Preliminary communication

Abnormal neural activities in first-episode, treatment-naïve, short-illness-duration, and treatment-response patients with major depressive disorder: A resting-state fMRI study

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Background: Abnormality of limbic–cortical networks was postulated in depression. Using a regional homogeneity (ReHo) approach, we explored the regional homogeneity (ReHo) of the brain regions in patients with first-episode, treatment-naïve, short-illness-duration, and treatment-response depression in resting state to test the abnormality hypothesis of limbic-cortical networks in major depressive disorder (MDD).

Methods: Seventeen patients with treatment-response MDD and 17 gender-, age-, and education-matched healthy subjects participated in the resting-state fMRI scans.

Results:
1. The MDD group showed a significant lower ReHo in the left cerebellum posterior lobe, the right fusiform gyrus, the left parahippocampal gyrus, and the right postcentral gyrus compared with healthy subjects (p<0.05, corrected).
2. Relative to healthy subjects, a significant higher ReHo was found in the right inferior temporal gyrus in the MDD group (p<0.05, corrected).

Conclusions: Our findings suggested the abnormality of limbic–cortical networks in first-episode, treatment-naïve, short-illness-duration, and treatment-response MDD patients, and added an expanding literature to the abnormality hypothesis of limbic-cortical networks in MDD.

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Resting state
Regional homogeneity

1. Introduction

Characterized by a persistent depressed mood, anxiety and dysphoria, psychomotor changes, alterations of motivation and social behavior, and sleep abnormalities (American Psychiatric Association, 1994), major depressive disorder (MDD) will be the second cause of global disease burden by the year 2020. As the most common psychiatric disorder and the most important precursor of suicide (Montgomery, 2006), MDD is remarkable by a decline in both well-being
and daily functioning, a high risk of functional impairment and mortality, and a high rate of medical service utilization (Taki et al., 2005). However, the diagnosis of MDD is merely dependent on clinical signs and symptoms, and the pathogenesis of MDD remains unclear.

Recent techniques such as imaging techniques make it feasible to explore the structural and functional abnormalities associated with MDD. Thus it may lead to a better understanding of the neuropathology and the development of effective antidepressants (Fagioli and Kupfer, 2003). During the last decade, numerous positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have greatly advanced our understanding of the pathogenesis of MDD. An abnormality of the limbic–cortical networks is assumed to play a vital role in the pathogenesis of MDD. Abnormal neural activity in MDD has been consistently postulated in these studies, with predominantly decreased neural activation of cortical brain areas such as the dorsolateral prefrontal cortex (Anand and Shekhar, 2003; Ketter, 1996; Mayberg et al., 1999) and anterior cingulate cortex (Drevets et al., 1997), but increased activation of limbic regions such as medial thalamus, striatum, and amygdala (Drevets, 2000; Mayberg et al., 1999; Sheline et al., 2001; Siegle et al., 2002). In addition, accumulating evidences have shown that tempo-limbic circuit in the limbic–cortical networks is a critical node in the neural circuitry mediating MDD (Mayberg, 2003; Phillips et al., 2003). However, brain regions shown in these studies are always, to some extent, different, and the results are not consistent yet. Multiple factors can confound the results. Confounds associated with illness chronicity, such as the illness duration, the number of episode, the antidepressive medication and the treatment response to the antidepressants, may have contributed to the inconsistency across studies. Thus it is helpful to explain the variety of results by considering such factors.

Yet the investigation of the first-episode, treatment-naive, short-illness-duration, treatment-response patients with depression may be important in elucidating the core pathogenesis of this illness.

