, the cortex thickness at the inferior part of the right anterior cingulate gyrus was higher (P<0.05, TFCE correction) (Table 2).

GRAY MATTER VOLUME

The gray matter volume at the left cuneus and the lingual gyrus as well as the right fusiform gyrus and lateral occipital lobe was smaller in the patient group than that of the control group (P<0.05, TFCE correction) (Table 3).

Table 2. *Cerebral cortex thickness*

	Left brain				Right brain			
Cortex area	Patient group (n=67)	Control group (n=67)	t	P	Patient group (n=67)	Control group (n=67)	t	P
Margin of superior temporal gyrus	2.48±0.21	2.54±0.16	1.860	0.065	2.59±0.26	2.64±0.17	1.317	0.190
Superior part of anterior cingulate gyrus	2.68±0.29	2.66±0.22	0.450	0.654	2.48±0.27	2.47±0.25	0.222	0.824
Superior part of middle frontal gyrus	2.41±0.16	2.46±0.15	1.866	0.064	2.39±0.15	2.41±0.16	0.746	0.457
Cuneus	1.82±0.20	1.87±0.14	1.676	0.096	1.83±0.16	1.87±0.12	1.637	0.104
Entorhinal cortex	3.22±0.41	3.13±0.37	1.334	0.185	3.37±0.43	3.38±0.41	0.138	0.891
Fusiform gyrus	2.65±0.22	2.71±0.17	1.766	0.080	2.68±0.26	2.79±0.14	3.049	0.003*
Inferior parietal lobule	2.33±0.24	2.39±0.13	1.799	0.074	2.35±0.20	2.44±0.11	3.227	0.002*
Inferior temporal gyrus	2.67±0.20	2.69±0.16	0.639	0.524	2.71±0.23	2.73±0.18	0.561	0.576
Isthmus of cingulate gyrus	2.39±0.24	2.50±0.18	3.001	0.003*	2.30±0.25	2.42±0.17	3.249	0.001*
Lateral occipital lobe	2.10±0.22	2.14±0.13	1.281	0.202	2.15±0.19	2.21±0.12	2.185	0.031*
Lateral orbitalfrontal cortex	2.52±0.24	2.53±0.16	0.284	0.777	2.44±0.18	2.42±0.13	0.737	0.462
Lingual gyrus	1.96±0.15	2.03±0.11	3.080	0.003*	1.95±0.20	2.08±0.13	4.461	0.000*
Medial orbitalfrontal cortex	2.39±0.21	2.40±0.15	0.317	0.752	2.30±0.19	2.29±0.15	0.338	0.736
Middle temporal gyrus	2.84±0.19	2.87±0.17	0.963	0.337	2.80±0.23	2.86±0.13	1.859	0.065
Parahippocampal gyrus	2.57±0.31	2.59±0.22	0.431	0.667	2.58±0.30	2.62±0.23	0.866	0.388
Precentral gyrus	2.34±0.22	2.40±0.15	1.844	0.067	2.34±0.23	2.39±0.14	1.520	0.131
Opercular part of inferior frontal gyrus	2.44±0.23	2.51±0.23	1.762	0.080	2.46±0.14	2.53±0.15	2.793	0.006*
Orbital part of inferior frontal gyrus	2.44±0.29	2.46±0.18	0.480	0.632	2.44±0.19	2.46±0.15	0.676	0.500
Triangular part of inferior frontal gyrus	2.35±0.23	2.39±0.15	1.192	0.235	2.36±0.15	2.36±0.17	0.000	1.000
Pericalcarine cortex	1.63±0.21	1.62±0.13	0.331	0.741	1.65±0.15	1.64±0.14	0.399	0.691
Postcentral gyrus	1.95±0.17	1.99±0.12	1.573	0.118	1.97±0.16	1.98±0.13	0.397	0.692
Posterior cingulate	2.55±0.20	2.60±0.17	1.559	0.121	2.43±0.25	2.48±0.15	1.404	0.163
Precentral gyrus	2.52±0.18	2.54±0.13	0.737	0.462	2.40±0.21	2.48±0.14	2.595	0.011*
Precuneus	2.29±0.22	2.33±0.11	1.331	0.185	2.26±0.20	2.33±0.14	2.347	0.020*
Inferior part of anterior cingulate gyrus	2.80±0.30	2.81±0.23	0.217	0.829	2.73±0.26	2.62±0.29	2.312	0.022*
Inferior part of middle frontal gyrus	2.16±0.19	2.20±0.13	1.422	0.157	2.15±0.13	2.13±0.15	0.825	0.411
Superior frontal gyrus	2.60±0.21	2.64±0.13	1.326	0.187	2.51±0.21	2.51±0.14	0.000	1.000
Superior parietal lobule	2.06±0.20	2.10±0.13	1.373	0.172	2.04±0.20	2.11±0.13	2.402	0.018*
Superior temporal gyrus	2.75±0.23	2.80±0.20	1.343	0.182	2.76±0.23	2.84±0.14	2.432	0.016*
Supramarginal gyrus	2.44±0.15	2.48±0.13	1.649	0.101	2.42±0.20	2.53±0.12	3.860	0.000*
Frontal pole	2.50±0.34	2.51±0.27	0.189	0.851	2.45±0.33	2.46±0.26	0.195	0.846
Temporal pole	3.31±0.49	3.34±0.48	0.358	0.721	3.44±0.39	3.45±0.30	0.166	0.868
Transverse temporal gyrus	2.33±0.27	2.38±0.24	1.133	0.259	2.33±0.28	0.39±0.22	1.379	0.170
Insula	2.94±0.22	3.00±0.14	1.883	0.062	2.96±0.25	2.99±0.12	0.886	0.377
Average thickness of hemisphere	2.38±0.18	2.42±0.10	1.590	0.114	2.38±0.14	2.41±0.09	1.475	0.142

