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Localization of cerebral functional deficits in treatment-naive, first-episode schizophrenia using resting-state fMRI

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ABSTRACT

Background: Spontaneous low-frequency fluctuations (LFF) in the blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal have been shown to reflect cerebral spontaneous neural activity, and the present study attempts to explore the functional changes in the regional brain in patients with schizophrenia using the amplitude of the BOLD signals.
Methods: A total of 66 treatment-naïve, first-episode schizophrenia (FES) patients and 66 normal age- and sex-matched controls were recruited. Resting-state fMRIs were obtained using a gradient-echo echo-planar imaging sequence. The amplitude of LFF (ALFF) was calculated using REST software. Voxel-based analysis of the ALFF maps between control and patient groups was performed with twos-sample *t*-tests using SPM2.
Results: Compared to the controls, the FES group showed significantly decreased ALFF in the medial prefrontal lobe (MPFC) and significant increases in the ALFF in the left and right putamen. Significant positive correlations were observed between ALFF values in the bilateral putamen in both the patient and control groups.
Conclusions: Alterations of the ALFF in the MPFC and putamen in FES observed in the present study suggest that the functional abnormalities of those areas are at an early stage of the disease.

Introduction

Cerebral functional abnormalities in patients with schizophrenia have been shown in many neuroimaging studies (Barch et al., 2002; Callicott et al., 1998, 2003; Johnson et al., 2006; Ragland et al., 2004; Stevens et al., 1998). However, the findings in these studies are inconsistent. Using aberrant function in the dorsolateral prefrontal cortex (DLPFC) as an example, it was reported that during working memory tasks, patients maybe demonstrate both underactivation (Callicott et al., 1998; Johnson et al., 2006; Menon et al., 2001b) or overactivation (Callicott et al., 2003; Manoach et al., 2000) of this area. The complex pattern of hyperactivation and hypoactivation found across studies implies that rather than focusing on the dysregulation of a particular area, researchers should consider the entire set of brain regions involved in a given task when making inferences about the biological mechanisms of schizophrenia (Glahn et al., 2005).

In addition, performance confounds have been suggested to play a role in the above-described controversial results, with tasks (Callicott et al., 2003). Recent assessments of brain function at resting state without performing a task have been developed to investigate cerebral networks free of task differences (Gusnard et al., 2001a). The so-called "resting state" fMRI not only avoids the above confounds for this cognitively-impaired patient group (Andreasen et al., 1998), but it is also relatively easy to obtain, which warrants further clinical application (Lui et al., 2008, 2009a; Morcom and Fletcher, 2007). In the past, the resting state in schizophrenia has been explored using PET (Bartlett et al., 1991; Fujimoto et al., 2007; Lahti et al., 2006; Molina et al., 2005) or EEG(Karson et al., 1987; Sponheim et al., 2000; Venables et al., 2009) as a coherence measure. More recently, low-frequency (0.01–0.08 Hz) fluctuations (LFF) of the blood oxygenation level-dependent (BOLD) signal in the resting-state fMRI are considered to be physiologically meaningful and related to spontaneous neural activity (Cordes et al., 2001), and its recent application has revealed alterations in brain function in the survivors of big

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earthquakes in China in 2008 (Lui et al., 2009b). There has been a dramatic increase in studies on schizophrenia using resting-state fMRI (Jafri and Calhoun, 2006; Jafri et al., 2008; Liang et al., 2006; Liu et al., 2006, 2008; Zhou et al., 2007a,b, 2008). Also, inter-regional relationships in brain activity have been observed to be disrupted in schizophrenia (Liang et al., 2006; Zhou et al., 2007a,b).

