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•ORIGINAL RESEARCH ARTICLE•

# An Association Study on the Cognitive Function and the Cerebral Grey Matter Volume of Patients with First-Episode Schizophrenia

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**Background:** The impairment of cognitive function is one of the core symptoms in schizophrenia, and the degree of recovery is closely related to whether patients are able to rejoin society successfully.

**Objective:** This study was to clarify the correlation between cognitive function and cerebral grey matter volume in schizophrenia.

**Methods:** The neuro-cognitive functions of thirty-seven patients with first-episode schizophrenia (the patient group) and thirty healthy controls (the control group) was evaluated with the Clock Drawing Test, Trail Marking Test, Digit Span Test, Auditory Verbal Learning Test, Wisconsin Card Sorting Test, Verbal Fluency Test, Semantic Similarity Test and Stroop Color-Word Test. The facial emotion cognitive task was employed to assess the facial emotion cognitive functions of thirty-two patients with first-episode schizophrenia (the patient group) and 29 healthy controls (the control group). The psychotic symptoms of patients with first-episode schizophrenia were evaluated using the Positive and Negative Syndrome Scale (PANSS). The brain imaging data of the patient group and control group were collected using the magnetic resonance imagine (MRI).

**Results:** The difference between the patient group and the control group in the results of Clock Drawing Test, Trail Marking Test, Digit Span Test, Auditory Verbal Learning Test, Wisconsin Card Sorting Test, Verbal Fluency Test, Semantic Similarity Test and Stroop Color-Word Test's reaction time were significant. These two groups' Slopes in the facial emotion cognitive task were also significantly different from each other. According to the comparison of cerebral grey matter volume between the patient group and the control group, it was found that the grey matter volume of the patient group increased in the left superior frontal gyrus, and decreased in the left occipital gyrus, lingual gyrus and upper cerebellum. Based on the analyses of neuro-cognitive data and brain imaging data of the patient group, the scores of the number of correct responses in Stroop Color-Word Test's Card C were negatively correlated with grey matter volumes of the left upper frontal gyrus, right upper frontal gyrus and middle frontal gyrus. The analyses on the facial emotion cognitive task and brain imaging data of the patient group showed that the slope data were positively correlated with grey matter volumes of the right superior temporal gyrus, middle temporal gyrus, left middle temporal gyrus, inferior temporal gyrus and fusiform gyrus.

**Conclusion:** There are general impairments in the neuro-cognitive functions and facial emotion cognitive functions of patients with first-episode schizophrenia, and the results suggest that brain areas with abnormal grey matter volumes are likely to be the brain structure and functional basis of the cognitive impairments.

**Key words:** first-episode schizophrenia; neuro-cognition; facial emotion cognition; grey matter volume

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## 1. Introduction

The clinical characteristics of schizophrenia are complicated and unique, with cognitive impairment being one of the core symptoms which generally persist.[1, 2] It mainly involves attention, executive function, working memory, abstract thinking, and integrating information, and the degree of its severity is closely related to patients' recovery in social functions. However, the mechanism of the cognitive impairment is not clear. Currently, the consensus opinion is that the brain structure of patients with schizophrenia is abnormal. There are many relevant imaging studies, but the results are vastly different from each other due to the influence of the course, age and medications on the brain structure.[21,23,25,29] Given that cognitive impairment exists at the early stage of the disease as its predisposing factor, studying the imaging data of schizophrenia at its early stage can be helpful to explore the biological basis of this disease at its early stage, which will clarify whether cognitive impairment is caused by the disease or causes the disease. We recruited drug naïve inpatients with first-episode schizophrenia as subjects, and evaluated their neuro-cognition and social cognition. In the meantime, voxel based morphometry (VBM) was employed to explore the volume changes in brain grey matter. We hope to clarify the relation between the brain structure of patients with cognitive impairments and this disease, thereby providing scientific proof for further discussion on the possible pathological mechanism and clinical treatment for schizophrenia.

## 2. Subjects and Methods

### 2.1 Subjects

The patient group: inpatients who were admitted into the department of psychiatry at the Nanjing Brain Hospital from February 2014 to May 2015. Inclusion criteria: ① subjects who met the diagnostic criteria for schizophrenia according to DSM-4 and diagnosed with SCID interviews; ② subjects having a first episode, with the duration of illness less than two years, and with no history of anti-psychotic medication or physical treatments; ③ Han ethnicity, right-handed; ④ aged between 18 and 44; ⑤ subjects whose education levels were equal to or above 9 years, and who were able to understand and read Chinese; ⑥ subjects who understood the contents of this study, participated voluntarily and signed the written consent forms. Exclusion criteria: ① subjects with a history of nervous system diseases and major medical conditions; ② subjects with mental retardation, dementia and other intellectual disabilities; ③ subjects with a history of head injuries, epilepsy episodes and color blindness; ④ females who were pregnant or breast feeding; ⑤ subjects with current or past substance addictions; ⑥ subjects who were not fit to receive fMRI scans.

The control group: healthy controls who matched the patient group in gender, age and education level were recruited. Inclusion criteria: ③ Han ethnicity, right-handed; ④ aged between 18 and 44; ⑤ subjects whose education levels were equal to or above 9 years, and who were able to understand and read Chinese; ⑥ subjects who understood the contents of this study, participated voluntarily and signed the written consent forms. Subjects who were enrolled had no history or family history of mental illness, and experienced no major mental trauma. The exclusion criteria for the control group was the same as those for the patient group.

Among 1315 inpatient cases who were admitted into the psychiatric department from February 2014 to May 2015, 1272 of them were excluded based on the diagnostic criteria and inclusion/exclusion criteria mentioned above. A total of 43 patients were enrolled. Due to 6 cases' incomplete neuro-cognitive data collection, 37 patient cases (25 males and 12 females) and 30 controls (17 males and 13 females) were enrolled in the neuro-cognitive study. The mean (SD) age of the patient group was 23.49 (4.81), and the mean (SD) education level was 12.38 (2.66) years with a range from 9 to 17 years. The mean (SD) age of the control group was 22.10 (3.53), and the mean (SD) education level was 13.90 (2.78) years with a range from 9 to 17 years. During the facial emotion cognitive task, due to 11 cases' incomplete facial emotion cognition data collection and drop-outs, 32 patient cases and 29 controls were included in the facial emotion cognitive task analysis. See Table 1 for detailed information on the demographic data and clinical characteristics of the patient group and the control group. There were no significant differences in age, gender and education level between the two groups. The present study was approved by the medical ethics committee of Nanjing Brain Hospital affiliated to Nanjing Medical University.