*P<0.05.

Table 3. *Brain regions with different gray matter volumes*

Cortex area	Left brain (mm3)		t	P	Right brain (mm3)		t	P
	Patient group (n=67)	Control group (n=67)			Patient group (n=67)	Control group (n=67)		
Margin of superior temporal gyrus	2568.34±482.51	2629.74±458.37	0.755	0.451	2518.64±425.92	2475.38±444.18	0.575	0.566
Superior part of anterior cingulate gyrus	1912.54±475.23	1826.35±488.54	1.035	0.302	2086.94±412.58	2130.28±454.32	0.578	0.564
Superior part of middle frontal gyrus	5938.74±1116.20	5982.16±1125.31	0.224	0.823	5619.51±1047.38	5526.17±1026.34	0.521	0.603
Cuneus	2886.18±631.86	3123.14±427.58	2.542	0.012*	3025.49±685.55	3168.42±483.57	1.395	0.165
Entorhinal cortex	1675.25±367.43	1681.57±349.18	0.102	0.919	1547.55±463.19	1527.32±401.87	0.270	0.788
Fusiform gyrus	10132.64±1808.47	10483.17±1749.46	1.140	0.256	9649.28±1738.81	10398.16±1675.24	2.539	0.012*
Inferior parietal lobule	12473.22±2371.10	12694.32±1869.77	0.599	0.550	14971.13±2973.48	15288.17±2127.02	0.710	0.479
Inferior temporal gyrus	10639.78±1834.48	10846.04±1792.35	0.658	0.511	10573.41±1861.38	10748.88±1691.30	0.571	0.569
Isthmus of cingulate gyrus	2648.54±676.17	2841.07±648.26	1.682	0.095	2451.74±549.19	2537.48±532.97	0.917	0.361
Lateral occipital lobe	10637.64±1683.92	11124.18±1700.61	1.664	0.098	10268.71±1732.44	11034.84±1826.03	2.491	0.014*
Lateral orbitalfrontal cortex	6954.11±982.34	7258.81±942.45	1.832	0.069	6874.64±1028.93	6824.35±824.14	0.312	0.755
Lingual gyrus	6472.68±1351.26	6903.42±1086.23	2.034	0.044*	6748.55±1178.59	7047.89±1128.43	1.502	0.136
Medial orbitalfrontal cortex	4520.95±647.58	4636.14±667.78	1.014	0.313	4682.86±604.99	4737.80±568.16	0.542	0.589
Middle temporal gyrus	10797.73±1640.22	11006.82±1724.69	0.719	0.473	11942.77±1768.35	12048.14±1822.69	0.340	0.735
Parahippocampal gyrus	2244.85±343.17	2273.94±924.15	0.242	0.810	2074.54±662.89	2026.11±379.48	0.519	0.605
Precentral gyrus	3284.41±587.46	3276.84±534.61	0.078	0.938	3684.68±603.76	3752.15±665.63	0.615	0.540
Opercular part of inferior frontal gyrus	4597.83±842.48	4687.49±801.64	0.631	0.529	3987.45±732.50	3940.56±728.91	0.371	0.711
Orbital part of inferior frontal gyrus	1804.63±258.94	1876.51±261.86	1.598	0.112	2293.45±364.12	2319.06±330.95	0.426	0.671
Triangular part of inferior frontal gyrus	3339.67±668.35	3482.93±503.18	1.402	0.163	4081.86±682.58	4163.89±716.61	0.678	0.499
Pericalcarine cortex	2106.87±386.98	2156.78±411.08	0.724	0.471	2461.52±438.59	2501.64±402.77	0.551	0.582
Postcentral gyrus	8935.82±1523.54	9267.13±1255.63	1.374	0.172	8894.61±1377.58	9036.33±1432.80	0.584	0.560
Posterior cingulate	3384.62±629.70	3289.17±561.91	0.926	0.356	3274.96±598.21	3458.15±809.46	1.490	0.139
Precentral gyrus	12964.62±2031.86	13301.55±1658.93	1.051	0.295	12834.70±1593.49	12941.25±1478.60	0.401	0.689
Precuneus	9347.26±1523.18	9461.83±1399.02	0.453	0.651	9696.19±1724.32	9735.80±1364.28	0.147	0.883
Inferior part of anterior cingulate gyrus	2676.15±503.28	2656.76±486.93	0.227	0.821	2077.84±428.64	2070.49±493.05	0.092	0.927
Inferior part of middle frontal gyrus	14034.85±2349.72	14233.19±1941.54	0.533	0.595	14573.24±1852.68	14479.31±2141.13	0.272	0.786
Superior frontal gyrus	20565.51±2509.84	20674.32±2701.10	0.242	0.809	19735.94±2377.25	19142.06±2539.42	1.397	0.165
Superior parietal lobule	12123.66±2014.85	12641.57±1947.08	1.513	0.133	12003.72±1942.51	12647.61±1978.97	1.901	0.060
Superior temporal gyrus	11547.80±1873.31	11816.72±1864.39	0.833	0.406	11341.56±1584.17	11571.35±1546.43	0.850	0.397
Supramarginal gyrus	10742.49±1824.74	10876.69±1913.54	0.415	0.678	10023.47±1620.96	10284.27±1772.14	0.889	0.376
Frontal pole	664.26±153.29	619.47±120.04	1.883	0.062	858.95±204.84	873.16±172.74	0.434	0.665
Temporal pole	2131.98±376.52	2122.56±432.45	0.134	0.893	1819.87±308.31	1859.16±279.90	0.772	0.441
Transverse temporal gyrus	1204.58±250.73	1267.85±245.31	1.476	0.142	914.27±200.83	942.16±203.24	0.799	0.426
Insula	6828.82±1010.44	6734.55±1062.96	0.526	0.600	6715.80±964.11	6632.74±965.32	0.498	0.619