However, thus far, all studies have investigated LFF from the perspective of temporal synchronization, i.e., have been focused on the correlation between selected areas (referred to as "functional connectivity") but not from the perspective of regional activity during a resting state. Although a result of abnormal functional connectivity between two remote areas can be comprehensive and integrative, no conclusion can be drawn about which area is abnormal, from such an examination. Thus, other approaches are required to characterize the regional signal dynamics. The amplitude of LFF (ALFF) for the BOLD signal is one of the ways to explore regional neural function. An early study (Biswal et al., 1995) confirmed that the ALFF is higher in grey matter than in white matter. Later studies attempted to correlate the fMRI BOLD signal with simultaneously measured neural activity by using a microelectrode that recorded the stimulus-driven unit activity and the local field potential in anesthetized monkeys, and researchers had found that the amplitude of the fMRI BOLD response was significantly correlated with the local field potential activity (Logothetis et al., 2001). Other research correlating the amplitude of cortical activation with reaction time found that the degree of signal change in the BOLD fMRI response of certain areas (the right occipital, left occipital, and left sensorimotor) reflects the speed of performance during the visuomotor response time task by the subject. Thus, the amplitude of activation can be used as a parameter to assess change in function (Mohamed et al., 2004). Regarding to the amplitude of LFF, Kiviniemi et al. (2000), using the power spectrum method, reported activation in the visual cortex due to LFF at approximately 0.034 Hz, which indicates that amplitude of LFF may be related to regional spontaneous neuronal activity. Such a conclusion was supported by later studies using healthy controls (Yang et al., 2007) and children with attention-deficit hyperactivity disorder (Zang et al., 2007).

As amplitude can also be used as a quantitative measure of brain function in the resting state, in the present study, we attempted to explore the functional changes of schizophrenia using the amplitude of BOLD signals. Another issue arises when brain anatomy and functional changes related to schizophrenia are explored—namely, the multiple factors that can confound the results. Confounds associated with illness chronicity, such as possible progressive grey matter atrophy and prolonged exposure to antipsychotic medication (Braus et al., 1999; Iacoboni et al., 2004), may have contributed to the inconsistency across studies. Compared to studies with chronic patients, relatively few functional studies have investigated treatment-naive patients with first-episode schizophrenia (FES) (Hofer et al., 2003). Yet the investigation of treatment-naive FES may be important in elucidating the core pathophysiology of this illness (Whitford et al., 2005).

The purpose of this study was to assess the alteration of cerebral function during the resting state using ALFF in treatment-naive patients with FES and their clinical correlates. We hypothesized that (1) brain function would be altered in the schizophrenia patients, even at rest, as measured by using the ALFF of the BOLD in the resting state and that (2) from a network point of view, the changes in ALFF of the BOLD in those aberrant areas would be inherently correlated.

Materials and methods

A total of 132 right-handed subjects were recruited, including 66 treatment-naive FES patients and 66 normal controls (Table 1). All patients and community controls were recruited at the Mental Health Centre of the West China Hospital. The study was approved by the local ethical committee, and all patients and controls provided written informed consent for their participation. Diagnoses of schizophrenia and durations of illness were determined by a consensus of the attending psychiatrist performing a clinical interview and a trained interviewer using the Structured Interview for the DSM-IV (SCID-P). Healthy controls were recruited from the local area by poster advertisement, and all controls were also screened using the SCID-NP to confirm the lifetime absence of psychiatric and neurological illnesses. In addition, control subjects were interviewed to ascertain that there was no history of psychiatric illness in first-degree relatives. All subjects' clinical variables—i.e., age, sex, height, weight, handedness (based on the Annett handedness scale (Annett, 1970)), years of education, and duration of illness—were obtained by two experienced clinical psychiatrists, before any treatment and MR examinations. Psychopathology associated with FES was evaluated using the PANSS (Kay et al., 1988), which provides a total score, positive and negative symptom scores, and indices of thought disturbance, activation, paranoia, depression, and anergia, by combining items, using a previously published six-factor structure of PANSS items (Gladsjo et al., 2004). Age, sex, height, weight, and years of education were matched between the schizophrenia group and the control subjects (Table 1). The following exclusion criteria applied to all of the above groups: the existence of organic brain disorder, alcohol or drug abuse, pregnancy or any physical illness, such as hepatitis, brain tumor, or epilepsy, as assessed based on medical records. Brain MR images (i.e., T1-weighted and T2-weighted images) were inspected by an experienced neuroradiologist, and no gross abnormalities were observed for all the subjects.

Table 1
Demographic information for antipsychotic-naive first-episode schizophrenia (FES) patients and healthy controls.