Increasing attention has been paid to resting-state fMRI since the first resting-state fMRI study of Biswal et al. (1995), who found that low-frequency fluctuation was highly synchronous among motor cortices in healthy humans, concluding that the low-frequency fluctuation was indeed a neurophysiological index. Since then, resting-state fMRI has been well conducted in patients with many psychiatric disorders, such as schizophrenia, depression and attention deficit hyperactivity disorder (ADHD) (Greicius et al., 2007; Tian et al., 2006; Yao et al., 2009; Zhou et al., 2007). However, most of these studies have measured the correlation coefficients of all brain regions with predefined region of interest (ROI) by using a functional connectivity analysis method (Greicius et al., 2007). One brain region exhibiting abnormal functional connectivity with other regions may not be necessarily abnormal itself. Therefore, it is important to explore the regional activity.

Regional homogeneity (ReHo), a recently proposed method, reflects the temporal homogeneity of the regional blood oxygen level-dependent (BOLD) signal rather than its density. Abnormal ReHo is possibly relevant to the changes of temporal aspects of neural activity in the regional area, and may be used to detect abnormal neural activity in the entire brain regions (Zang et al., 2004). Kendall’s coefficient of concordance (KCC) was used to measure the similarity or synchronization of the time series of nearest neighboring voxels (usually 27 voxels) on the assumption that a voxel was temporally similar to those of its neighbors (Tononi et al., 1998). The ReHo method had been well used to investigate regional neural activity in the resting state in the studies of other psychiatric disorders, including schizophrenia (Liu et al., 2006; Shi et al., 2007) and ADHD (Cao et al., 2006). To update, only five papers, including our study (Guo et al., 2011), were found to detect regional neural activity in depression in the resting state by using the ReHo method (Liu et al., 2010; Wu et al., 2010; Yao et al., 2009; Yuan et al., 2008). Two of them revealed that abnormal brain activity was distributed extensively in remitted geriatric depression (Yuan et al., 2008) and major depression (Yao et al., 2009) in the resting state. Liu et al. (2010) found that subjects with MDD and those at high risk for MDD exhibited significantly decreased ReHo in the right insula and the left cerebellum. Two resting-state fMRI studies on treatment-resistant depression (TRD) reported that the TRD patients showed abnormal neural activities in multiple cerebral regions (Guo et al., 2011; Wu et al., 2010). Little attention was paid to the heterogeneity of MDD when recruiting patients in these studies. So it is meaningful to perform a resting-state fMRI in the first-episode, treatment-naive, short-illness-duration, treatment-response MDD patients.

To address these questions, in this resting-state study, we try to purify the MDD patients by recruiting merely the first-episode, treatment-naive, short-illness-duration, treatment-response patients. We hypothesize that abnormal ReHo will be discovered in certain regions of the limbic–cortical networks in the early course of the treatment-response MDD patients. These abnormalities may be a stable trait marker for the diagnosis of MDD. To test this hypothesis, we compared the ReHo of the whole brain regions between the treatment-response MDD patients and healthy subjects.

2. Methods

2.1. Subjects

Twenty-six right-handed MDD patients, age 18–43 years, were originally recruited from the Mental Health Institute, the Second Xiangya Hospital, Central South University, China. Major depression was diagnosed by two qualified psychiatrists (Dr Zhao J and Dr Liu Z) using the Structured Clinical Interview according to the DSM-IV criteria (American Psychiatric Association, 1994). All patients were at their first episode of MDD and treatment-naive. Exclusion criteria included any history of loss consciousness, substance abuse within the 6 months prior to the scan, mental retardation, or any history of serious medical or neurological illness, and any lifetime psychiatric disorder. An additional exclusion criterion for the patients was that the current illness duration was no more than 6 months. The severity of depression was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). After fMRI scanning, all patients were directed to take antidepressants at a minimum dose of 150 mg/day of imipramine equivalents (dose converted using a conversion table; Idaka et al., 1997) for 6 weeks by two qualified psychiatrists (Dr Zhao J and Dr Liu Z). The drugs included one of the three typical classes of antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor
(SSRIs) and serotonin–norepinephrine reuptake inhibitor (SNRIs). The treatment-response was defined as a more than 50% reduction in the HRSD score after the antidepressive treatment, consistent with previous studies (Gong et al., 2011; Furtado et al., 2008; Shah et al., 2002; Nierenberg and Amsterdam, 1990). Data from seven patients were excluded due to treatment non-response, and data from two patients were excluded from further analysis due to excessive head motion (see ReHo data analysis).