### 2.2 Methods

Clinical evaluation: (1) evaluation of psychotic symptoms: both diagnoses and evaluations with scales were conducted by two resident doctors with more than 10 years of experience. On the first day of enrollment, Positive and Negative Syndrome Scale (PANSS) [5] (with good reliability and validity [3, 4]) was employed to evaluate clinical symptoms of patients. (2) Neuro-cognition evaluation: on the second day of enrollment, the Clock Drawing Test, Trail Marking Test, Digit Span Test, Auditory Verbal Learning Test, Wisconsin Card Sorting Test, Verbal Fluency Test, Semantic Similarity Test and Stroop Color-Word Test were conducted, and the scores were calculated. (3) The facial emotion recognition evaluation: on either the first day or the second day of enrollment, the facial emotion cognition test was conducted with the facial emotion recognition test, which was designed by Jia Huang and colleagues.[6] The pictures of this facial emotion category recognition

**Table 1. Comparison of demographic data, clinical characteristics and facial emotion cognition data between patients with first-episode schizophrenia and controls**

| | Patients with first-episode schizophrenia (n=32) | control group (n=29) | *p* | Statistical values |
|---|---|---|---|---|
| Age (year-old) | 22.7 (4.0) | 22.1 (3.6) | *p*=0.550 | t=-0.72 |
| Gender (male/female) | 22/10 | 17/12 | *p*=0.411 | $x^2$=0.68 |
| Education level (years) | 13.1 (2.4) | 13.8 (2.8) | p=0.263 | t=1.20 |
| Duration of illness (months) | 10.3 (8.9) | | | |
| Total score of positive symptoms (PANSS) | 26.2 (4.6) | | | |
| Total score of negative symptoms (PANSS) | 25.6 (7.4) | | | |
| Total score of general psychosis (PANSS) | 52.4 (10.0) | | | |
| Total score (PANSS) | 104.3 (17.8) | | | |
| **Facial emotion cognition task** | | | | |
| Shift point | 3.1 (0.4) | 2.9 (0.4) | *p*=0.056 | t=-1.95 |
| Slope | 0.2 (0.04) | 0.1 (0.02) | *p*=0.045 [a] | t=-2.05 |

Note: [a] $p<0.05$; mean (SD) ; df=59.

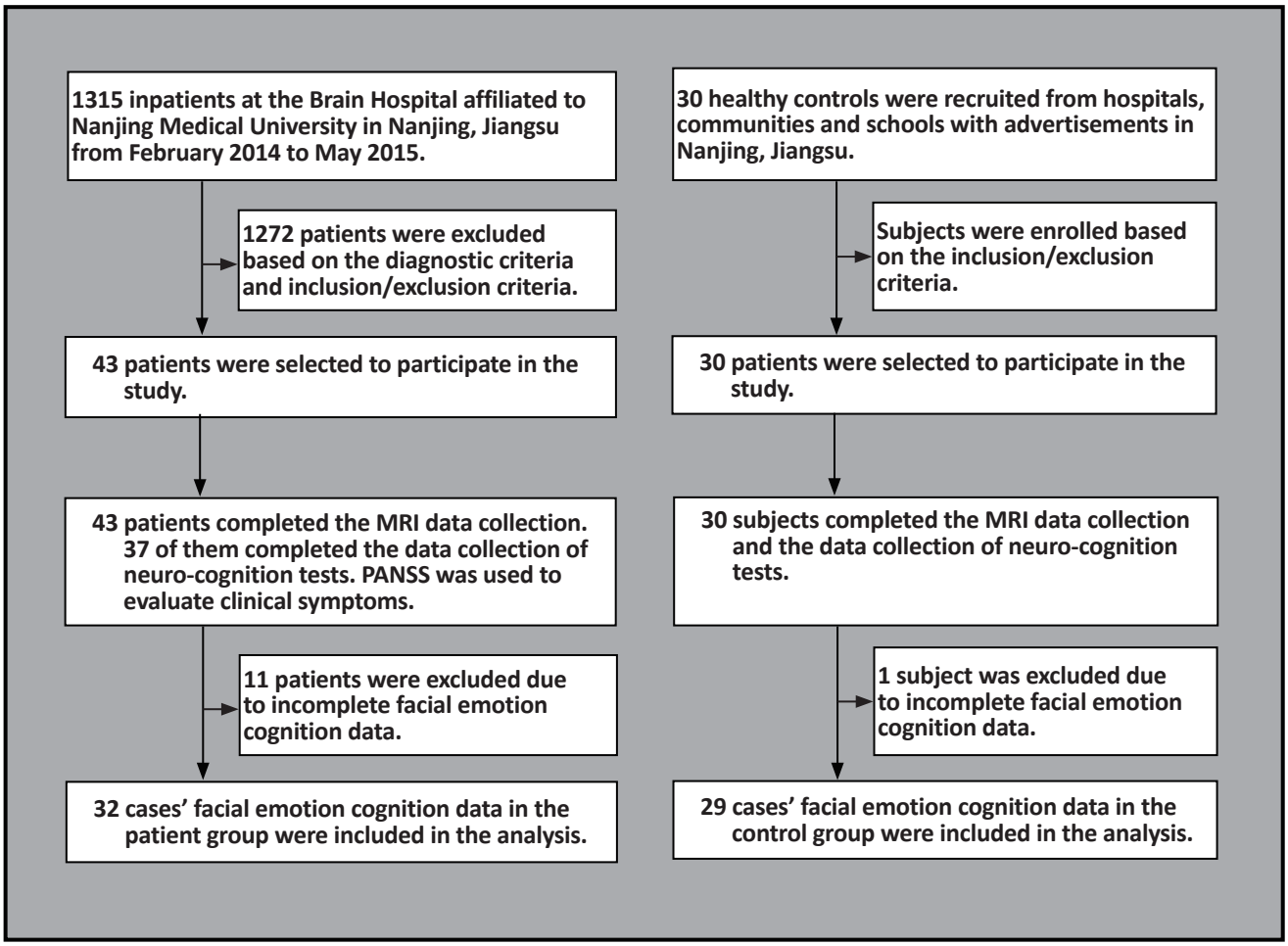
paradigm consist of 5 levels of facial emotions: 100% pleasure and 0% anger indicate level 1; 75% pleasure and 25% anger indicate level 2; 50% pleasure and 50% anger indicate level 3; 25% pleasure and 75% anger indicate level 4; 0% pleasure and 100% anger indicate level 5 (See Figure 1). The task requires subjects to recognize whether facial emotion on the screen is pleasure or anger and react to it as soon as possible. Pictures were displayed in a random order. The number of correct responses, the rate of correctness and the reaction time for each emotion were calculated. For the data analysis of facial emotion cognition, we employed the method used by Pollak and Krislter [7] in one study. This method is to get each subject's classification shift point and shift slope of facial emotion recognition by analyzing each subject's facial emotion cognition data with a logical function curve fitting equation, and to compare the difference of this function between the two groups. In order to acquire more reliable results, borderline classification values were evaluated by calculating their corresponding *p*=0.05 signal values. The classification shift point indicated one point on the logical curve, which represents the point where subjects shift from one emotion to another emotion during facial emotion recognition (i.e., the separation point of recognizing pleasure and anger). The shift slope indicates the suddenness of emotion transition. The higher the shift slope's value is, the more sudden the transition from pleasure to anger; while the lower the shift slope's value is, the more vague the transition from pleasure to anger. The fitting equation is described as the following:

