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# Hippocampal and orbital inferior frontal gray matter volume abnormalities and cognitive deficit in treatment-naive, first-episode patients with schizophrenia

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ABSTRACT

*Background:* Cognitive impairment is a core feature of schizophrenia. Some evidence suggests an association between cognition deficits and gray matter reductions. In this study, we investigated the relationship between cognitive performance and gray matter volumes in patients with treatment-naïve, first-episode schizophrenia.
*Method:* First-episode patients with treatment-naïve schizophrenia and healthy controls went through brain imaging scan using high resolution magnetic resonance imaging. A neuropsychological battery including 8 neurocognitive tests was used to assess cognitive function. Voxel-based methods were used for volumetric measure in the brain.
*Results:* Fifty-one patients and 41 healthy controls were included in the analysis. Patients exhibited a poorer performance on all 7 cognitive function tests compared with healthy controls ($ps < 0.006$). There were significant gray matter volume differences between the two groups in bilateral hippocampus gyri, right superior temporal gyrus, left fusiform gyrus and orbital inferior frontal gyri (FDR, $ps < 0.05$). Within the schizophrenia group, multiple regression analysis demonstrated that poorer performance on the working memory, verbal learning and visual learning was associated with smaller hippocampal gray matter volume, and poorer executive function was associated with smaller left orbital inferior frontal gray matter volume after controlling for potential confounding variables ($\beta \geq 0.420$, $ps \leq 0.010$).
*Conclusions:* Our findings suggest that cognitive deficits are associated with hippocampal and orbital inferior frontal gray matter volume abnormalities in treatment-naïve, first-episode patients with schizophrenia.


## 1. Introduction

Cognitive deficits may represent a core pathophysiological feature of schizophrenia because these deficits are clearly present at the first episode of illness (Elvevag and Goldberg, 2000). Findings revealed that individuals with first episode of schizophrenia showed a pattern of deficits on tasks related to frontal and temporal lobe functioning, including attention, processing speed, executive functioning, verbal fluency, verbal memory, and learning (Gold et al., 2002; Harvey et al., 2005; Keefe et al., 2005; Lesh et al., 2011).

Brain gray matter (GM) volume abnormalities, primarily in the frontal and temporal lobes, have been consistently reported in first episode of psychosis (Bachmann et al., 2004; Nakamura et al., 2008). Investigations using voxel-based morphometry (VBM) have shown reduced GM volumes in the frontal and temporal regions, anterior cingulate cortex, insula, hippocampus and parahippocampal gyrus (Job et al., 2002; Kubicki et al., 2002; Honea et al., 2005; Chua et al., 2007; Morgan et al., 2007; Schaufelberger et al., 2007; Glahn et al., 2008).

A number of studies have attempted to determine the relationship between brain structure and neurocognition in schizophrenia (Cocchi et al., 2009; Minatogawa-Chang et al., 2009; Wojtalik et al., 2012). Temporal lobe, hippocampus and parahippocampal gyrus correlate with cognitive functions such as processing speed and accuracy, memory, executive function, verbal abstraction and categorization in schizophrenia (Cocchi et al., 2009; Minatogawa-Chang et al., 2009; Wojtalik et al., 2012). Most patients in these studies had chronic schizophrenia, and had been exposed to antipsychotics prior to study participation; therefore changes in brain structure could be caused by both the disease itself and/or by antipsychotic treatment (Navari and Dazzan, 2009; Moncrieff and Leo, 2010; Boonstra et al., 2011).

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Few studies have focused on the possible relationship between cognitive function and brain structure in treatment-naïve, first-episode schizophrenia (FES). The present study used the VBM approach to examine the relationship between cognitive function and gray matter volume in treatment-naïve, first-episode patients with schizophrenia.

## 2. Methods

### 2.1. Subjects

Antipsychotic drug treatment naive patients with first-episode schizophrenia were recruited from outpatient psychiatric clinics at The Second Xiangya Hospital of Central South University, China. The diagnosis of schizophrenia was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version administered by clinicians (First et al., 1996). Patients had never received antipsychotic drug treatment prior to the study, and the duration of illness was less than 2 years. Healthy individuals with no psychiatric history from the local community, matched with the patients by age, gender, handedness, and education level, were recruited as controls. All subjects were within the age range of 16 to 30 years old, of Han Chinese ethnicity, right-handed, and had more than 9 years of formal education. The exclusion criteria included neurological disorders or organic disorders affecting the central nervous system, substance-related disorders or mental retardation as defined by the DSM-IV criteria, history of head injury or electroconvulsive therapy, and contraindications for MRI scanning.

The study was approved by the Institutional Review Board at The Second Xiangya Hospital of Central South University. A written informed consent was obtained from each subject, or his or her legal guardians. All subjects underwent the cognitive assessment and MRI scanning before any antipsychotic treatment.