Characteristics	FES ($n=66$)	Controls ($n=66$)	P value
Female/male	36:30	36:30	1
Mean age (years)	24.2 ± 8.4	24.5 ± 8.6	0.9
Education (years)	11.5 ± 3.1	12.7 ± 2.5	0.79
Height (cm)	167.7 ± 4.5	167.2 ± 6.2	0.88
Weight (kg)	59.7 ± 12.3	58.8 ± 10.4	0.82
Illness duration (months)	8.8 ± 14.1	–	–
Global assessment function	26.2 ± 7.3	–	–
PANSS scores			
Total	107.2 ± 15.1	–	–
Negative	20.7 ± 6.3	–	–
Positive	26.4 ± 5.2	–	–
General	51.3 ± 9.2	–	–
Thought disturbance	14.8 ± 3.6	–	–
Activation	10.3 ± 2.7	–	–
Paranoid	11.5 ± 2.7	–	–
Depression	10.3 ± 4.6	–	–
Anergia	10.0 ± 4.3	–	–
Impulsive aggression	17.5 ± 5.1	–	–

Data acquisition

High-resolution T1-weighted images were obtained using a 3T MR imaging system (EXCITE, General Electric, Milwaukee, USA) with a volumetric 3D spoiled gradient recall (SPGR) sequence (TR = 8.5 ms, TE = 3.4 ms, flip angle = 12°, slice thickness = 1 mm) using an 8-channel phased-array head coil. A field of view (FOV) of 240 × 240 mm^2 was used, with an acquisition matrix comprising 256 readings of 128 phase-encoding steps, producing 156 contiguous coronal slices, with a slice thickness of 1.0 mm and an in-plane resolution of 0.47 × 0.47 mm^2. MR images sensitized to changes in the BOLD signal levels (TR/TE = 2000/30 ms; flip angle = 90°) were obtained using a gradient-echo echo-planar imaging (EPI) sequence. The slice thickness was 5 mm (no slice gap), with a matrix size of 64 × 64 and a FOV of 240 × 240 mm^2, resulting in a voxel size of 3.75 × 3.75 × 5 mm^3. Each brain volume was comprised of 30 axial slices, and each functional run contained 200 image volumes. During rfMR scanning, an online software (Brainwave 2.0) was used to assess

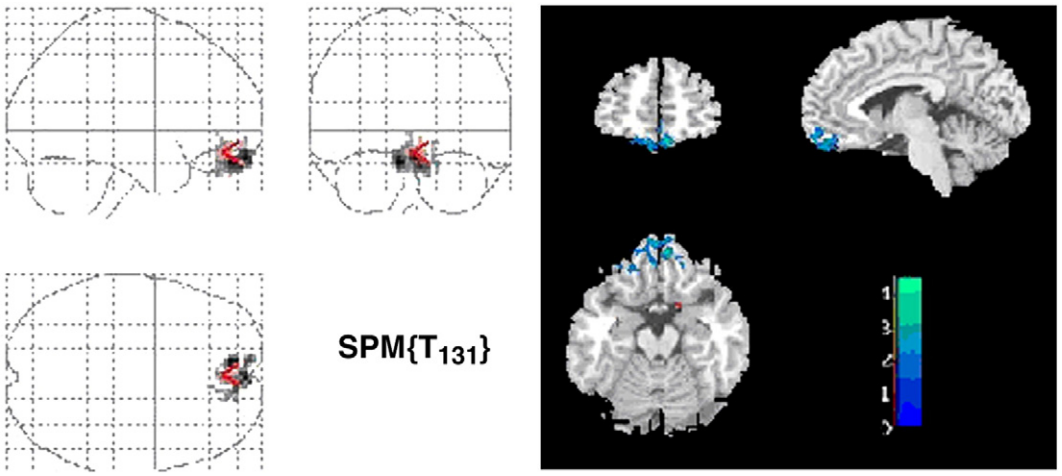

Fig. 1. Glass brain images (left panel) and axial statistical parameter images (right panel) show results of decreased (blue) ALFF in the orbital/medial frontal lobe in first-episode schizophrenia, compared with controls.

the head motion of the subject. If the head translation movement was more than 0.5 mm or rotation was more than 0.5°, the data would be excluded from the present study.

Functional image preprocessing and statistical analysis was carried out using the SPM2 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/). For each subject, EPI images were slice–time corrected and realigned to the first image in the first series and were subsequently unwarped to correct for susceptibility-by-movement interaction. All the realigned images were spatially normalized to the Montreal Neurological Institute (MNI) EPI template in SPM2, and each voxel was resampled to $3\times3\times3$ mm^3.

