Abnormal regional spontaneous neural activity in first-episode, treatment-naive patients with late-life depression: A resting-state fMRI study

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Keywords:
Coherence-based regional homogeneity
First-episode
Late-life depression
Resting-state fMRI
Treatment-naive

Article history:
Received 22 May 2012
Received in revised form 29 June 2012
Accepted 3 July 2012
Available online 10 July 2012

Abstract

Background: The previous resting perfusion or task-based studies have provided evidence of functional changes in the brains of patients with late-life depression (LLD). Little is known, so far, about the changes in the spontaneous brain activity in LLD during the resting state. The aim of this study was to investigate the spontaneous neural activity in first-episode, treatment-naive patients with LLD by using resting-state functional magnetic resonance imaging (fMRI).

Methods: A novel analytical method, coherence-based regional homogeneity (Cohe-ReHo), was used to assess regional spontaneous neural activity during the resting state in 15 first-episode, treatment-naive patients with LLD and 15 age- and gender-matched healthy controls.

Results: Compared to the healthy controls, the LLD group showed significantly decreased Cohe-ReHo in left caudate nucleus, right anterior cingulate gyrus, left dorsolateral prefrontal cortex, right angular gyrus, bilateral medial prefrontal cortex, and right precuneus, while significantly increased Cohe-ReHo in left cerebellum posterior lobe, left superior temporal gyrus, bilateral supplementary motor area, and right postcentral gyrus (p < 0.005, corrected for multiple comparisons).

Conclusions: These findings indicated abnormal spontaneous neural activity was distributed extensively in first-episode, treatment-naive patients with LLD during the resting state. Our results might supply a novel way to look into the underlying pathophysiology mechanisms of patients with LLD.

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1. Introduction

Late-life depression (LLD) is associated with emotional suffering, cognitive impairment, disability and poor compliance with medical treatments (Alexopoulos, 2005; Charney et al., 2003). As one of the most common mental disorders and the most important precursor of suicide in the old people, LLD leads to a decline in both well-being and daily functioning (Taki et al., 2005). At present, the diagnosis of depression is mainly dependent on clinical signs and symptoms, and the exact neural basis underlying LLD is still not fully understood.

Recent advances in imaging techniques open the way to provide a greater understanding of the neuropathology of depression. Functional neuroimaging approaches make it feasible to explore the changes of brain function that can be responsible for variability in mood and cognitive responses to treatment (Gunning and Smith, 2011). Therefore, thoughtful use of functional neuroimaging techniques can guide treatment decisions of depression. During the past years, ample evidence from functional neuroimaging studies has described changes of cerebral activity in patients with depression. A recent positron emission tomography (PET) study demonstrates that cerebral glucose metabolism is increased in patients with LLD relative to healthy control subjects in superior frontal gyrus and precuneus (PCU) regions (Smith et al., 2009). In addition, Kumar and colleagues reveal that the depressed subjects...
showed significant reductions in the regional cerebral metabolic rate of glucose in the subcortical and paralimbic regions (Kumar et al., 1993). Moreover, hypoactivation of the dorsal anterior cingulate cortex (ACC) and the hippocampus are detected in patients with geriatric depression during a word activation task (de Asis et al., 2001). Recently, functional magnetic resonance imaging (fMRI) has appeared as a popular technology due to its advantage of non-invasive and not requiring exposure to radioactive tracers and thus may provide new insights into the pathophysiology of depression. An fMRI study has found that activation in the ACC is significantly decreased in elderly patients who have experienced multiple depressive episodes when performed a verbal fluency task (Takami et al., 2007). Further, Aizenstein et al. observe decreased dorsolateral prefrontal cortex (DLPFC) while increased caudate nucleus (CAU) activation in response to an explicit sequence-learning task (Aizenstein et al., 2005). Although aforementioned studies have demonstrated functional abnormalities in patients with LLD, there are fewer consensuses on the changes in functional brain activity. Confounds associated with illness chronicity, such as the number of episode and prolonged exposure to antidepressants, may lead to the inconsistency across studies (Guo et al., 2011a; Zou et al., 2010). Compared with studies using chronic patients, relatively few studies have investigated first-episode, treatment-naive patients with LLD. The study of the first-episode, treatment-naive patients with LLD may be significant for elucidating the core pathogenesis of this illness. Besides, another issue pertains that the task-related functional neuroimaging studies require patients to follow relatively complicated cognitive tasks and thus the performance may confounds the results (Callicott et al., 2003).