Seventeen right-handed healthy subjects, partially came from our previous ReHo study (Guo et al., 2011), were recruited from the community. They were also interviewed by two qualified psychiatrists (Dr Zhao J and Dr Liu Z) using the Structured Clinical Interview for DSM-IV, nonpatient edition (American Psychiatric Association, 1994). None of them had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives, and were well matched with the patients for age, gender, years of education.

Clinical and demographic data from the remaining 34 participants are shown in Table 1. All subjects were given information about the procedures and gave written informed consent via forms approved by the Ethics Committee of the Second Xiangya Hospital, Central South University.

### 2.2. Scan acquisition

Imaging was performed on a 1.5T GE scanner (General Electric, Fairfield, Connecticut, USA) equipped with high-speed gradients. The participants were asked to use a prototype quadrature birdcage head coil fitted with foam padding to minimize head movement. They were informed to remain motionless, keep their eyes closed and not think of anything in particular. The following parameters were used for T1 anatomical imaging axially: repetition time/echo time (TR/TE) = 1924/7.5 ms, 20 slices, 256×256 matrix, 90° flip angle, 24 cm field of view (FOV), 5 mm section thickness and 1 mm gap. At the same locations to anatomical slices, functional images were acquired by using an echoplanar imaging sequence with the following parameters: TR/TE = 2000/40 ms, 20 slices, 64×64 matrix, 90° flip angle, 24 cm FOV, 5 mm section thickness and 1 mm gap. For each participant, the fMRI scanning lasted for 6 min and 180 volumes were obtained.

### 2.3. ReHo data analysis

Image preprocessing was conducted using statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuro-science, London, UK). The fMRI images were corrected for the acquisition delay between slices and for the head motion. Motion time courses were obtained by estimating the values for translation (mm) and rotation (degrees) for each subject. The participants should have no more than 3 mm maximum displacement in x, y, or z and 3° of angular motion during the whole fMRI scan. Two patients’ data were excluded from further analysis because of excessive head movement. After slice acquisition correction and head-motion correction, the fMRI images were normalized to the standard SPM8 echoplanar imaging template, resampling to 3 * 3 * 3 mm³. The resulting fMRI data were temporally band-pass filtered (0.01–0.08 Hz) to reduce low-frequency drift and physiological high frequency respiratory and cardiac noise for further ReHo analysis, also including time series linear detrending.

Regional homogeneity analysis was performed with in-house software REST (http://resting-fmri.sourceforge.net). Individual ReHo maps were generated by calculating the KCC of the time series of a given voxel with those of its nearest neighbors (26 voxels) in a voxel-wise analysis. The formula for calculating the KCC value has been expounded in a previous study (Zang et al., 2004). To reduce the influence of individual variations in the KCC value, normalization of ReHo maps were done by dividing the KCC among each voxel by the averaged KCC of the whole brain. Then the averaged ReHo maps were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum and we performed group statistical analysis using SPM8.

The resulting statistical map was set at p<0.05 (corrected for multiple comparison, with a combined individual voxel p value<0.005 with cluster size >1323 mm³).

### 3. Results

#### 3.1. Subjects

Seventeen MDD patients and 17 healthy subjects completed the whole study. The results of HRSD rating are shown in Table 1. The MDD group and the control group did not differ significantly in age, gender and years of education.

#### 3.2. ReHo: MDD patients vs control subjects

As shown in Tables 2 and 3 and Fig. 1, the MDD group showed a significant lower ReHo in the left cerebellum posterior lobe, the right fusiform gyrus, the left parahippocampal gyrus, and the right postcentral gyrus (p<0.05, corrected). A significant higher ReHo was found in the right inferior temporal gyrus (p<0.05, corrected).

