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Decreased gray matter volume in the left middle temporal gyrus as a candidate biomarker for schizophrenia: A study of drug naive, first-episode schizophrenia patients and unaffected siblings

Wenbin Guo [a,b,1], Maorong Hu [a,c,1], Xiaoduo Fan [d,1], Feng Liu [e,1], Renrong Wu [a], Jindong Chen [a], Xiaofeng Guo [a], Changqing Xiao [b], Meina Quan [d], Huafu Chen [e], Jinguo Zhai [f], Jingping Zhao [a,g,*]

[a] Mental Health Institute of the Second Xiangya Hospital, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, Changsha, Hunan 410011, China
[b] Mental Health Center, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi 530021, China
[c] Mental Hospital of Nanchang University & Mental Health Center of Jiangxi Province, Nanchang, 330029, China
[d] University of Massachusetts Medical School, UMass Memorial Medical Center, One Biotech, Suite 100, 365 Plantation Street, Worcester, MA 01605, United States
[e] Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, Sichuan 610054, China
[f] School of Mental Health, Jining Medical University, Jining, Shandong 272067, China
[g] The Second Affiliated Hospital of Xinxiang Medical University, Henan Province Key Lab of Biological Psychiatry, Xinxiang Medical University, Xinxiang, Henan 453002, China

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ABSTRACT

Background: Studies have shown that patients with schizophrenia and their siblings share decreased gray matter (GM) volumes in certain brain regions, which may represent candidate endophenotypes of schizophrenia. However, the specificity and utility of these possible endophenotypes in relation to schizophrenia remain unclear.
Methods: Twenty drug-naive, first-episode schizophrenia patients and 20 first-degree unaffected siblings from the same families as the patients (USS group), a separate group of 25 first-degree unaffected siblings of schizophrenia patients from other families (USO group), and 43 healthy controls were recruited. Voxel-based morphometry (VBM) was used to analyze structural imaging data.
Results: The VBM analysis showed a significant difference in GM volume between the combined sibling group and the control group in the left middle temporal gyrus (MTG). Group comparison showed that the patients, the USS, and the USO had significantly decreased GM volume of the left MTG compared with the controls; such a difference did not exist among the patients and the two sibling groups. A receiver operating characteristic curve (ROC curve) analysis showed good predictive value of the mean cluster volume in the left MTG to distinguish patients, USS, and USO from healthy controls. There were no significant correlations between the mean cluster volume in the left MTG and clinical variables in the patients.
Conclusions: The GM volume decrease of the left MTG may be utilized as a candidate biomarker for schizophrenia. The novel design of including a USO group in our study enhances both the specificity and the heritability of the biomarker identified.

1. Introduction

Current understanding is that schizophrenia may be due to several genes of small effect that interact with environmental factors (Harrison and Weinberger, 2005). The endophenotype concept posits a characterization of psychiatric disorder informed by traits intermediate to clinical symptoms and underlying genetically based pathogenesis; the genetic architecture of an endophenotype is likely to be less complex than that associated with the heterogeneous and more subjective clinical criteria of schizophrenia (Greenwood et al., 2007). An endophenotype is defined as follows: (1) it is shown to differ between groups of unrelated patients and controls; (2) it is heritable; (3) it is shown to segregate with illness within families; (4) it may or may not be also present in unaffected relatives of the patient within families, but the patient should have it (Gottesman and Gould, 2003). Candidate endophenotypes can be neuroanatomical, neurophysiological, biochemical, endocrine, or cognitive measures.

The whole brain gray matter (GM) volume decreases were reported in both chronic and first episode schizophrenia (Wright et al., 2000; Vita et al., 2006). In addition, volume decreases in various GM regions have been found in the schizophrenia brain, such as the anterior cingulate cortex, frontal and temporal cortices, hippocampus, amygdala, thalamus, and insula (Honea et al., 2005; Prasad and Keshavan, 2008; Allen

* Corresponding author at: Mental Health Institute of the Second Xiangya Hospital, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, Changsha, Hunan 410011, China. Tel.: +86 731 85360921.
E-mail addresses: edsgwb@126.com, zhaojingpingcsu@163.com (J. Zhao).
[1] These authors contributed equally to this work.

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et al., 2009; Fornito et al., 2009; Adriano et al., 2010; Bora et al., 2011; Chan et al., 2011). The inconsistent and non-specific findings in GM volume decrease in schizophrenia reported by the above-mentioned studies might be explained by various reasons including genetic heterogeneity of the disease, time duration of the illness, antipsychotic medication exposure, environmental stress, study sample size, and the data analysis approach (Lieberman et al., 2005).

Reduced GM volumes in the prefrontal cortex, the anterior cingulate cortex, the amygdala-hippocampal complex, the thalamus, and the temporal gyrus have also been observed in first-degree relatives similar to their schizophrenia probands (Rajarethinam et al., 2004; Hulshoff Pol et al., 2006; Goghari et al., 2007; Gogtay et al., 2007; Honea et al., 2008; MacDonald et al., 2009). Regional GM volume abnormalities found in unaffected first-degree relatives tend to be milder than in their schizophrenia probands (MacDonald et al., 2009). However, there are also studies that reported no significant brain structural abnormalities in the first-degree relatives of schizophrenia patients (McDonald et al., 2006; Goldman et al., 2009). The specificity and utility of GM volume decrease in specific brain regions as possible endophenotypes for schizophrenia remain uncertain.