Resting-state fMRI has been viewed as a promising way to studying depression because of the persistent and pervasive nature of depressive symptoms (Greicius et al., 2007). The resting-state fMRI, unlike task-based fMRI, is relatively easy to obtain and ask patients nothing but to remain still with eyes closed, which is of more potential applications in clinical studies. So far, by using resting-state fMRI functional connectivity method, Greicius et al. observe the thalamic and subgenual cingulate functional connectivity is significantly greater in the depressed subjects compared with healthy controls (Greicius et al., 2007). When the graph theory analysis, Zhang and colleagues find that the increased nodal centralities are mainly in the CAU and default mode regions, and decreased nodal centralities in the orbital frontal, and temporal regions (Zhang et al., 2011). However, these above-described studies can only reveal the aberrant functional connectivity between two remote areas but not from the perspective of regional activity in the resting state. Although a result of abnormal functional connectivity between two remote regions can be integrative and comprehensive, no conclusion can be drawn about which region is aberrant from such an investigation. Therefore, it is important to explore the regional activity by using other approaches.

Several existing local measurements are complementary to functional connectivity methods. For example, regional homogeneity (ReHo), has been developed to explore that a given voxel is temporally similar to its neighbors within a single region (Zang et al., 2004). ReHo analysis hypothesizes that spatially neighboring voxels should have similar temporal patterns. Abnormal ReHo possibly reflects the changes of temporal aspects of neural activity in the regional area. It has been shown that the major regions of default mode network (DMN) have increased ReHo than other brain regions during resting state (Long et al., 2008). Additionally, the ReHo method has been used to investigate the brain function in healthy subjects (Zang et al., 2004) and psychiatric and neurological disorders (Bai et al., 2008; Guo et al., 2011b; He et al., 2007; Qiu et al., 2011; Wu et al., 2011).

The aforementioned ReHo method uses Kendall’s coefficient of concordance (KCC) to measure the similarity or synchronization of the time courses. However, KCC is based on temporal information (particularly rank information) of time series. The KCC value will be decreased if there is time lag among the time courses and be susceptible to random noise induced by phase delay among the time courses. To overcome such limitations, a novel ReHo method, coherence-based ReHo (Cohe-ReHo) is recently proposed to measure the local synchronization of resting-state fMRI signal (Liu et al., 2010a). Moreover, Liu and colleagues demonstrate that Cohe-ReHo is more sensitive to the differences of spontaneous activity between different conditions and between different groups (Liu et al., 2010a).

To the best of our knowledge, Cohe-ReHo has not been used to measure local synchronization in depressed patients, let alone in patients with LLD. Thus, in this resting-state study, we used a well-defined cohort of patients by recruiting merely the first-episode, treatment-naive patients with LLD and carefully matched healthy control subjects. The purpose of the present study was to assess the alteration of regional activity underlying LLD pathophysiology. We hypothesized that patients with LLD may have different local activity when compared with normal controls.

2. Materials and methods

2.1. Subjects

Fifteen depressed patients aged from 60 to 79 years old and 15 age- and gender-matched healthy controls were recruited from the Mental Health Institute, the Second Xiangya Hospital, Central South University, China. This study was approved by the local ethical committee, and written informed consent was obtained from all subjects. All patients met the following inclusion criteria: (1) the diagnosis of major depressive disorder was made with the structured clinical interview for DSM-IV (SCID) by two trained and senior psychiatrists (Association AP, 1994); (2) All patients were drug-naive and at their first episode of depression; (3) 17-item Hamilton rating scale for depression (HRSQ) (Hamilton, 1967) were higher than 18 and mini-mental state examination (MMSE) (Folstein et al., 1975) scores were higher than 24; (4) absence of history of other major psychiatric illness, such as schizoaffective disorder, bipolar disorder or personality disorders and mental retardation, and history of loss consciousness, cardiovascular disease, neurological illness, and lifetime alcohol or drug abuse; (5) no history of receiving electroconvulsive therapy (ECT). All healthy controls were cognitively intact, had no history or clinical evidence of dementia, and all scored 24 or more on the MMSE. None of them had primary medical illness or neurological illness including cardiovascular illness, dementia or organic brain disorders. Additionally, T2-weighted MRI of all subjects did not show any white matter changes such as infarction or other vascular lesions and gray matter atrophy.