$$P=c + (d - c) / (1 + e - (x - \alpha) / b)$$

P represents the probability of recognition; x represents the intensity of the signal; e represents the exponential function, which estimates four parameters; α represents the median of the function; 1/b represents the slope; c and d represent upper and lower asymptote respectively.

(4) Magnetic resonance data collection and analysis: on the third day of patients with clear diagnoses of schizophrenia being admitted, the magnetic resonance data collection was completed. The collection of imaging data was conducted in the magnetic resonance chamber of the radiology department of Nanjing Brain Hospital affiliated to Nanjing Medical University by an experienced professional technician from the radiology department. All subjects were scanned with a SIEMENS 3T VERO (SIEMENS, Germany), and the signals were received by a standard head coil. During the scan, subjects lie on their backs. They were required to fixate their heads with supporting foam pads, and to lower the noise with rubber ear buds. They were asked to be still, conscious and relaxed with eyes closed, and not to think about anything. First, the T1 structure images were collected, and subjects with no abnormal results continued to enter next scanning sequence. The three-dimensional structure MRI image uses a planar imaging sequence of gradient echoes. The scanning parameters are the following: pulse repetition time = 2530ms; echo time = 2.3ms; turn angle was 7 degrees; matrix = 256*256; thickness was 1mm; interval was 0.5mm; scanning layers = 192; scanning time = 5min53s. Structural MRI data were analyzed and processed with Matlab and SPM8. The sub-tool VBM8 in SPM was employed in the preprocessing. Images of grey matter

**Figure 1. Flowchart of the study**




were obtained by removing the first 10 time points, correction of time layer, head motion correction, space standardization, segmentation, tuning, and data smoothing with half height and full width 6mm, which represented the grey matter volume. The comparison and analyses of brain grey matter were conducted on the images after smoothing. A double sample t-test was conducted to compare the volume of grey matter between the two groups with the functional section in REST. The correlation analysis based on voxels was used to explore the correlation between the imaging data and the cognitive test scores of the patient group, with age, gender and education level as covariates. The potential confounding effect was controlled, and Alphasim multiple correction ($p$<0.05) was employed.

### 2.3 Statistical analysis

The demographic data, facial emotion cognitive tests' data and the neuro-cognition data of the patient group and the control group were analyzed with SPSS 19.0. The categorical data was analyzed with Pearson chi-square tests. The independent sample t-test was used to analyze continuous data which fit the normal distribution. All values were indicated by means (SD), and all statistical tests were conducted as two-tailed tests. The value of $p$ being smaller than 0.05 indicates statistical significance.

## 3. Results

### 3.1 The analyses on clinical characteristics and cognitive functions

Neuro-cognitive tests comparisons: the mean age of 37 subjects in the patient group was 23.49 (4.81), and the mean education level was 12.38 (2.66) years with a range from 9 to 17 years. The mean age of 30 subjects in the control group was 22.10 (3.53), and the mean education level was 13.90 (2.78) years with a range from 9 to 17 years. There were no significant differences in age ($t$=-1.32, $p$=0.192), gender ($x^2$=0.84, $p$=0.359) and education level ($t$=2.28, $p$=0.260) between two groups. The neuro-cognitive tests' results of these two groups

satisfied the normal distribution. There were significant differences between two groups in Trail Marking Test, the forward Digit Span Test, the backward Digit Span Test, the total score of Digit Span Test, Auditory Verbal Learning Test, Wisconsin Card Sorting Test's number of responses, number of sorting, number of correct responses and the rate of correct responses, Verbal Fluency Test, Semantic Similarity Test and the reaction

**Table 2. Comparison of neuro-cognition test scores between patients with first-episode schizophrenia and controls**

| Variables (mean(SD)) | Patients with first-episode schizophrenia (n=37) | Control group (n=30) | *p* | Statistical values |
|---|---|---|---|---|
| Age (year-old) | 23.49(4.81) | 22.10(3.53) | 0.192 | t=-1.32 |
| Gender (male/female) | 25/12 | 17/13 | 0.359 | $x^2$=0.84 |
| Education level (year) | 12.38(2.66) | 13.90(2.78) | 0.260 | t=2.28 |
| Duration of illness (month) | 10.57(9.18) | | | |
| Clock Drawing Test | 8.73(1.41) | 9.33(0.88) | 0.045 [a] | t=2.04 |
| **Trail Marking Test** | | | | |
| Trail A | 58.05(19.12) | 38.80(8.86) | <0.001 [a] | t=-5.45 |
| Trail B | 119.38(29.25) | 75.33(14.99) | <0.001 [a] | t=-7.96 |
| Digit Span Test | | | | |
| Forward | 8.05(1.08) | 8.87(1.48) | 0.012 [a] | t=2.60 |
| Backward | 5.30(1.22) | 6.30(1.82) | 0.009 [a] | t=2.69 |
| Total score | 13.35(1.86) | 15.17(2.79) | 0.002 [a] | t=3.18 |
| **Auditory Verbal Learning Test** | | | | |
| First trial | 3.27(1.43) | 5.27(1.60) | <0.001 [a] | t=5.40 |
| Second trial | 5.22(1.78) | 7.97(2.04) | <0.001 [a] | t=5.89 |
| Third trial | 6.22(1.80) | 9.47(1.81) | <0.001 [a] | t=7.33 |
| Forth trial | 4.43(2.46) | 8.33(2.15) | <0.001 [a] | t=6.83 |
| **Wisconsin Card Sorting Test** | | | | |
| Number of responses | 119.95(14.86) | 105.13(21.08) | 0.001 [a] | t=-3.37 |
| Number of sorting | 3.19(2.21) | 5.30(1.34) | <0.001 [a] | t=4.817 |
| Number of correct responses | 67.84(12.64) | 75.30(11.64) | 0.015 [a] | t=2.49 |
| Correct rate (%) | 57.85(14.55) | 73.31(11.95) | <0.001 [a] | t=4.68 |
| Verbal Fluency Test | 19.62(5.25) | 27.07(5.84) | <0.001 [a] | t=5.49 |
| Semantic Similarity Test | 16.32(4.58) | 20.93(3.36) | <0.001 [a] | t=4.59 |
| **Stroop Color-Word Test** | | | | |
| Card A reaction time | 24.54(6.00) | 18.83（3.11） | <0.001 [a] | t=-4.72 |
| Card A number of correct answers | 49.73(0.65) | 49.87（0.51） | 0.350 | t=0.94 |
| Card B reaction time | 46.86(18.41) | 30.53（6.65） | <0.001 [a] | t=-4.62 |
| Card B number of correct answers | 48.97(3.06) | 49.87（0.43） | 0.118 | t=1.59 |
| Card C reaction time | 88.70(37.07) | 55.70（11.55） | <0.001 [a] | t=-4.69 |
| Card C number of correct answers | 48.86(1.78) | 49.93（1.80） | 0.018 [a] | t=2.43 |