The ALFF was calculated using REST software (downloaded from http://resting-fmri.sourceforge.net). The following procedure for calculating the ALFF is similar to that used in our earlier research (Yang et al., 2007). After band-pass filtering (0.01–0.08 Hz) (Biswal et al., 1995) and linear trend removing, the time series were transformed to frequency domains using fast Fourier transforms (FFTs) (parameters: taper percent = 0, FFT length = shortest), and the power spectrum was obtained. Because the power of a given frequency is proportional to the square of the amplitude of the frequency component, the power spectrum obtained by FFT was square-rooted and then averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value. The standardized ALFF of each voxel should have a value of approximately 1, and this standardization procedure is analogous to that used in PET studies (Raichle et al., 2001). In this study, the global mean ALFF was calculated only within the brain, i.e., the background and other tissues outside the brain were removed. Finally, all processed images were smoothed with an isotropic Gaussian kernel (full-width at half-maximum = 8 mm).

Statistical analysis

Two-sample *t*-tests were performed to assess the differences in age, sex, height, weight, handedness, and years of education between the patient and control groups using SPSS (version 11.5), and a $P<0.05$ was deemed significant. To avoid the interference of head motion, the shift and rotation parameters revealed by realignment in SPM2 were also assessed using two-sample *t*-tests between the two groups.

To characterize the alteration of ALFF in treatment-naive FES, voxel-based analysis of the ALFF maps between the control and patient groups was performed with two-sample *t*-tests using SPM2. Significant differences were set at the threshold of a corrected cluster level of $P<0.05$ and voxel-wise $t>3.12$ (corresponding to $P<0.001$). The MNI coordinates were transformed to Talairach coordinates using mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Results are presented using the voxel of peak significance.

To identify the association between the alteration of ALFF and the clinical symptom severity, the average ALFF values of all voxels in the abnormal areas revealed by voxel-based analysis were extracted separately using the volume of interest (VOI) in SPM2 and were input into SPSS. Then, the Pearson correlation coefficient was used to indicate the relationships between the ALFF values of all patients and the PANSS scores, and the significance levels were set at $P<0.05$ (two-tailed).

Results

There were no significant age, sex, height, weight, handedness, years of education, or head motion differences between the two groups. The shift of all subjects was no more than 1 mm, and rotation was lower than 1°.

Compared to the controls, the FES group showed significantly decreased ALFF in only one area, the orbital/medial frontal lobe (Talairach: −9, 48, −20; 4671 mm^3, $P<0.05$, corrected at cluster level; Fig. 1). Interestingly, significant increases in ALFF were found in left (Talairach: −30, −3, 6; 4185 mm^3, $P<0.05$, corrected at cluster level) and right (Talairach: 30, 0, 12; 2673 mm^3, $P<0.05$, corrected at cluster level) putamens in the FES group, compared to the healthy controls (Figs. 2, 3).

To identify the association between the alteration of ALFF in different areas and with clinical symptom severity, the average ALFF values of all voxels in the orbital/medial frontal lobe and bilateral putamens were extracted separately. Significant positive correlations were observed between ALFF values in the bilateral putamens in the patient ($r=0.81$, $P=0.0004$) and control ($r=0.83$, $P=0.0003$) groups. However, no correlation for either of the items of the PANSS scores was found for the putamens and the frontal area.

Discussion

The present study assessed cerebral function during the resting state using the ALFF in a large cohort of treatment-naive FES patients. Compared to controls, reduced ALFF was found only in the orbital/medial frontal lobes, whereas increased ALFF was observed in the bilateral putamens.

The MPFC is assumed to play a general role in emotional processing, such as attention to emotion, identification, or regulation of emotion (Teasdale et al., 1999), and guides motivational behavior

