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Dissociation of functional and anatomical brain abnormalities in unaffected siblings of schizophrenia patients

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HIGHLIGHTS

- A dissociation phenomenon suggested that brain functional and anatomical abnormalities might be present independently in unaffected siblings of schizophrenia patients.
- The recruitment of unaffected siblings offers insight into the pathophysiology of schizophrenia independently of the clinical and treatment issues that complicate studies of the patients themselves.
- Several possible factors were given to the increase of gray matter volume in the left putamen in the sibling group.

ABSTRACT

Objective: Schizophrenia patients and their unaffected siblings share similar brain functional and structural abnormalities. However, no study is engaged to investigate whether and how functional abnormalities are related to structural abnormalities in unaffected siblings. This study was undertaken to examine the association between functional and anatomical abnormalities in unaffected siblings.
Methods: Forty-six unaffected siblings of schizophrenia patients and 46 age-, sex-, and education-matched healthy controls underwent structural and resting-state functional magnetic resonance imaging scanning. Voxel-based morphometry (VBM), amplitude of low-frequency fluctuation (ALFF) and fractional ALFF (fALFF) were utilized to analyze imaging data.
Results: The VBM analysis showed gray matter volume decreases in the fronto-temporal regions (the left middle temporal gyrus and right inferior frontal gyrus, orbital part) and increases in basal ganglia system (the left putamen). Functional abnormalities measured by ALFF and fALFF mainly involved in the fronto-limbic-sensorimotor circuit (decreased ALFF in bilateral middle frontal gyrus and the right middle cingulate gyrus, and decreased fALFF in the right inferior frontal gyrus, orbital part; and increased ALFF in the left fusiform gyrus and left lingual gyrus, and increased fALFF in bilateral calcarine cortex). No significant correlation was found between functional and anatomical abnormalities in the sibling group.
Conclusions: A dissociation pattern of brain regions with functional and anatomical abnormalities is observed in unaffected siblings.
Significance: Our findings suggest that brain functional and anatomical abnormalities might be present independently in unaffected siblings of schizophrenia patients.

1. Introduction

Considering schizophrenia is a highly heritable psychiatric disorder, the siblings of schizophrenia patients have an 8–10-fold

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higher risk for developing schizophrenia than general population (Gottesman and Gould, 2003). Moreover, unaffected siblings share similar genetic backgrounds and early-life environments with the patients, and exhibit brain abnormalities that are also observed in the patients (MacDonald et al., 2009; Jang et al., 2011; Pettersson-Yeo et al., 2011; van Buuren et al., 2011, 2012; Guo et al., 2014a,c). Thus, unaffected siblings provide an opportunity for us to examine brain abnormalities related to the pathophysiology of schizophrenia, reducing the progressive effect caused by possible confounders such as medication use and long duration of untreated psychosis.

Previous anatomical studies have shown that unaffected siblings may share gray matter volume (GMV) abnormalities with their sick siblings in the amygdala-hippocampal complex, thalamus, and temporal cortices (Seidman et al., 2002; Honea et al., 2008), perhaps most notably in the temporal cortex (Hu et al., 2013). Meanwhile, the major functional abnormalities revealed by functional magnetic resonance imaging (fMRI) in unaffected siblings have been localized in the prefrontal, temporal, and parietal regions (Jang et al., 2011; Guo et al., 2014a), particularly in the default-mode network (DMN) (van Buuren et al., 2012; Guo et al., 2014c). Previously, few studies have examined anatomical and functional abnormalities together in the same sample of schizophrenia patients (Lui et al., 2009; Rubinov and Bassett, 2011; Ren et al., 2013), and the findings exhibited that functional and anatomical abnormalities were in different brain regions, suggesting that functional and anatomical abnormalities are significantly dissociated in schizophrenia. However, no study is devoted to examining anatomical and functional abnormalities together in unaffected siblings of schizophrenia patients, and it remains unclear whether and how the functional abnormalities are related to the anatomical abnormalities in unaffected siblings.

Voxel-based morphometry (VBM), a useful automatic technique, is capable of assessing anatomical abnormalities in the whole brain, and avoids operational bias to particular brain regions (Antonova et al., 2005; Honea et al., 2005). Amplitude of low-frequency fluctuation (ALFF) and fractional ALFF (fALFF) can be applied to identify regional neural activity, which is considered to be physiologically meaningful and associated with regional neural activity (Zang et al., 2007; Zou et al., 2008). Up to now, these methods have been successfully used to examine anatomical and functional abnormalities in clinical studies (Zang et al., 2007; Bora et al., 2011; Liu et al., 2012, 2013; Guo et al., 2013; Yao et al., 2014), including schizophrenia patients and their unaffected siblings (Hoptman et al., 2010; Hu et al., 2013).