### 2.2. Cognitive function and clinical symptom measures

A neuropsychological test battery was administered to all participants. The battery included the following 7 tests:

The category fluency test (CFT)—animal naming (Benton and Hamsher, 1978): This is an oral test in which subjects name as many animals as she/he can in 1 min. Scores are calculated from the number of words produced.

The trail making test part A (TMT-A) (Reitan and Wolfson, 1997): This is a timed paper-and-pencil in which the subject draws a line to connect a set of 25 dots as fast as possible while still maintaining accuracy. The measured outcome is the time required to complete the test.

Brief assessment of cognition in schizophrenia (BACS)—symbol coding (Wechsler, 1987): In this test, subjects are asked to write numerals 1–9 to match symbols on a response sheet for 90 s. The measured outcome is the number of correct numerals (range: 0–110).

The Wechsler memory scale—3rd edition spatial span (WMS-III SST) (Wechsler, 1987): In this test, the respondent must remember the order in which an administrator points to a series of cubes in both the forward and reverse orders. The outcome measure is the number of correctly recalled trials in each condition.

The Hopkins verbal learning test—revised (HVLT-R) (Benedict, 1997): This test is an oral test in which a list of 12 nouns (targets) from each of three semantic categories is presented; the respondent is asked to recall as many words as possible. The performance is measured by the total number of correctly recalled words.

The brief visual-spatial memory test—revised (BVMT-R) (Brandt and Benedict, 2001): This test involves reproducing six geometric figures from memory. The respondent views the stimulus page for 10 s and is asked to draw as many figures as possible in the correct locations on a page in the response booklet. The performance is measured by the total number of correctly recalled figures.

Stroop color and word test (SCWT) (Golden, 1978): This test contains three parts: word page (the names of colors printed in black ink), color page (rows of Xs printed in colored ink) and word-color page (the words from the first page are printed in the colors from the second page; however, the word meanings and ink colors are mismatched). Each trial contains 100 items, and the subjects must read as quickly as possible in 45-s intervals. The number of correct names is recorded for every trial.

These 7 tests were grouped into 5 cognitive domains: processing speed (Category fluency, BACS-symbol-coding, Trail making A), working memory (WMS-III spatial span), verbal learning (HVLT revised), visual learning (BVMT revised) and executive function (Stroop color and Word test).

The severity of psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

### 2.3. Imaging acquisition and processing

Imaging data were acquired using a 3.0 T Philips scanner (Philips Medical Systems). The first sequence was a transverse spin-echo scan, which acquired both T2- and proton-density weighted images of the brain. High-resolution whole brain volumetric T1-weighted images were acquired sagittally with an inversion-recovery prepared three-dimensional spoiled gradient echo (SPGR) pulse sequence (repetition time = 7.4 ms, echo time = 3.4 ms, inversion time = 875 ms, flip angle = 9°, field-of-view, matrix = 228 × 228, field of view = 250 × 250 $mm^2$, slice thickness = 1.1 mm, gap = 0 mm, slices = 301).

All structural data were processed using the VBM toolbox (VBM8) (http://dbm.neuro.uni-jena.de/vbm) with the Statistical Parametric Mapping 8 software package (http://www.fil.ion.ucl.ac.uk/spm). The VBM preprocessing is briefly described here. First, all T1-weighted anatomical images were normalized to standard SPM T1-MRI template and then segmented into gray matter, white matter, and cerebrospinal fluid images. After this preprocessing, segmented images were checked to ensure all images were unabridged. Then an 8 mm full width at half-maximum Gaussian kernel was used to smooth the gray matter images, which was made to reduce the individual difference of brain anatomy and to increase the signal to noise ratio.

### 2.4. Statistical analysis

Demographic and clinical characteristics were compared between the two groups using one-way analysis of variance (ANOVA) or chi-square test. One-way analysis of covariance (ANCOVA) was used to compare VBM and cognitive performance differences between the two groups controlling for gender, age and years of education. A p value of 0.05 (two tailed) was used for statistical significance.

To examine the relationship between cognitive function and the gray matter volumes within the schizophrenia patient group, we extracted the sum volumes of the clusters in the brain regions that showed significant differences between the two groups in VBM analysis. Multiple linear regression analysis was performed using SPM8 with cognitive domain scores as dependent variable and gray matter volumes as predictor variable controlling for, gender, age, years of education and PANSS total scores. For each cognitive domain score, 5 regression models were examined with 1 of the 5 different anatomical regions as the predictor in each model; therefore the Bonferroni correction for the significance threshold ($p = 0.05/5 = 0.01$) was used for the regression coefficient value ($\beta$) of the predictor.

To calculate the cognitive domain scores, all test raw scores were first converted to standardized z-scores by setting the sample mean of each measure to zero and the standard deviation to one. For domains with more than one test, a domain z-score was created by calculating