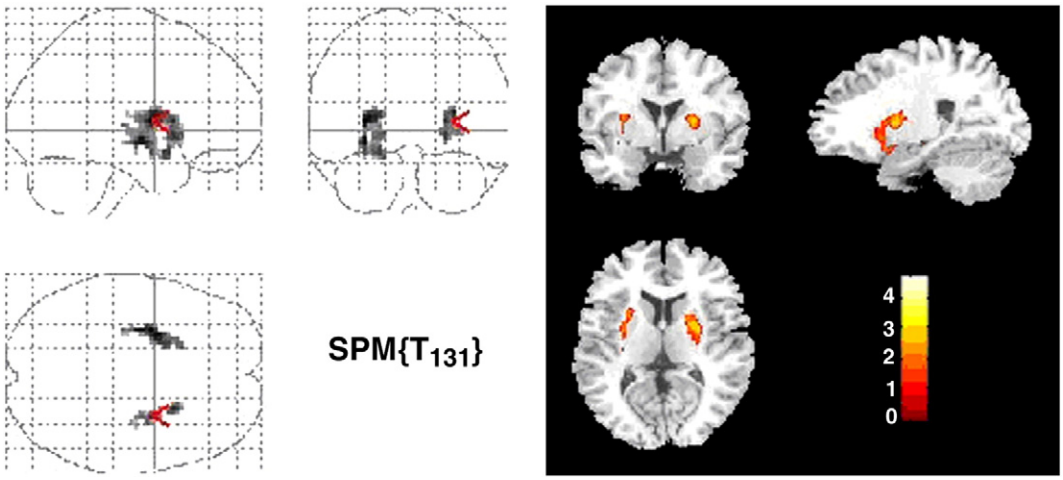

Fig. 2. Glass brain images (left panel) and axial statistical parameter images (right panel) show results of increased (red) ALFF in the bilateral putamens in first-episode schizophrenia, compared with controls.

by modulating or appraising autonomic emotional responses (Phillips et al., 2003). It had been consistently identified as part of the default network associated with self-referential processing (Gusnard et al., 2001a) and is activated when attention is directed to the self (self-awareness) (Johnson et al., 2002). The common engagement of this area for representing the mental states of others and the self may provide the neural basis for intersubjectivity, the interplay between two different subjective minds. With regard to this engagement, it is important to note that the decreased activation in the medial prefrontal cortex was associated with decreased "illness insight" in people with schizophrenia.

Structural abnormalities of the MPFC were found to be correlated with certain symptoms of schizophrenia (Yamada et al., 2007), whereas decreased activation in the MPFC appears to be an important finding related to dysfunctional emotional behavior in schizophrenia (Takahashi et al., 2004). The specific association between improved illness insight and medial prefrontal activation has been observed in previous research (Lee et al., 2006), which found increased activation in the left medial prefrontal cortex to be significantly correlated with improved insight and social functioning in patients with schizophrenia, after recovery from an acute episode. Moreover, neuropsychiatric research has demonstrated that the prefrontal cortical areas mediating different cognitive tasks may be distinguished by specific neurocognitive assessments (Ritter et al., 2004) and that there are different roles for the ventral MPFC (vMPFC) and dorsal MPFC (dMPFC). Abnormalities of the dMPFC in schizophrenia have been found in many fMRI studies, both with tasks (Barch et al., 2002; Harrison et al., 2007; Williams et al., 2007) and in the resting state (Zhou et al., 2007b). Although the vMPFC has been recognized as the core region associated with the brain's default network (Buckner et al., 2008), until now, no previous study had directly located the abnormality of schizophrenia in terms of resting-state functions in the vMPFC. To the best of our knowledge, our study located, for the first time, the functional problem in the vMPFC in first-episode schizophrenia patients.

The putamen had been suggested to have a possible association with the pathology of schizophrenia by numerous studies considering different aspects of the disease, such as increased levels of the apolipoprotein (Digney et al., 2005), hyperperfusion in the resting state (Malaspina et al., 2004), increased synthesis (Lindstrom et al., 1999) in drug-free patients, and turnover of dopamine (Kumakura et al., 2007), which suggests that there may be functional enhancement of the putamen in the early stages of the disease.

Although enlargement of the putamen had been found in relative large-sample studies (Antonova et al., 2005; Goldman et al., 2008; Mamah et al., 2007; Volz et al., 2000) and even in unaffected relatives (Mamah et al., 2008) and was also correlated with cognitive function (Laywer et al., 2006), no such differences were found in FES in a relative large sample of 51 patients (Gunduz et al., 2002). Direct comparisons of first-episode and chronic patients suggest that putamen enlargement may be an effect of antipsychotic drugs (Gur et al., 1998; Lang et al., 2001; Premkumar et al., 2006). However, other studies suggested that the volume increase in the putamen in schizophrenia may be used as an eigenimage to help with the classification of the disorder (Kawasaki et al., 2007), and larger putamen volume was associated with good outcomes (Brickman et al., 2006; Buchsbaum et al., 2003).

