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

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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.

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

Abbreviations: LLD, late-life depression; fMRI, functional magnetic resonance imaging; Cohe-ReHo, coherence-based regional homogeneity; PET, positron emission tomography; PCU, precuneus; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; CAU, caudate nucleus; DMN, default mode network; KCC, Kendall's coefficient of concordance; SCID, structured clinical interview for DSM-IV; HRSD, Hamilton rating scale for depression; MMSE, mini-mental state examination; ECT, electroconvulsive therapy; AC–PC, anterior commissure–posterior commissure; MNI, Montreal Neurological Institute; ANG, angular gyrus; MPFC, medial prefrontal cortex; STG, superior temporal gyrus; SMA, supplementary motor area; POCG, postcentral gyrus; CCN, cognitive control network.

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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). With 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 diagnose 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 (HRSD) (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 of anything in particular. A total of 180 volumes were acquired using a single-shot, gradient-recalled echo-planar imaging sequence (repetition time = 2000 ms, echo time = 40 ms and flip angle = 90°). Twenty axial slices (field of view = 24 cm, in-plane matrix = 64×64, slice thickness = 5 mm, gap = 1 mm, voxel size = $3.75 \times 3.75 \times 6$), aligned along the anterior commissure–posterior commissure (AC–PC) line were acquired. After the experiment, each participant was asked some questions to confirm the degree of cooperation.

2.3. Data preprocessing

Image preprocessing was carried out using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Briefly,