Note: [a] $p<0.05$; mean (SD); df=59.

time of Stroop Color-Word Test. The scores of the patient group were higher than those of the control group in Trail Marking Test, the number of responses of Wisconsin Carding Sorting Test and the reaction time of Stroop Color-Word Test. In contrast, as for the rest of tests with significant results, the scores of the patient group were lower than those of the control group (see Table 2).

Facial emotion cognitive task's comparisons: due to the drop-outs, there were 32 patients (22 males and 10 females) who participated in the facial emotion cognitive task. Their mean age was 22.7 (4.0), and their mean education level was 13.1 (2.4) years with a range from 9 to 17 years. There were 29 subjects in the control group (17 males and 12 females). Their mean age was 22.1 (3.6), and their mean education level was 13.8 (2.8) years with a range from 9 to 17 years. There were no significant differences between the two groups in age ($t$=-0.72, $p$=0.550), gender ($x^2$=0.68, $p$=0.411) and education level ($t$=1.20, $p$=0.263). Each subject's classification shift point and shift slope were calculated by establishing the fitting equation. The results showed that the mean score of the classification shift point of the facial emotion cognitive task in the patient group was 3.1 (0.4), and that in the control group was 2.9 (0.4); there was no significant difference between the two groups ($t$=-1.95, $p$=0.056). By contrast, the mean score of the facial emotion cognitive task's slope in the patient group was 0.2 (0.04), and that in the control group was 0.1 (0.02); the difference between two groups was significant ($t$=-2.05, $p$=0.045).

The PANSS scores of the patient group: the mean of the total scores of the positive symptom scale in the patient group was 26.2 (4.6), and that of the negative symptom scale was 25.6 (7.4). The meanof the total scores of the general psychosis scale was 52.4 (10.0). The mean of the PANSS total scores was 104.3 (17.8) (see Table 1).

### 3.2 The analyses on imaging data

After variance analyses (with Alphasim correction) on the whole brain's grey matter volume with two groups' imaging data, it was found that compared to the control group, the grey matter volume of the patient group increased in the left superior frontal gyrus ($t$=4.41), and decreased in the left occipital gyrus ($t$=-4.27), lingual gyrus ($t$=-4.55) and upper cerebellum ($t$=-3.54) (see Table 3 and Figure 2).

**Table 3. Brain areas with differences in grey matter volumes between patients with first-episode schizophrenia and controls**

| Brain areas | Voxel size | MINI coordinates | | | *t* |
|---|---|---|---|---|---|
| | | x | y | z | |
| Brain areas where grey matter volumes increase | | | | | |
| Left superior frontal gyrus | 102 | -18 | 70 | 9 | 4.41 |
| Brain areas where grey matter volumes decrease | | | | | |
| Left lingual gyrus | 79 | -17 | -88 | -15 | -4.55 |
| Occipital gyrus of left occipital lobe | 43 | -18 | -92 | -9 | -4.27 |
| Upper part of left cerebellar | 4 | -10 | -80 | -154.41 | -3.54 |

Note: $p$=0.001; with Alphasim correction.

**Figure 2. Facial emotion recognition paradigm**

**Note: from left to right: Level 1, Level 2, Level 3, Level 4, Level 5**

### 3.3 Correlation analyses on cognition data

Neuro-cognition and grey matter volume: correlation analyses based on voxels were conducted on the imaging data and scores of neuro-cognition tests in the patient group with age, gender and education level as covariates. It was found that the number of correct responses of Card C in the Stroop Color-Word Test was negatively correlated with the grey matter volumes of the upper lateral frontal gyrus ($r$=-0.38), the right dorsolateral upper frontal gyrus ($r$=-0.45), the upper left medial frontal gyrus ($r$=-0.50), the right medial frontal gyrus ($r$=-0.62), and the right middle frontal gyrus ($r$=-0.62), and the correlation was statistically significant ($p$=0.050, with Alphasim correction) (see Table 4 and Figure 3). There were no significant correlations found between the remaining neuro-cognition tests' scores and imaging data on cerebral grey matter volumes.

Emotion cognition and grey matter volume: correlation analyses based on voxels were conducted on the shift slopes of the facial emotion cognition test in the patient group with age, gender and education level as covariates. It was found that the slopes were positively correlated with the right temporal gyrus ($r$=0.46), right middle temporal gyrus ($r$=0.60), left middle temporal gyrus (r=0.75), left inferior temporal gyrus ($r$=0.43) and left fusiform gyrus ($r$=0.48), and the correlation was statistically significant (with Alphasim correction) (see Table 5 and Figure 4). However, based on the results of correlation analyses, there was no significant correlation found between the shift points and imaging data.

**Table 4. Brain areas negatively correlated with the number of correct responses for Card C in Stroop Color-Word Test in patients with first-episode schizophrenia**

| Brain areas | Voxel size | MINI coordinates | | | r values |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right dorsolateral upper frontal gyrus | 232 | 24 | 67 | 9 | -0.45 |
| Left dorsolateral upper frontal gyrus | 181 | -24 | 64 | 12 | -0.38 |
| Right medial upper frontal gyrus | 407 | 3 | 45 | 51 | -0.62 |
| Left medial upper frontal gyrus | 293 | -1 | 35 | 48 | -0.50 |
| Right middle frontal gyrus | 165 | 29 | 49 | 30 | -0.54 |

Note: $p$=0.050; with Alphasim correction.