2.2. Data acquisition

Scanning took place on the 1.5-T GE scanner (General Electric, Fairfield, Connecticut, USA) at the Second Xiangya Hospital of Central South University in Changsha, Hunan Province, China. Headphones and foam padding were used to reduce scanner noise and minimize head movement. During the scanning, the subjects were instructed to hold still, rest with their eyes closed but not fall asleep and not think about their conditions and between different groups (Liu et al., 2010a).

2.3. Data preprocessing

Image preprocessing was carried out using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Briefly,
for each subject, the first 10 volumes were discarded to ensure stable magnetization, and for the subjects to adapt to the scanner noise. The remaining 170 volumes were first corrected for the acquisition delay between slices and head motion (a least squares approach and a 6-parameter spatial transformation). None of the subjects had more than 2 mm maximum displacement in x, y, or z and 2° of angular motion during the whole fMRI scan. Subsequently, the functional scans were spatially normalized to the Montreal Neurological Institute (MNI) EPI template in SPM8 and resampled to 3×3×3 mm³. The linear trend of the time series was removed and band-pass filtering (0.01–0.08 Hz) was performed to reduce the effects of low-frequency drift and high-frequency noises, such as the respiratory and cardiac rhythms.

Cohe-ReHo analysis was performed using the software REST (http://resting-fmri.sourceforge.net), and details were described in a recently previous study (Liu et al., 2010a). In brief, the algorithm for calculating Cohe-ReHo included three following steps. First, for any two timeseries in a given cluster, Welch’s modified periodogram averaging methods were utilized to estimate the power spectrums and cross spectrum. Second, for the two timeseries above-mentioned, their coherence across low-frequency (0.01–0.08 Hz) band with their band-averaged estimates of the cross spectrum and power spectrums was evaluated. Finally, the Cohe-ReHo within the given cluster was calculated, and the averaged coherence coefficient of the cluster was assigned to its center voxel to represent Cohe-ReHo of the cluster. Therefore, we obtained an individual Cohe-ReHo map in a voxel-wise way. The resulting data were spatially smoothed by convolution with an 8 mm full width at half maximum Gaussian kernel.

2.4. Statistical analysis

Two-sample t-tests were performed to examine the differences in age, years of education, HRSD scores and MMSE scores and chi-square test was performed to assess the differences in gender between LLD and healthy controls. The p value less than 0.05 (two-sided) was considered statistically significant. In addition, we also assessed the group differences by using two-sample t-tests between the two groups in translation and rotation of head motion according to the following formula to avoid the interference of head motion (Liu et al., 2008):

\[
\text{Headmotion/rotation} = \frac{1}{L-1} \sum_{i=2}^{L} |x_i - x_{i-1}|^2 + |y_i - y_{i-1}|^2 + |z_i - z_{i-1}|^2
\]

where L is the length of the time series (L = 170 in this study), \(x_i, y_i, \) and \(z_i\) are translations/rotations at the \(i\)th time point in the \(x\), \(y\), and \(z\) directions, respectively. To characterize the ReHo differences between two groups, voxel-based analysis of the Cohe-ReHo maps were performed with two-sample t-tests using SPM8. The resulting statistical map was corrected for multiple comparisons to a significant level of \(p<0.05\) by combining an uncorrected individual voxel \(p<0.005\) and cluster size \(>1485\) mm³ (Parameters were: individual voxel \(p \) value = 0.005, FWHM = 8 mm, 1000 simulations, confined within a gray matter mask). This correction was performed by Monte Carlo simulations to calculate the probability of false-positive detection by considering both the individual voxel probability threshold and the cluster size (Forman et al., 1995).

2.5. Correlation analysis

To examine whether clinical features of depression were related to the alteration of Cohe-ReHo, linear correlation analyses were performed. The Cohe-ReHo values for each patient were extracted from the significant clusters of the comparison and then used for the correlation analyses. Correlations between mean Cohe-ReHo values within each significant cluster and patients’ HRSD total score were analyzed. The threshold of \(p<0.05\) was considered to be significant for these analyses.