However, the inconsistency of structural changes in the putamen does suggest that there may be some type of functional change in the putamen at early stages of the disease. Past fMRI research showed that schizophrenia patients had significant bilateral deficits in the posterior putamen, globus pallidus, and thalamus, and functional connectivity analysis revealed that the deficits in thalamic activation were related to deficits in posterior putamen and globus pallidus activation (Menon et al., 2001a). However, no past study has confirmed the abnormality of this particular critical structure using

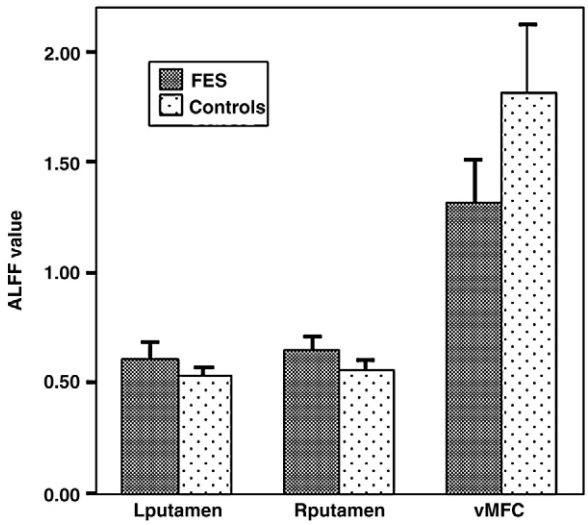

Fig. 3. Column figure shows differences in the ALFF between schizophrenia and controls as reduced ALFF in the ventral medial frontal lobes (vMFC) ($P = 0.002$), and increased ALFF in the left ($P = 0.009$) and right ($P = 0.001$) putamens (Lputamen and Rputamen in the figure). Error bars reflects standard errors for the mean values.

resting-state fMRI. Our study showed, for the first time, the altered function of the putamen at a resting state in vivo, which indicates hyperfunction at early stages of the disease and may account for the pathology of the disorder.

A volume reduction of the frontal area with enlargement of the putamen (Gaser et al., 1999) and hyperactive limbic metabolism (Molina et al., 2005) have been recognized in previous studies on FES. Recent research has confirmed the significant association between basal symptoms and DLPFC atrophy and limbic hyperactivity at rest in recent-onset schizophrenic patients (Molina et al., 2003). BOLD fMRI with task has shown that patients with schizophrenia have abnormal neural network patterns of reduced left prefrontal activation and increased subcortical activation when challenged with motor response inhibition (Rubia et al., 2001). Our result adds evidence to the above observations with an entirely new functional parameter and without the interference of cognitive tasks.

No correlation of either item of the PANSS scores was found for either the putamen or the frontal areas, indicating that amplitude cannot be used as a quantitative marker for the assessment of symptoms of schizophrenia at this stage, although it can be used in a qualitative way to help locate functional aberrant areas.

The most significant advantage of this study is the recruitment of a relatively large group of first-episode, drug-naive schizophrenia patients. Atypical antipsychotic drugs such as olanzapine and risperidone have been shown to have an effect on the MPFC (Abekawa et al., 2008). Areas close to the vMPFC, such as the ACC, have been suggested to be especially sensitive to antipsychotic treatment in the short term (Snitz et al., 2005). The drug's effect on the putamen volume has also been confirmed by past MRI research (Corson et al., 1999).

Another common reason for the past inconsistent results in schizophrenia studies may be the non-homogeneity of symptom profiles; e.g., the function of the MPFC differs in deficit and non-deficit schizophrenia (Delamillieure et al., 2004). The smaller the sample size, more likely the result would be affected by those confounds. In this study, the relative large sample size has a second advantage. It provides a relatively robust result for generalizing to the common schizophrenia population and in terms of understanding the common path for the pathology of schizophrenia.

Several methodological issues concerning the use of ALFF should be considered when interpreting these results. As in all the resting-state fMRI studies (Cordes et al., 2001; Gusnard et al., 2001b), we reduced but could not eliminate the effects of physiological noise, such as cardiac pulsation, by modeling low-frequency (0.01–0.08 Hz) fluctuations of the BOLD signal, into which cardiac and respiratory noises are aliased because of the relatively low sampling rate (TR = 2 s) for multislice acquisitions (Yang et al., 2007). In future studies, simultaneous cardiac recording may provide a more direct correction.

In conclusion, functional abnormalities or imbalances of the default network related to the MPFC and basal ganglia in FES have been revealed at the resting state. Further work combining different modalities may help to provide more information about the disorder.

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