**Figure 3. The brain areas with different brain grey matter volumes between patients with first-episode schizophrenia and the control group**

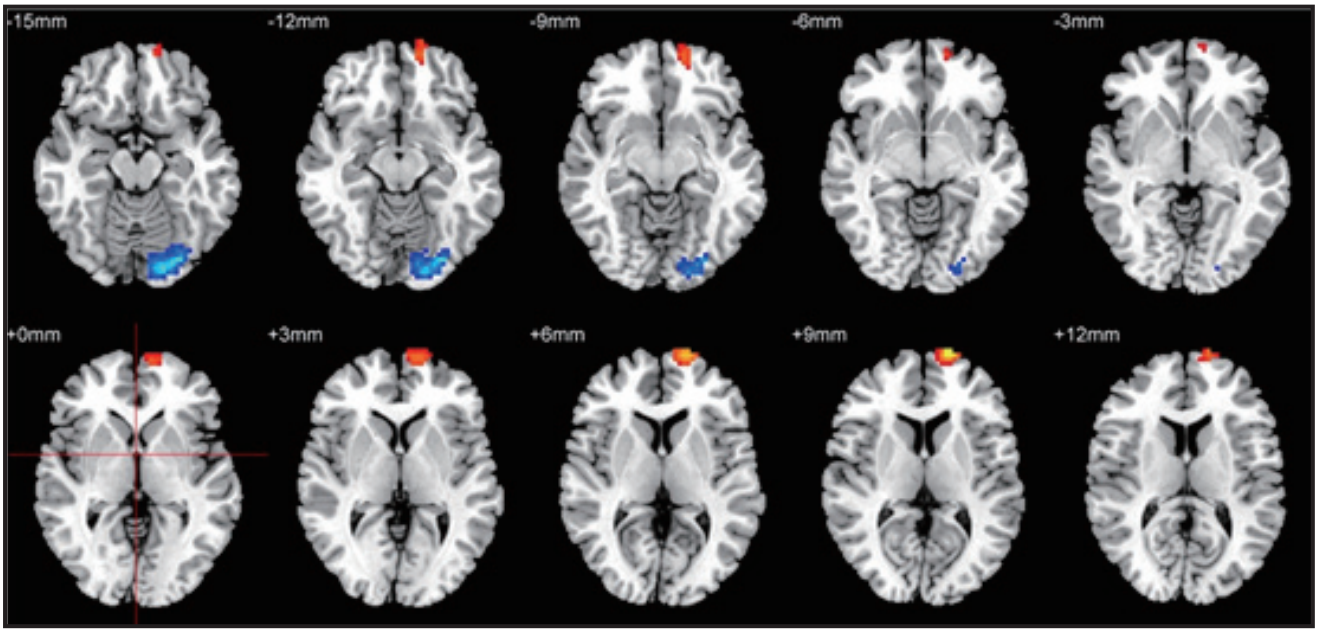
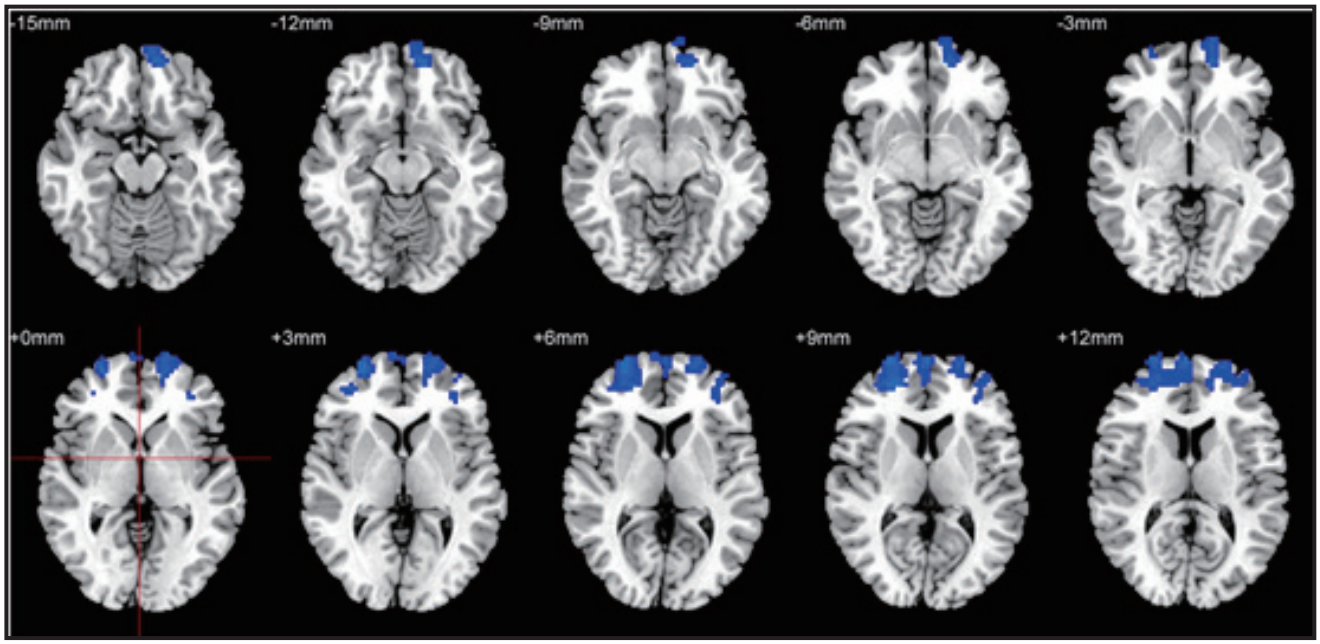


**Table 5. Brain areas positively correlated with the scores of facial emotion cognition tests in Stroop Color-Word Test in patients with first-episode schizophrenia**

| Brain areas | Voxel size | MINI coordinates | | | r values |
|---|---|---|---|---|---|
| | | x | y | z | |
| Right superior temporal gyrus | 274 | 49 | -20 | 0 | 0.46 |
| Right middle temporal gyrus | 138 | 30 | 12 | -36 | 0.60 |
| Left middle temporal gyrus | 505 | -48 | -63 | 3 | 0.75 |
| Left temporal gyrus | 309 | -59 | -61 | -6 | 0.43 |
| Left fusiform gyrus | 132 | -25 | -42 | -12 | 0.48 |

Note: $p$=0.01; with Alphasim correction.