*P<0.05.

WHITE MATTER INTEGRITY

In comparison with the control group, the patient group exhibited reduced FA values for major forceps, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus in the left brain, and corticospinal tract, minor forceps, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus in the right brain (P<0.05, TFCE correction), raised MD values for major forceps, minor forceps, inferior fronto-occipital fasciculus and anterior thalamic radiation in the left brain (P<0.05, TFCE correction), and increased RD values for left major forceps, minor forceps, anterior thalamic radiation, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus as well as right inferior fronto-occipital fasciculus and inferior longitudinal fasciculus (P<0.05, TFCE correction) (Table 4).

CORRELATIONS OF CHANGES IN CEREBRAL CORTEX THICKNESS, GRAY MATTER VOLUME AND WHITE MATTER INTEGRITY WITH COGNITIVE IMPAIRMENT

The results of correlation analysis manifested that the brain regions with changes were related to the occurrence of cognitive impairment (Table 5).

Table 4. *Brain regions with different white matter integrity*

Anatomical position	Hemisphere	MAX Z (mm)	MAX Y (mm)	MAX X (mm)	Z	Number of voxels	No.
							FA value
Major forceps		36.2	-31.1	-20.3	0.986	4261	4
Inferior fronto-occipital fasciculus	Left brain						
Superior longitudinal fasciculus							
Uncinate fasciculus							
Corticospinal tract	Right brain	13.9	-54.8	-23.4	0.965	966	3
Minor forceps		15.8	-60.2	28.1	0.973	675	2
Inferior fronto-occipital fasciculus	Right brain						
Inferior longitudinal fasciculus							
Superior longitudinal fasciculus	Left brain	28.9	-52.2	-37.8	0.950	53	1
							MD value
Major forceps		16.3	-53.9	-27.7	0.980	10336	1
Minor forceps	Left side						
Inferior fronto-occipital fasciculus							
Anterior thalamic radiation							
							RD value
Major forceps		29.9	2.2	-12.1	0.988	17575	1
Minor forceps	Left side						
Anterior thalamic radiation							
Inferior fronto-occipital fasciculus							
Superior longitudinal fasciculus							
Uncinate fasciculus							
Inferior fronto-occipital fasciculus	Right side						
Inferior longitudinal fasciculus							