### Table 2

| Brain regions with higher ReHo in the treatment-response MDD patients. |
|------------------|---|---|---|---|---|
| Brain regions of higher ReHo | X | Y | Z | T | Voxel size |
| MDD-HS patients vs controls (MDD-HS) | 51 | −3 | −48 | 4.015 | 65 |
| p<0.05 (corrected for multiple comparison, with a combined individual voxel p value<0.005 with cluster size >1323 mm³). |

MDD = major depressive disorder.

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Table 3
Brain regions with lower ReHo in the treatment-response MDD patients.

<table>
<thead>
<tr>
<th>Brain regions of lower ReHo patients vs controls (MDD-HS)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>T</th>
<th>Voxel size</th>
</tr>
</thead>
<tbody>
<tr>
<td>The left cerebellum posterior lobe</td>
<td>−30</td>
<td>−54</td>
<td>−60</td>
<td>−3.996</td>
<td>70</td>
</tr>
<tr>
<td>The right fusiform gyrus</td>
<td>42</td>
<td>−30</td>
<td>−15</td>
<td>−4.108</td>
<td>98</td>
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<tr>
<td>The left parahippocampal gyrus</td>
<td>−21</td>
<td>−39</td>
<td>−9</td>
<td>−4.102</td>
<td>94</td>
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<tr>
<td>The right postcentral gyrus</td>
<td>66</td>
<td>−6</td>
<td>15</td>
<td>−4.061</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Brain regions with higher ReHo in the treatment-response MDD patients.</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>T</th>
<th>Voxel size</th>
</tr>
</thead>
<tbody>
<tr>
<td>The left parahippocampal gyrus</td>
<td>62</td>
<td>−62</td>
<td>−15</td>
<td>5.996</td>
<td>94</td>
</tr>
<tr>
<td>The right postcentral gyrus</td>
<td>47</td>
<td>52</td>
<td>−15</td>
<td>5.996</td>
<td>94</td>
</tr>
</tbody>
</table>

4. Discussion

To the best of our knowledge, this is the first resting-state fMRI to examine MDD by means of the ReHo analysis in an attempt to purify MDD by recruiting the first-episode, medication-naïve, treatment-response, and short-illness-duration MDD patients. The primary finding in this study is that the MDD group exhibited a significant lower ReHo in the left cerebellum posterior lobe, the right fusiform gyrus, the left parahippocampal gyrus, and the right postcentral gyrus, and a significant higher ReHo in the right inferior temporal gyrus, relative to the healthy subjects group. The brain regions detected in the current study are mainly involved in the limbic–cortical networks. Thus the present study adds an additional literature to the dysregulation model of the limbic–cortical networks in the treatment-response MDD patients.

The lower ReHo in the left cerebellum was unexpected in the current study. The cerebellum is traditionally regarded as a region affecting mood and cognitive processing, however, remains unclear. The cerebellum not only projects to multiple areas of the prefrontal cortex, but also connects with the limbic regions, including the amygdala, the hippocampus and the septal nuclei. Recently, decreased ReHo in the cerebellum was found in MDD patients and their first-degree relatives (Liu et al., 2010). Additionally, cerebellar volume reduction has been reported in patients with depression (Pillay et al., 1997). Although the relation between cerebellar volume reduction and decreased ReHo in the cerebellum is unknown due to lack of structural analysis in the current study, our results are consistent with the above findings, suggesting that abnormal neural activities in the cerebellum exist in the early stage in the patients with treatment-response depression. Impairments of the neural activities in the cerebellum may partially underlay emotional and cognitive symptoms seen in the MDD patients.