**Figure 4. Brain areas negatively correlated with the number of correct responses for Card C in the Stroop Color-Word Test in patients with first-episode schizophrenia**



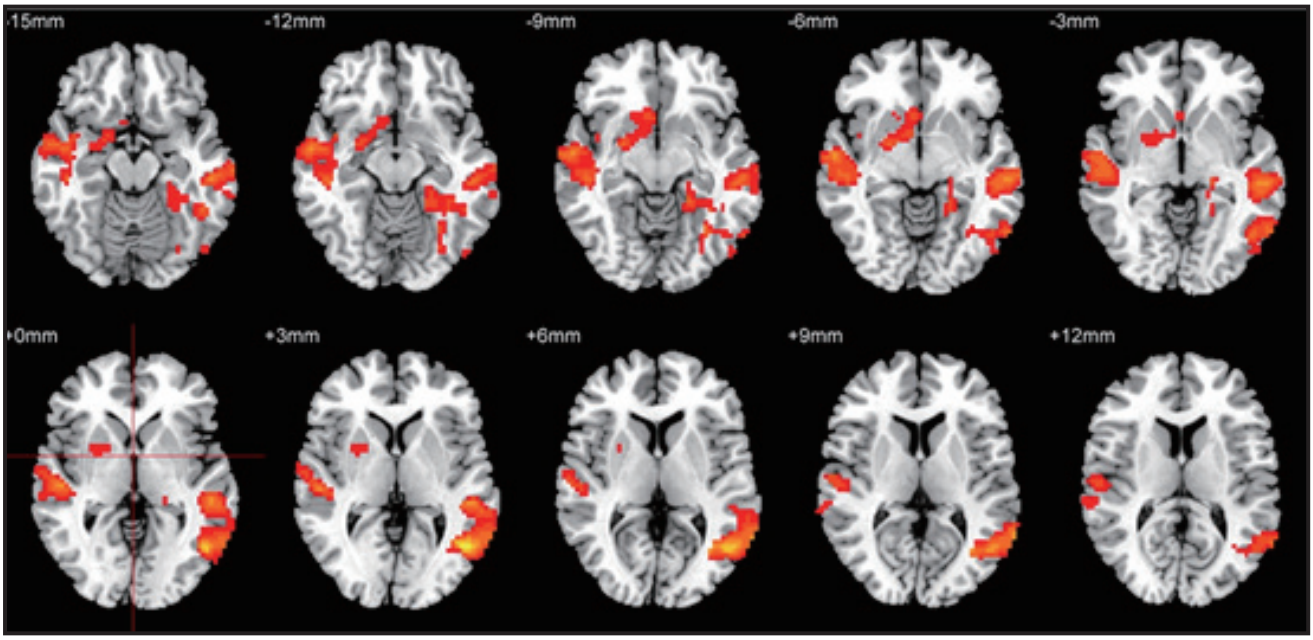

## 4. Discussion

### 4.1 Main findings

The present study recruited drug-naïve inpatients with first-episode schizophrenia whose age range was from 18 to 44, therefore the influence of long term course and medication on brain structure and the influence of age on nervous system development and degeneration were avoided. It was found in the results that in neuro-cognition tests and facial emotion cognition tests, the scores of the patient group were lower than those of the control group, which suggests that there are general impairments in neuro-cognitive functions and facial emotion cognitive functions of patients with first-episode schizophrenia. Based on the results of the comparative analyses on MRI data of patients with first-episode schizophrenia and the control group and the correlation analyses on MRI data and patients' cognition tests' scores, it was found that the brain areas with abnormal grey matter volumes were mainly located in the frontal, occipital, and upper parts of the cerebellum. These brain areas are likely to be the brain structure and functional foundation for cognitive function impairments.

As opposed to previous studies which suggest that grey matter volume in the frontal lobe of patients with chronic schizophrenia decreases,[19] it has been found in our study that the grey matter volume in the frontal lobe of patients with first-episode schizophrenia increases.

**Figure 5. The brain areas positively correlated with the scores of facial emotion cognition tests in Stroop Color-Word Test in patients with first-episode schizophrenia**




One possible explanation for this phenomenon is that drug-naïve patients with first-episode schizophrenia are still in the early stage of their disease, and there is compensatory increase in the volume of frontal grey matter. Furthermore, other correlation studies also suggest that the change of frontal grey matter volume is correlated to the course change of schizophrenia to some extent.[20] In the present study, we did not find any change of the temporal lobe volume. Previous research has suggested that the brain areas whose volumes decrease in patients with schizophrenia include the temporal lobe, and it is correlated with genetic factors; there are vast differences in structural changes in the temporal lobe between patients with different onset ages.[21] The inconsistency between the present study's results and previous studies' could be attributed to the fact that subjects with different onset ages were not classified based on their family histories when they were assessed in the present study. In addition, a meta-analysis [22] points out that the changes of temporal lobe grey matter is correlated to the severity of psychotic symptoms; as the course of disease extends and the symptoms aggravate, significant abnormalities of the temporal lobe are more likely to appear. Moreover, compared to patients with chronic schizophrenia, the changes of brain grey matter in patients with first-episode schizophrenia are limited; the impairments in grey matter being affected by the course of disease are likely to be the reason why there was no significant differences based on the imaging data analyses.[23, 24]

The present study suggests that the grey matter volume of cerebellar areas decreases, and this is in line with the results of previous meta-analyses on grey matter volume.[25] The cerebellar areas are related to not only physical activities but also perception and thinking, so its functional impairments could represent one basic aspect of the cognitive impairments in psychotic symptoms; it is likely to be one of the reasons for the diversity of cognitive impairments and symptoms observed in patients with schizophrenia.[26] At present, neuro-anatomy studies have confirmed that the cerebellum connects with the multiple areas of the cerebral cortex through the cortex-cerebellum-thalamus-cortex loop; other studies have also confirmed that the cerebellum participates in regulating individuals' cognition and emotions by forming a feedforward loop through the thalamus and a feedback loop through the pons.[19] That the grey matter volume of the upper part of cerebellum in patients with first-episode schizophrenia decreases suggests that patients' cognition and emotional functions have already been impaired at the early stage of the disease, which leads to facial emotion cognitive impairments. The main functions of the occipital lobe are processing visual signals, language and movement perception and abstract thinking; the abnormality in this area suggests that the cognitive functions, such as memory and abstract thinking, in patients with schizophrenia are impaired. Our research results indicate that in accordance with previous studies, the grey matter volume of this area decreases,

which suggests that there are structural and functional impairments of the left occipital cortex area in patients with schizophrenia.[27]