3. Results

3.1. Participants

As presented in Table 1, the two groups were matched for age (mean±SD) (67.53±6.12 years for LLD group; 64.87±7.60 years for control group; \(t=1.30, df=28, p=0.159\)), gender (both groups have 6 males and 9 females) and head motion differences (mean±SD) (Translation: 0.06±0.03 for LLD group; 0.07±0.07 for control group; \(t=0.46, df=28, p=0.650\); Rotation: 0.04±0.01 for LLD group; 0.04±0.01 for control group; \(t=0.74, df=28, p=0.460\)). Compared with healthy control subjects, patients with LLD showed significantly lower levels of MMSE score (mean±SD) (25.04±1.45 for LLD group and 28.06±1.71 for healthy controls; \(t=4.60, df=28, p<0.001\)). The shift of all subjects was no more than 2 mm, and rotation was no more than 2°.

3.2. Differences in Cohe-ReHo values between patients with LLD and control subjects

The results obtained from the two-sample t-test showed significant differences in Cohe-ReHo between LLD and healthy controls (\(p<0.005\), corrected for multiple comparisons). As shown in Table 2 and Fig. 1, compared to the healthy controls, the LLD group showed significantly decreased Cohe-ReHo in left CAU, right ACC, left DLPFC, right angular gyrus (ANG), bilateral medial prefrontal cortex (MPFC), and right PCU; and significantly increased Cohe-ReHo in left cerebellum posterior lobe, left superior temporal gyrus (STG), bilateral supplementary motor area (SMA), and right postcentral gyrus (POCG).

3.3. Correlation analysis between Cohe-ReHo values and clinical features

Linear correlation analyses showed no significant correlation between the Cohe-ReHo values in the above-mentioned significant clusters and HRSD total scores.

4. Discussion

The present study was an effort in employing Cohe-ReHo method in LLD. The most advantage of the present study is the recruitment of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics and clinical characteristics of patients with LLD and healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables (mean±SD)</td>
<td>LLD</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>6/9</td>
</tr>
<tr>
<td>Age, years</td>
<td>67.53±6.12</td>
</tr>
<tr>
<td>MMSE score</td>
<td>25.40±1.45</td>
</tr>
<tr>
<td>Illness duration, months</td>
<td>5.93±3.41</td>
</tr>
<tr>
<td>HRSD score</td>
<td>21.60±2.16</td>
</tr>
<tr>
<td>Factors in HRSD</td>
<td>–</td>
</tr>
<tr>
<td>1 Anxiety</td>
<td>5.86±1.95</td>
</tr>
<tr>
<td>2 Weight loss</td>
<td>0.37±0.68</td>
</tr>
<tr>
<td>3 Cognitive disturbance</td>
<td>4.84±1.23</td>
</tr>
<tr>
<td>4 Retardation</td>
<td>7.85±1.15</td>
</tr>
<tr>
<td>5 Sleep disturbance</td>
<td>3.59±1.58</td>
</tr>
<tr>
<td>Head motion</td>
<td>–</td>
</tr>
<tr>
<td>Translation (mm)</td>
<td>0.06±0.03</td>
</tr>
<tr>
<td>Rotation (°)</td>
<td>0.04±0.01</td>
</tr>
</tbody>
</table>

LLD, late-life depression; MMSE, mini-mental state exam; HRSD, Hamilton rating scale for depression.

<sup>a</sup> The \(P\) value for gender distribution in the two groups was obtained by chi-square test.

<sup>b</sup> The \(P\) values were obtained by two sample t-test.
a group of first-episode, treatment-naive patients with LLD. Recent studies demonstrated that the antidepressants could make the brain function of patients with depression more similar to that of healthy controls (Anand et al., 2005; Delaveau et al., 2011; Fu et al., 2007). However, previous studies usually recruited depressed patients on antidepressants; thus their findings might have been biased by the possible effects of medication.

To the best of our knowledge, no study has yet investigated alterations in cerebral function using Cohe-ReHo analysis by recruiting the first-episode, treatment-naive patients with LLD. Compared with healthy controls, significantly decreased Cohe-ReHo was found in the left CAU, right ACC, left DLPFC, right ANG, bilateral MPFC, and right PCU while significantly increased Cohe-ReHo was found in the left cerebellum posterior lobe, left STG, bilateral SMA, and right POCG. Our results suggested the presence of aberrant activities might further improve our understanding of the neural substrates in LLD.