DISCUSSION AND CONCLUSION

Patients with schizophrenia have multiple manifestations of cognitive impairment, and most studies are concentrated on memory and language. The majority of studies on the specific pathogenesis of schizophrenia focus on the changes in neurotransmitter and related kinase levels in the brain as well as the activation and inhibition of signaling pathways. In recent years, such studies have been gradually combined with brain imaging and brain localization, thereby providing a more objective basis for research on the pathogenesis of schizophrenia (14). There is a wide range of pathological changes in the brain of schizophrenia patients (15). Based on the results of many studies (16-19), it has been discovered that the brain regions causing cognitive dysfunction in schizophrenia patients include frontal lobe, temporal lobe, parietal lobe and cingulate gyrus, whose morphological changes are highly consistent. Working memory refers to the ability to temporarily store and process the information received, which is more flexible and dynamic than short-term memory. In addition, it can predict some circumstances and process abstract concepts such as image and thought, so working memory is an essential memory mode of advanced cognitive skills (20). The frontal lobe is the foundation of cognitive function, and the parietal lobe cortex, thalamus and other brain regions are also involved in working memory (21). The structural changes in brain regions related to cognition and memory may abnormally activate some brain regions and reduce memory capacity during the implementation of working memory tasks by schizophrenia patients, which are manifested as a decline in working memory ability. Some neuropsychological test results (22-24) have revealed that schizophrenia patients suffer from severer cognitive impairment in verbal learning than that in other aspects, which is probably associated with structural abnormality in several brain regions. Both frontal lobe and temporal lobe are the core brain regions for language management. A study indicated that partial areas of the frontal and temporal lobes are abnormally activated when schizophrenia patients are organizing language themselves, resulting in difficulties in encoding and extracting words and manifesting decreased verbal learning ability (25). Schizophrenia patients have visual perception defects. It has been researched that the abnormality in lingual gyrus can induce visual network impairment in schizophrenia patients, which is one of

Table 5. *Correlations of changes in cerebral cortex thickness, gray matter volume and white matter integrity with cognitive impairment*

	Working memory		Verbal learning		Visual learning	
Factor	r	P	r	P	r	P
Cerebral cortex thickness						
Left isthmus of cingulate gyrus	0.381	<0.05	0.397	<0.05	0.385	<0.05
Left lingual gyrus	0.602	<0.05	0.597	<0.05	0.586	<0.05
Right fusiform gyrus	0.538	<0.05	0.588	<0.05	0.571	<0.05
Right inferior parietal lobule	0.451	<0.05	0.426	<0.05	0.472	<0.05
Right isthmus of cingulate gyrus	0.436	<0.05	0.448	<0.05	0.427	<0.05
Right lateral occipital lobe	0.584	<0.05	0.576	<0.05	0.580	<0.05
Right lingual gyrus	0.404	<0.05	0.438	<0.05	0.415	<0.05
Right opercular part of inferior frontal gyrus	0.394	<0.05	0.386	<0.05	0.377	<0.05
Right precentral gyrus	0.462	<0.05	0.457	<0.05	0.443	<0.05
Right precuneus	0.486	<0.05	0.452	<0.05	0.491	<0.05
Right inferior part of anterior cingulate gyrus	0.433	<0.05	0.495	<0.05	0.412	<0.05
Right superior parietal lobule	0.474	<0.05	0.459	<0.05	0.448	<0.05
Right superior temporal gyrus	0.429	<0.05	0.435	<0.05	0.458	<0.05
Right supramarginal gyrus	0.461	<0.05	0.475	<0.05	0.402	<0.05
Gray matter volume						
Left cuneus	0.412	<0.05	0.430	<0.05	0.428	<0.05
Left lingual gyrus	0.594	<0.05	0.593	<0.05	0.588	<0.05
Right fusiform gyrus	0.573	<0.05	0.572	<0.05	0.591	<0.05
Right lateral occipital lobe	0.566	<0.05	0.587	<0.05	0.596	<0.05
White matter integrity						
Left major forceps	0.398	<0.05	0.396	<0.05	0.420	<0.05
Left minor forceps	0.454	<0.05	0.423	<0.05	0.417	<0.05
Left inferior fronto-occipital fasciculus	0.384	<0.05	0.377	<0.05	0.402	<0.05
Left superior longitudinal fasciculus	0.410	<0.05	0.427	<0.05	0.375	<0.05
Left uncinate fasciculus	0.439	<0.05	0.418	<0.05	0.425	<0.05
Left anterior thalamic radiation	0.393	<0.05	0.385	<0.05	0.374	<0.05
Right corticospinal tract	0.378	<0.05	0.395	<0.05	0.400	<0.05
Right minor forceps	0.424	<0.05	0.403	<0.05	0.432	<0.05
Right inferior fronto-occipital fasciculus	0.436	<0.05	0.395	<0.05	0.389	<0.05
Right inferior longitudinal fasciculus	0.428	<0.05	0.410	<0.05	0.435	<0.05