Studies on social cognition mainly include three aspects: emotion cognition, the theory of mind and attributional bias. Emotion cognition is referred to as the ability to recognize others' emotions through their facial expressions and change in tone. Furthermore, previous studies[8,9] have indicated that emotion cognitive impairments appear before the onset of the disease, which suggests that it is more likely closer to a biological cause of schizophrenia. The facial emotion recognition function in patients with schizophrenia is impaired so that they have difficulty in recognizing others' intentions precisely, thereby misunderstanding them, which leads to social cognitive impairments. Therefore, processing and perceiving facial emotions are critical factors of social functions in patients with schizophrenia, and they are also a part of the core social cognitive abilities.[15] The present study analyzed the social cognition of patients with schizophrenia through facial emotion cognition tasks, and the results have shown that there are no significant differences in the shift point between the patient group and the control group. This suggests that the cognitive ability of recognizing pleasure and anger facial emotions in patients with first-episode schizophrenia is not impaired significantly; this means that their ability to differentiate positive and negative emotions does not degenerate, and they are completely capable of recognizing pleasure and anger facial emotions when they face them. However, after we categorized the results according to the emotion gradient, it was found that the patients tended to classify positive emotions (i.e., pleasure) as negative ones (i.e., anger). This suggests that patients are more likely to develop misunderstandings about others and society in general because they classify others' positive behavior as negative, thereby developing persecutory delusions and other psychotic symptoms. This hypothesis will be tested in future studies with a larger sample size. The shift slope of the patient group is higher than that of the control group, and the statistically significant difference suggests that the shift of recognizing facial emotions is more sudden in the patient group. When the pleasure emotion changes into neutral and anger emotions, the shift of emotion recognition in the patient group is more sudden than that in the control group. In other words, patients' ability to recognize vague facial emotions precisely is impaired. When patients face negative emotions, more attention is put into avoiding this kind of stimuli, and they are more willing to classify those as positive ones; so when negative stimuli reach a certain point and patients cannot avoid them anymore, they finally recognize the negative emotions which leads to a very sudden shift in the continuous emotion recognition process. The abnormality of precise facial emotion recognition is an important aspect of social cognition impairment. When patients are unable to recognize the facial emotions they are facing correctly, their social cognitive functions and adaptability begin to degenerate. As previous studies have pointed out, patients with schizophrenia avoid noticing the stimuli of negative emotions.[17] This suggests that in daily communications, patients' strain functions in the face of negative emotion declines, which predicts the decline of their social adaptability.[18] According to the results of correlation analyses conducted on patients' facial emotion cognition task data and brain imaging data, it has been found that the brain areas with abnormal grey matter which are positively correlated with the shift slope are the right superior temporal gyrus, middle temporal gyrus, left middle temporal gyrus, inferior temporal gyrus and fusiform gyrus. Multiple brain areas being impaired suggests that brain areas collaborate to recognize, code and process facial emotion cognition; the abnormal grey matter volume in the temporal lobe especially suggests that the temporal lobe is the important abnormal structural basis for emotion cognitive impairments. Studies have pointed out that the fusiform gyrus is involved in processing and coding faces,[29] which suggests that the changes of grey matter of the temporal lobe and fusiform gyrus in patients with first-episode schizophrenia are related to the decline of their facial emotion recognition ability. The more obvious the changes are, the more severe the impairments are. In addition, previous studies have also pointed out that the change of the frontal cortex system is likely to be one of the important factors which cause patients' difficulty in processing facial expressions.[17] Moreover, with the frontal lobe deactivated by repetitive transcranial magnetic stimulations, the ability to recognize negative emotions, such as anger, declines drastically.[30] However, the results of the correlation analyses on facial emotion cognition tests in the present study do not show the correlation between the grey matter volume of the frontal lobe and this ability, which is different from the theory that the frontal cortex system is involved in the facial emotion cognition process suggested by previous studies. Compared to the control group, the grey matter volume of the left frontal gyrus in the patient group increased, which is considered to be related to the compensatory function when emotion cognition is impaired; therefore, imaging data did not show any significant results. Furthermore, previous studies [15] have pointed out that the structural change of the medial frontal gyrus in schizophrenia is correlated with the course of disease. It is possible that the limited grey matter volume decrease of the frontal lobe in patients with first-episode schizophrenia is responsible for the lack of significant results of imaging data.

It is possible that neuro-cognition is one of the internal presentations in schizophrenia, and one study [10] finds that there is no significant aggravation of the relatively stable cognitive functions in patients with schizophrenia in a 10-year-long follow up. The present study employed neuro-cognition tests, including the Clock Drawing Test, Trail Marking Test, Digit Span

Test, Auditory Verbal Learning Test, Wisconsin Card Sorting Test, Verbal Fluency Test, Semantic Similarity Test and Stroop Color-Word Test's reaction time, and they assessed the cognitive function impairments in schizophrenia on a more comprehensive level. The results indicate that the neuro-cognitive functions of patients with first-episode schizophrenia, including language, memory, attention, abstract thinking, expressing and using verbal memory, and calculation, suffer from degenerations to different extents, which is in line with previous studies.[11] Compared to the control group, the time of trail marking in the patient group is longer, and their scores in the Verbal Fluency Test are significantly lower. This suggests that patients with schizophrenia suffer from difficulties in integrating information, the decline of information processing speed in the brain, and the degeneration of ability to process information with knowledge at the early stage, thereby causing impairments in their problem solving ability and social function, which is also in line with previous studies.[12] The patient group's reaction time in the Stroop Color-Word Test is significantly higher than that of the control group, while there is no significant difference in the number of correct responses between the two groups; this suggests that patients' perception shift and selective attention abilities are not impaired significantly, and they just need a longer time to process and react. This indicates that the brain function impairments mainly involve the decline of executive and processing speed in the brain and the extension of the time spent on transferring information inside the brain, thereby suggesting impaired brain functional connection in patients with schizophrenia indirectly.[13] The differences found in the Digit Span Test, Auditory Verbal Learning Test, Semantic Similarity Test and Wisconsin Card Sorting Test all suggest generally impaired neuro-cognitive function in patients with first-episode schizophrenia, including working, learning memory and executive functions, which is in line with previous studies.[14] This indicates that the social function, problem solving ability and the ability to learn new skills in patients with schizophrenia are impaired. According to the results of the correlation analyses on patients' neuro-cognition test data and their imaging data, it was found that Color-Word Test is correlated with the frontal lobe. Stroop Color-Word Test mainly reflects the function of the left frontal lobe, and the functions of the frontal lobe include the judgement and analysis of memory information. In the correlation analysis on the imaging data and the Stroop Color-Word Test data, it was found that the brain areas which are negatively correlated with the number of correct responses in Card C are mainly clustered in the frontal gyrus of the bilateral frontal lobe and the frontal middle gyrus of the right frontal lobe; and according to the results of comparisons on grey matter volumes between the two groups, it was found that the grey matter volume of the patient group's left frontal gyrus increases. This suggests that the change of the frontal lobe is related to cognitive impairments and it is in accordance with previous studies. The analyses on the rest of neuro-cognition tests' data and imaging data show a general abnormality in the whole brain without any significant specific related brain area. The possible reason for this phenomenon is that completing cognition tests usually requires combined effects of multiple sensory functions instead of a single function of one brain area, which means that it requires the combined participation of the whole brain. Therefore, a general grey matter abnormality of the whole brain in patients with first-episode schizophrenia could result in the abnormal connection of nerve loops or brain functions, which is also the neuropathological basis of schizophrenia.[28]