The fusiform gyrus is assumed to be involved in facial processing (Kanwisher et al., 1997). Accurate facial processing is important for social function, and it may in turn affect individual emotion. A negative emotional bias in the activity of the right fusiform gyrus was reported by Surguladze et al. (2005). In their study, depressed individuals demonstrated a positive response to sad expressions and neutral response to happy expressions in the right fusiform gyrus, while healthy subjects showed positive response to happy expressions in the bilateral fusiform gyrus. Our study showed a lower ReHo in the right fusiform gyrus in the patients with treatment-response depression, together with the previous studies, indicated a participation of the fusiform gyrus in the negative cognitive models (Beck, 1976; Yao et al., 2009), and might result in social avoidance observed in the MDD patients.

Surrounding the hippocampus, the parahippocampal gyrus plays an important role in memory encoding and retrieval (Reuter, 2005). Previous fMRI studies indicate that this brain region becomes highly active when healthy subjects view topographical scene stimuli such as images of landscapes, or cityscapes (Aguirre et al., 1996; 1998; Epstein and Kanwisher, 1998; Ishai et al., 1999). The observation of decreased ReHo in the left parahippocampal gyrus is in line with previous reports.
of hippocampal abnormalities in MDD patients (Mervaala et al., 2000; Shah et al., 2002; Zhang et al., 2009). Recently, Furtado et al. (2008) found a volume reduction in the entorhinal cortex which has intimate anatomical and functional connections with the parahippocampal gyrus. Moreover, parahippocampal gyrus communicates with higher-order association cortical regions (i.e. the anterior cingulate) (Zhang et al., 2009). Abnormal neural activities in the left parahippocampal gyrus may lead to a disconnection syndrome and partly contribute to hypomnesia exhibited by the MDD patients.

In addition, the patients with treatment-response depression showed a lower ReHo in the right postcentral gyrus, and a higher ReHo in the right inferior temporal gyrus. The postcentral gyrus is conceived as primary somatosensory cortex, and receives the bulk of the thalamocortical projection from the sensory input fields. The inferior temporal gyrus connects with the inferior occipital gyrus and extends around the infero-lateral border on to the inferior surface of the temporal lobe. A recent study shows that the right inferior temporal gyrus is a critical node in a widespread network of frontal, temporal, parietal, occipital and sub-cortical structures, which have diagnostic and prognostic prediction to the antidepressive treatment response (Gong et al., 2011). Our results are in line with this study. It is one of the higher levels of the ventral stream of visual processing. Abnormal neural activities in the right postcentral gyrus and the right inferior temporal gyrus may be related to hypomnesia or senestopathy in the patients with depression.

5. Study limitations

The current study is firstly limited by the heterogeneous pharmacological profiles. Though directed by two qualified psychiatrists, one patient may show treatment nonresponse to an antidepressant but treatment response to another. Thus some possible treatment response patients might be classified as treatment nonresponse patients and excluded from the study. This heterogeneity might limit the translational value of our findings.

In addition to a relatively small sample size, potential heterogeneity might have biased our results because detailed subtypes of MDD were not comprehensively undertaken, though we attempted to purify the MDD patients by the relatively critical recruitment criteria in the current study.

Like other studies using resting-state fMRI, we could reduce but could not completely eliminate the effects of physiological noises such as respiratory and heart rhythm by using a relatively low sampling rate (TR = 2 s). However, it would be difficult to cover the whole brain by using a relatively short TR (i.e. 200 ms). In the future, a more rigorous approach should be applied to remove such physiological noises.

6. Conclusions

Despite these limitations, our findings first suggested that the patients with treatment-response depression have had abnormal neural activities in several brain regions in the limbic–cortical networks, mainly in the temporoparietal, postcentral gyrus and the cerebellum, even in the early course of the disease, with a significant lower ReHo in the left cerebellum posterior lobe, the right fusiform gyrus, the left parahippocampal gyrus, and the right postcentral gyrus, and a significant higher ReHo in the right inferior temporal gyrus. The current findings encourage replication and emphasize the need for larger scale prospective ReHo studies to determine whether the abnormalities could be referred to trait or state marks in MDD patients.

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Conflict of interest

No conflict of interest declared.

Acknowledgments

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References