the causes of hallucination in such patients (26). Various cognitive function tests have common points in spite of different emphases, and cognitive dysfunction at varying dimensions can reflect the impairment of corresponding functional areas in the brain, whereas exerting different cognitive functions may require the joint participation of multiple brain regions (27). The change in cortex thickness is probably implicated in the pathological mechanism of schizophrenia, and the decreased cortex thickness indirectly reflects the apoptosis of neurons or neuroglial cells at the corresponding part (28). The gray matter volume of brain region is composed of cortex thickness and cortex surface area (29), of which the change in cortex thickness can affect the gray matter volume. Information transmission and integration in human brain regions is accomplished by white matter fiber connectivity, and the abnormal diffusion of white matter and abnormal connection of partial nerve fibers can affect information integration in the brain of schizophrenia patients, resulting in overall decline in cognitive function (30).

In the present study, the results of MRI scanning showed that the patient group had a smaller cortex thickness at the isthmus of cingulate gyrus and lingual gyrus in the left brain, and a fusiform gyrus, inferior parietal lobule, isthmus of cingulate gyrus, lateral occipital lobe, lingual gyrus, opercular part of inferior frontal gyrus, precentral gyrus, precuneus, superior parietal lobule, superior temporal gyrus and supramarginal gyrus in the right brain, but greater cortex thickness at the inferior part of the right anterior cingulate gyrus than the control group, suggesting that the change in cerebral cortex thickness may be involved in the pathogenesis of schizophrenia. Furthermore, the gray matter volume at the left cuneus and lingual gyrus as well as right fusiform gyrus and lateral occipital lobe decreased, illustrating that there may be an apoptosis of neurons or neuroglial cells at these parts. The FA values for major forceps, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus in the left brain, and corticospinal tract, minor forceps, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus in the right brain were diminished. The MD values for the left major forceps, minor forceps, inferior fronto-occipital fasciculus and anterior thalamic radiation were increased. In addition, the RD values for the left major forceps, minor forceps, anterior thalamic radiation, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate fasciculus as well as right inferior fronto-occipital fasciculus and inferior longitudinal fasciculus were raised. All these results demonstrated that the changes in white matter integrity

may serve as the pathophysiologic basis of cognitive dysfunction in schizophrenia patients, and they are correlated with cognitive impairment. Marques et al. (31) found that patients with first-episode schizophrenia had increased mean FA values in some brain regions after 12 weeks of antipsychotic treatment. Wang et al. (32) found that the mean FA value of the frontal lobe reduced in patients with first-episode schizophrenia after 6 weeks of antipsychotic treatment. Additionally, Szeszko et al. (33) found that the mean FA value of some brain regions of patients with first-episode schizophrenia decreased after drug treatment. Since antipsychotic treatment was an important factor in white matter alterations over an 8-week period, its effect far outweighed that of disease progression.

Peng et al. (34) performed diffusion tensor imaging (DTI) and found that decreased white matter integrity was associated with the cognitive deficits in patients with drug-naive first-episode schizophrenia. Moreover, Zeng et al. (35) conducted DTI for drug-naive first episode schizophrenia patients and healthy controls, and repeated it after 8 weeks during which the patients were given antipsychotics. They measured the white matter integrity with FA, MD, AD and radial diffusivity. The FA values of schizophrenia patients were correlated with working memory, symptoms and visual learning. Nevertheless, the longitudinal changes in the FA values of the left superior longitudinal fasciculus were correlated with the changes of processing speed and positive symptoms.

In conclusion, in patients with first-episode schizophrenia, damage to the gray and white matter, including reduced cortex thickness and gray matter volume, as well as impaired white matter integrity, has occurred prior to drug treatment, being associated with cognitive impairment. Regardless, this study still has limitations. This is only a cross-sectional study with a small sample size, without follow-up. In the future, therefore, longitudinal studies with larger sample sizes are ongoing in our group to further explore the effects of cerebral cortex thickness, gray matter volume and white matter integrity on the cognitive impairment of schizophrenia patients.

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