The CAU, a key brain structure in brain networks that is involved in the regulation of cognition and mood (Lehericy and Gerardin, 2002). Depressed patients showed decreased gray matter volume in the CAU (Kim et al., 2008; Krishnan et al., 1992), and abnormal brain activities

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Table 2
Regions of decreased/increased Cohe-ReHo in patients with LLD.

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>BA</th>
<th>Volume (mm³)</th>
<th>MNI coordinates (mm)</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohe-ReHo decreased regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left CAU</td>
<td>–</td>
<td>72</td>
<td>−18 3 18</td>
<td>−3.63</td>
</tr>
<tr>
<td>Right ACC</td>
<td>32</td>
<td>57</td>
<td>12 45 12</td>
<td>−3.68</td>
</tr>
<tr>
<td>Left DLPFC</td>
<td>9</td>
<td>177</td>
<td>−42 24 36</td>
<td>−4.14</td>
</tr>
<tr>
<td>Right ANG</td>
<td>39</td>
<td>166</td>
<td>51 −48 48</td>
<td>−4.62</td>
</tr>
<tr>
<td>Bilateral MPFC</td>
<td>8/9</td>
<td>201</td>
<td>3 33 45</td>
<td>−4.50</td>
</tr>
<tr>
<td>Right PCU</td>
<td>31</td>
<td>90</td>
<td>18 −57 27</td>
<td>−3.82</td>
</tr>
<tr>
<td>Cohe-ReHo increased regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebellum posterior lobe</td>
<td>–</td>
<td>258</td>
<td>−42 −84 −24</td>
<td>5.02</td>
</tr>
<tr>
<td>Left STG</td>
<td>42</td>
<td>98</td>
<td>−60 −30 15</td>
<td>4.53</td>
</tr>
<tr>
<td>Bilateral SMA</td>
<td>4/6</td>
<td>173</td>
<td>0 −18 51</td>
<td>4.37</td>
</tr>
<tr>
<td>Right POCG</td>
<td>3</td>
<td>71</td>
<td>63 −15 21</td>
<td>3.33</td>
</tr>
</tbody>
</table>

X, y, z, coordinates of primary peak locations in the MNI space; T statistical value of peak voxel showing Cohe-ReHo differences between the LLD patients and healthy subjects. Positive T value indicates increased Cohe-ReHo, and negative T value indicates decreased Cohe-ReHo.

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Fig. 1. Cohe-ReHo differences between LLD patients and healthy controls. The color bars represent the T value of the group analysis.
during specific tasks and even during resting state (Brody et al., 2001; Wu et al., 2011). In particular, Norbury and colleagues found that patients with depression exhibited increased neuronal responses in the CAU to emotional faces during a facial expression matching task (Norbury et al., 2010). Therefore, our finding is in line with these previous studies. The ACC is a key structure in brain networks which is involved in mood regulation (Caetano et al., 2006). In addition, the ACC is thought to play a crucial role in allocating attentional resources in situations of conflicting cognitive and emotional demand (Bush et al., 2000; Kerns et al., 2004). Patients with geriatric depression had bilateral activation deficits in the dorsal ACC relative to the healthy comparison subjects in brain activation paradigms (de Asis et al., 2001). Mannie et al. found that people at high familial risk of depression showed changed modulation of the ACC in an emotional Stroop task compared with healthy controls (Mannie et al., 2008). Particularly, PET studies show decreased glucose utilization in the ACC (Drevets et al., 1997; Mayberg et al., 1999). Thus, our finding that decreased Cohe-ReHo in the ACC is compatible with these previous studies. These findings suggest that functional alteration in the CAU and ACC are closely associated with the pathophysiology of depression.

Significantly decreased Cohe-ReHo was found in the MPFC, PCC and ANG, which are located in the DMN. The DMN exhibits increased activity in the resting state and decreased activity for processing externally oriented mental activity, induced by a range of cognitive and sensory tasks (Buckner et al., 2008; Raichle et al., 2001). DMN is known to be involved in self-referential activity (Greicius et al., 2003; Raichle et al., 2001). Abnormality of the DMN in depression is found in several previous studies (Andreescu et al., 2011; Bluhm et al., 2009; Zhou et al., 2010). Therefore, it may be reasonable to assume that alterations in DMN may dysregulate some self-referential functions in LDL. The DLPC, as an important region in the cognitive control network (CCN) (Sheline et al., 2010), was altered with respect to the Cohe-ReHo in the patients with LDL. The CCN, which is involved in working memory and cognitive control function (Corbetta and Shulman, 2002), is impaired in depressed adolescents (Killgore et al., 2007). Previous study also suggested that the involvement of DLPC in depression was closely associated with the cognitive symptoms of depression (Dolan et al., 1993). Taken together, the abnormal local activities in the DLPC strongly implicates that this region is central to the pathophysiology of LDL.