### 4.2 Limitations

The present study has a few limitations. The Alphasim correction employed by the present study is a correction method based on Gaussian Random Fields Theory, and its correction is relatively loose. Therefore, the threshold was set at a stricter value to reduce false positive results as much as possible. Future studies need to be more rigorous on the methodology. In addition, the sample size of the present study is relatively small, and the patients who were enrolled were all capable of cooperating with the cognitive tests and MRI scanning. Patients who were too uncooperative or impulsive to participate in the cognitive and MRI data collection were not included, so these patients' data were missing in the analyses. As for the exploration of social cognition, assessing only the facial emotion cognition system is relatively monotonous. In addition, the continuous facial emotions tested were pleasure and anger, which are far fewer general emotion types compared to those more complicated emotions in reality. Future studies need to recruit a larger sample size, assess cognitive functions on a more comprehensive level by exploring cognitive impairments on multiple dimensions, and measure the change of the brain structure and functions of patients with schizophrenia by employing multiple imaging models to benefit manifesting the mechanism of cognitive function abnormalities in patients with schizophrenia, in order to provide treatments and intervention at an early stage and help patients return to society with a better state of mind.

### 4.3 Implications

The present study focuses on the cognitive symptoms of patients with first-episode schizophrenia, and the recovery of cognitive functions is closely correlated with patients' prognosis. The present study examined patients' attention, executive function, working memory, abstract thinking, information integration and facial emotion recognition with multiple neuro-cognitive tests and facial emotion cognitive tests combined with imaging data of the changes in grey matter volume. Therefore, it provides scientific evidence for discussing the possible neuropathological mechanism for cognitive impairments in schizophrenia.

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**Conflict of interest statement**

Authors declare no conflict of interest related to this manuscript.

**Informed consent**

All participants provided consent before they entered this study.

**Ethical approval**

The study was approved by the Ethics Committee of the Brain Hospital affiliated to Nanjing Medical University. (Ethics Committee approval number: (2013) Ethics Approval (KY010))

**Authors' contributions**

Yuxiu Sui participated in the design of the project, and the revision of the drafts and the final draft. Jingjing Yao, Yiding Lv and Yuan Li participated in recruiting patients and healthy controls, data collection and scheduling clinical assessments; Yiding Lv and Xiaoxin Zhao conducted the statistical analyses. Xinyue Zhang conducted data analyses and wrote the draft.

## 首发精神分裂症患者的认知功能与脑灰质体积的相关研究

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**背景：**认知功能损害是精神分裂症的核心症状之一，其恢复程度关系到患者能否重新回归社会。

**目的：**明确精神分裂症认知功能与脑灰质体积的关系。

**方法：**采用画钟测试、连线测试、数字广度测试、听觉词语测试、威斯康星卡片分类测验、言语流畅性测试、语义相似性测验、斯特鲁色词测试对 37 例首发精神分裂症住院患者（病例组）和 30 名健康对照组（对照组）进行神经认知功能检测，采用面孔情绪认知任务测试对 32 例首发精神分裂症住院患者（病例组）和 29 名健康对照组（对照组）进行面孔情绪认知功能检测，采用阳性和阴性症状量表（Positive and Negative Syndrome Scale，PANSS）评定首发精神分裂症住院患者的精神症状，利用磁共振分别对病例组和对照组进行脑部影像学数据的采集。

**结果：**病例组和对照组在画钟测试、连线测试、数字广度测验、听觉词语测验、威斯康星卡片分类测验、言语流畅性测验、语义相似性测验、斯特鲁色词测验反应时间中，两组间的差异有统计学意义；面孔情绪认知任务测试斜率（Slope）之间有统计学意义；病例组与对照组的脑灰质体积差异比较发现病例组的左侧额上回的灰质体积增加，左侧枕下回、舌回和小脑上部灰质体积减少；病例组神经认知数据与脑影像学数据分析，斯特鲁色词测验中的卡片 C 正确反应个数测验分数，显示与左侧额上回和右侧额上回、额中回灰质体积负相关；病例组面孔情绪认知任务与脑影像学数据分析，病例组转换斜率数据的相关灰质异常脑区为与右侧颞上回、颞中回，左侧颞中回、颞下回和梭状回灰质体积成正相关。

**结论：**首发精神分裂症住院患者的神经认知功能和面孔情绪认知功能存在广泛性损害，上述结果提示灰质体积异常脑区可能为认知功能障碍的脑结构和功能基础。

**关键词：**首发精神分裂症；神经认知；面孔情绪认知；脑灰质体积

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## Retraction

***Shanghai Archives of Psychiatry*** **is retracting the paper by Simone Schwank, "The fantasmatic and imaginary child of the pregnant woman" (Shanghai Archives of Psychiatry 2017; 29: 161-170 and http://www.shanghaiarchivesofpsychiatry.org/Issue.aspx?Issue=a59e79c3-c802-4d21-b10b-fcd15438c389) at the request of Dr. Olle Söder and Prof. Eva Nissen. In April 2018, the Karolinska Institutet found that the findings in the article are unreliable as a result of an experimental honesty error.**