In the present study, we used VBM, ALFF and fALFF to investigate functional and anatomical abnormalities in unaffected siblings of schizophrenia patients. Our aim was to examine the association between functional and anatomical abnormalities, as well as the relationship of these abnormalities in unaffected siblings. According to the findings from schizophrenia patients (Lui et al., 2009; Rubinov and Bassett, 2011; Ren et al., 2013), we hypothesized that a similar dissociation pattern of brain regions with functional and anatomical abnormalities would be present in unaffected siblings.

2. Materials and methods

2.1. Subjects

Forty-six unaffected siblings of schizophrenia patients were recruited from Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, China. The diagnosis of schizophrenia for their sick siblings was confirmed by the Structured Clinical Interview of the DSM-IV (SCID), patient edition (First et al., 1997). To minimize the symptom heterogeneity and potentially underlying pathology, only unaffected siblings with a patient diagnosed as paranoid schizophrenia were enrolled in the study. Patients and unaffected siblings were brothers or sisters who shared an early home environment with an age interval of less than 4 years. Forty-six healthy controls were recruited from the community. All subjects were right-handed and unrelated to each other. All subjects were screened by using SCID, non-patient edition (First et al., 1997), and they endorsed no items of the SCID, non-patient edition. The exclusion criteria for all subjects included neurological or psychiatric disorders, substance-related disorders or mental retardation, or contraindications for MRI scanning. Healthy controls with a first-degree relative suffering from a psychiatric disorder were also excluded. The two subject groups were matched in age, sex and years of education.

The study was approved by the ethics committee of the First Affiliated Hospital, Guangxi Medical University. A written informed consent was obtained from each subject.

2.2. Scan acquisition

Imaging data were acquired using a Siemens 3T scanner. Subjects were required to lie motionless, keep their eyes closed, and remain awake. Head motion and scanner noise were reduced by using foam padding and earplugs. High-resolution whole brain volumetric T1-weighted images were obtained with a three-dimensional magnetization prepared rapid acquisition gradient echo (3D-MPRAGE) sequence, and the following parameters were used: repetition time = 8.5 ms, echo time = 2.98 ms, inversion time = 900 ms, flip angle = 9°, acquisition matrix = 256 × 256, field of view = 240 mm × 240 mm, slice thickness = 1 mm, no gap, and 176 slices. Resting-state functional images were acquired using a gradient-echo echo-planar imaging (EPI) sequence with the following parameters: repetition time/echo time = 2000/30 ms, 30 slices, 64 × 64 matrix, 90° flip angle, 24 cm field of view, 4 mm slice thickness, 0.4 mm gap, and 250 volumes (500s). The degree of cooperation for each participant was confirmed by asking some questions after scanning.

2.3. Data processing

Each structural image was checked for scan artifacts and gross anatomical alterations. All structural images were processed using the VBM toolbox (VBM8, http://dbm.neuro.uni-jena.de/vbm) with the Statistical Parametric Mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The VBM preprocessing is briefly described as follows. First, all T1-weighted anatomical scans were spatially normalized to the customized template ($1.5 \times 1.5 \times 1.5$ mm^3), and then segmented into gray matter, white matter, and cerebrospinal fluid images. After that, an 8 mm full-width at half-maximum (FWHM) Gaussian kernel was used to smooth the gray matter images to reduce the individual difference of brain anatomy and to increase the signal to noise ratio. Finally, the resulting images were transformed to z-maps by subtracting the global mean and dividing the global standard deviation.

Functional data were preprocessed with Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan and Zang, 2010) in Matlab (Mathworks). After head-motion and slice-timing correction, no participant had more than 2 mm of maximal translation in x, y, or z and 2° of maximal rotation during scanning. Then, images were spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template in SPM8 and resampled to $3 \times 3 \times 3$ mm^3. The generated images were smoothed with an 8 mm FWHM Gaussian kernel. Finally, the generated images were temporally bandpass filtered (0.01–0.08 Hz) and linearly detrended.

ALFF was calculated with the REST software (Song et al., 2011). The time series for each voxel were transformed with a Fast Fourier