Increased Cohe-ReHo in the cerebellum regions was an unexpected finding in the present study. In contrast to the many neuroimaging studies investigating cerebral cortex in depression, little attention has been paid to the alterations in the cerebellum. The cerebellum is traditionally thought as a region which coordinates motor behavior (Stein and Glickstein, 1992), but the notion that this region involved in emotional control played an important role in the perception of emotional stimuli has recently gained popularity (Lekeu et al., 2002; Schmahmann, 2000). Anatomically, the cerebellum is connected with brainstem reticular nuclei and limbic regions, including hypothalamus (Dietrichs and Zheng, 1984; Haines et al., 1984), hippocampus, and amygdala (Heath and Harper, 1974). Also, the cerebellum receives projections from the caudal and rostral anterior cingulate via the pons (Vilensky and van Hoesen, 1981). Thus, these connections may provide an anatomical foundation for the cerebellum's emotional role. Moreover, numerous neuroimaging studies have exhibited altered neural response in the cerebellum in depressed patients. Dolan et al. revealed that depressed patients with cognitive impairment have an increased blood flow in the cerebellar vermis (Dolan et al., 1992). In addition, Peng and colleagues found decreased gray matter density in the cerebellum in patients with depression compared with healthy controls (Peng et al., 2010). Recently, two studies found significantly increased KCC-ReHo in the cerebellum (Guo et al., 2011b; Liu et al., 2010b). However, the relationship between the abnormal Cohe-ReHo in the cerebellum and cerebellar volume alteration in unknown attributed to lack of structural analysis in the present study. Despite this, our results are in line with the above-mentioned findings indicating the involvement of cerebellar dysfunction in LDL.

In addition, patients with LDL showed abnormal Cohe-ReHo in the left STG, right POCG and bilateral SMA. These regions provide the critical hub in the auditory network and somato-motor network. In some sense, the perceptual systems representing the sensory system, including the auditory, visual and somato-motor networks, can be thought as the lower-order of the cognitive processing hierarchy. According to our results, the significantly abnormal in the auditory processing network (STG) and sensory processing (POCG and SMA) may contribute to perceptual impairments in patients with LDL, which are consistent with previous studies (Guo et al., 2011b; Yuan et al., 2008).

Unfortunately, no correlation was found between the abnormal Cohe-ReHo in any significantly different brain region detected in our study in patients with LDL and the HRSD total scores. Although this finding might be confounded by the small sample size, it is possible that the alterations of Cohe-ReHo in these regions may be a trait marker for patients with LDL regardless of the severity of symptoms.

5. Study limitations

In addition to the limited sample size, several methodological issues should be considered in explaining the results. First, as in all the resting-state fMRI studies, some inevitable physiological noise, such as respiratory and cardiac fluctuations of the subject during scanning may influence the stability of resting-state fMRI signals. Although we tried to correct such noises, we could not fully eliminate the effects of these noises. In future studies, simultaneous cardiac recording may provide a rigorous correction. Second, although Cohe-ReHo analysis is regarded as a complementary method to reveal human brain function, its exact neural mechanism remains to be fully characterized. Further investigation should be focused on the neural mechanism underlying Cohe-ReHo. Finally, we merely focused on the low frequency BOLD signals (0.01–0.08 Hz) by employing a band filtering. Thus, there might be a loss of higher frequency information about LDL.

6. Conclusion

In summary, in our present study, we observed abnormal local activity in patients with LDL compared to the healthy controls. These results indicated that the altered activity have already existed in the initial stage of LDL, because our case group only included first-episode, treatment-naive patients with LDL. Moreover, such findings shed light on the pathophysiological mechanisms underlying LDL. Further work combining different modalities may contribute to providing more information about this disorder.

Acknowledgments

The authors thank the editor and anonymous reviewers for constructive suggestions. This work was supported by the 973 project 2012CB517901, the Natural Science Foundation of China 61125304, 30900483, 81171406 and 91132721, and the Fundamental Research Funds for the Central Universities.

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