Our group recently reported decreased left middle temporal gyrus (MTG) volume in drug-naive, first episode patients with schizophrenia and their unaffected siblings in a Han Chinese population, suggesting that the left MTG might be a potential endophenotype for schizophrenia (Hu et al., 2013). In the present study, we were trying to replicate our recent findings in GM volume decrease in a separate but similar patient sample of drug-naive, first episode patients with schizophrenia and their unaffected siblings. In addition, we included unaffected siblings of schizophrenia patients from different families in the present study. We hypothesized that both the patient group and the two sibling groups would share similar GM volume decreases in the brain.

2. Materials and methods

2.1. Participants

Twenty drug-naive, first-episode schizophrenia patients (patient group), 20 first-degree unaffected siblings from the same families as the patients who participated in the study (USS group, each patient had a sibling involved in the present study), and a separate group of 25 first-degree unaffected siblings of schizophrenia patients from other families (USO group) were recruited from the Mental Health Institute of the Second Xiangya Hospital, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, China. Forty-three healthy controls without family history of schizophrenia in first- and second-degree relatives (control group) were also recruited from the community.

The diagnosis of schizophrenia and the screening to rule out schizophrenia or other psychiatric disorders for unaffected siblings and healthy controls were conducted using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997). All patients had disease duration of less than two years. The symptoms of schizophrenia were rated using the Positive and Negative Symptom Scale (PANSS) at the time of imaging scan. All participants had more than nine years of formal education, were in the age range of 16 to 30 years old, and were right-handed. The patients and the siblings were well matched with regard to age, and group-matched in sex and education level.

The exclusion criteria for all participants included: 1) any other Axis I disorders such as depression, bipolar disorder, and substance abuse; 2) any Axis II disorders; 3) history of serious medical or neurological disorders; 4) history of loss of consciousness; and 5) family history of major mental or neurological disorders in first- or second-degree relatives (except schizophrenia for unaffected siblings) based on medical records and interviews of subjects and their family members.

All participants provided written informed consent to participate in the study. The study was approved by the ethics committee of the Second Xiangya Hospital.

2.2. Image acquisition

A brain imaging scan was performed for all participants using a 3.0 T Philips scanner (Philips Medical Systems). A high-resolution T1-weighted sequence was applied using a three-dimensional magnetization prepared rapid acquisition gradient echo (3D-MPRAGE) sequence. The whole brain images were obtained in a sagittal orientation with the following parameters: repetition time = 7.4 ms, echo time = 3.4 ms, inversion time = 875 ms, flip angle = 9°, acquisition matrix = 228 × 228, field of view = 250 mm × 250 mm, slice thickness = 1.1 mm, no gap, and 301 slices.

2.3. Imaging data processing

Each image was manually inspected for image artifacts and gross anatomical abnormalities. Image processing was performed using a voxel-based morphometry (VBM) toolbox (VBM8) (http://dbm.neuro.uni-jena.de/vbm) of the Statistical Parametric Mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The images were normalized to the same standard stereotactic space by registering each image to the same template image and estimating the 12-parameter affine transformation. Then the images were segmented for signal intensity and prior probability information, and spatially normalized to the customized template. After intensity modulation, the GM images were smoothed with an 8 mm full-width at half-maximum Gaussian kernel. The SPM-T maps were superimposed onto the customized template to determine the anatomical localization. The automated anatomical labeling (AAL) atlas software and anatomical atlases were used to identify the localization (Tzourio-Mazoyer et al., 2002).

2.4. Statistical analysis

For imaging data, we first compared the difference in GM volume of various brain regions between the combined sibling group (USS plus USO) and the control group ($p < 0.001$, uncorrected, with a minimum cluster size of 10 voxels, 1 voxel = $1.5 \times 1.5 \times 1.5$ mm^3). The AAL of the regions with significant group difference was utilized as a mask in the analysis of covariance analysis (ANCOVA) to avoid circular analysis (Kriegeskorte et al., 2009). The ANCOVA ($p < 0.001$, uncorrected) was conducted among the 4 study groups to compare regional brain GM volume with the whole brain GM volume, age, and sex as covariates, followed by post hoc *t*-tests ($p < 0.001$, uncorrected). The mean cluster volumes for the clusters that had shown significant group difference in VBM analysis were extracted. Mean volume measurements were calculated using MarsBar 0.41 (http://marsbar.sourceforge.net/) and log_roi_batch v2.0 (http://www.aimfeld.ch).

ANCOVA was performed to compare the mean cluster volume among the 4 study groups with the whole brain GM volume, age, and sex as covariates. A receiver operating characteristic curve (ROC curve) and the area under the curve (AUC) were calculated to examine the predictive value of the mean cluster volume to distinguish the patients, the USS, or the USO from healthy controls. Demographic and clinical data were compared among the 4 groups using analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. In addition, zero-correlation analysis was performed within the patient group to examine the relationships between the mean cluster volume and demographic/clinical variables including the disease duration, age, education level, as well as the PANSS total and subscale scores. These analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS Inc., Chicago, IL). A $p < 0.05$ (two-tailed) was considered as significant.