Abnormal neural activity of brain regions in treatment-resistant and treatment-sensitive major depressive disorder: A resting-state fMRI study

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1. Introduction

Major depressive disorder (MDD) is characterized by persistent and pervasive feelings of sadness, guilt, anhedonia, and worthlessness. Patients with MDD have remarkably declined well-being and daily functioning, and a high rate of medical service utilization (Petersen et al., 2001; Taki et al., 2005). Despite the progress in the development of antidepressants over the past 50 years, approximately 30% of patients do not respond to standard antidepressant treatments. Patients who fail standard antidepressant treatments are classified as having treatment-resistant depression (TRD) (Stimpson et al., 2002; Williams et al., 2011). Treatment of...
TRD remains a serious challenge for psychiatrists (Bschor, 2010; Little, 2009).

To develop more effective treatment for MDD, especially for TRD, it requires better understanding of the neurobiological basis of MDD (Fagioli and Kuperf, 2003). During the last decade, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have greatly advanced the knowledge of the pathogenesis of MDD. Abnormal neural activity in the limbic-cortical networks has been observed. Some studies demonstrate 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 others found 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). The inconsistency suggests that the pathogenesis of depression may depend on a disturbed limbic-cortical networks rather than an abnormal function of a discrete brain region (Davidson et al., 2002). Undoubtedly, to assess the neural activity of all brain regions will help us to understand the pathogenesis of MDD.

During the first resting-state fMRI (RS-fMRI) study, Biswal et al. (1995) found that low-frequency (0.01–0.08 Hz) fluctuations in blood oxygenation level-dependent (BOLD) signals are highly synchronous among the sensorimotor cortices of healthy human brain. Since then, RS-fMRI has gained popularity. The RS-fMRI has been used in patients with different psychiatric disorders such as schizophrenia, depression, or attention deficit hyperactivity disorder (ADHD) (Greicius et al., 2007; Tian et al., 2006; Yao et al., 2009; Zhou et al., 2007). However, the vast majority of these studies have investigated the correlation coefficients of all brain regions with predetermined region of interest (ROI) by using a functional connectivity analysis (Greicius et al., 2007). The limitation of this method is that even if one brain region shows abnormal functional connectivity with other region(s), it does not mean that the ROI is abnormal itself. For this reason, functional connectivity study provides little information about local regional neural activity. Therefore, it is important to explore regional activity of brain regions with different methodology.

Regional homogeneity (ReHo), a recently proposed method (Zang et al., 2004), can measure the similarity or synchronization of the time series of nearest neighboring voxels (usually 27 voxels). This method is based on the assumption that a voxel is temporally similar to those of its neighbors (Tononi et al., 1998). The ReHo method has been applied to detect local abnormality in some psychiatric disorders, such as schizophrenia (Liu et al., 2006; Shi et al., 2007), ADHD (Cao et al., 2006) and autism (Paakki et al., 2010). Up to now, only six studies including two of our own studies (Guo et al., 2011a, 2011b) have used the ReHo method to measure the resting-state regional neural activity in patients with MDD (Liu et al., 2010b; Wu et al., 2011; Yao et al., 2009; Yuan et al., 2008). Extensive abnormal brain activity was observed in patients with remitted geriatric depression (Yuan et al., 2008) and young adults with major depression (Guo et al., 2011a; Yao et al., 2009). Decreased ReHo in the right insula and the left cerebellum was found in the subjects with MDD and those at high risk for MDD (Liu et al., 2010b). Similarly, abnormal neural activities in multiple cerebral regions were identified in patients with TRD (Guo et al., 2011b; Wu et al., 2011). The above-mentioned ReHo method is also known as KCC–ReHo because it adopts Kendall’s coefficient of concordance (KCC) (Kendall and Gibbons, 1990) to measure the similarity of time-series of voxels. The KCC–ReHo is based on temporal information (particularly rank information) of the time-series. The KCC value will decrease if there is time lag among the time courses. Therefore, the KCC value is susceptible to random noise induced by phase delay among the time-series. To overcome this limitation, the coherence-based ReHo (Cohe-ReHo) has been developed to measure the local synchronization of RS-fMRI signals (Liu et al., 2010a). Coherence is insensitive to phase variability such as random noise across the time-series. The increased sensitivity to detecting the differences in spontaneous neural activity between ADHD and normal controls with Cohe-ReHo is believed due to the insensitivity of the Cohe-ReHo to random noises (Liu et al., 2010a).

To the best of our knowledge, the Cohe-ReHo has not been used to measure local synchronization in patients with MDD. The aim of the current study was to use the Cohe-ReHo to measure the local synchronization of RS-fMRI signals in patients with TRD or treatment-sensitive depression (TSD) and healthy subjects (HS). We hypothesized that the abnormal neural activity in different brain regions of patients with TRD would be different from those with TSD and/or HS.

2. Methods

2.1. Subjects

Twenty-four right-handed patients with TRD were originally recruited from the Mental Health Institute of the Second Xiangya Hospital at the Central South University, China. Patients were consecutively recruited between July 2006 and August 2007. The diagnosis of MDD was confirmed by two experienced psychiatrists (Dr Zhao J and Dr Liu Z) using the Structured Clinical Interview according to the DSM-IV criteria (First et al., 1997). Depression severity was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). Treatment-resistance was determined as nonresponsiveness to at least two adequate trials of different types of antidepressants. The adequate trial was defined as adequate dose (a minimum dose of 150 mg/day of imipramine equivalents), adequate duration (6 weeks), and compliance, which was consistent with previous studies (Furtado et al., 2008; Guo et al., 2011b; Shah et al., 2002). The dose conversion was used as a conversion table (Idak et al., 1997). The nonresponsiveness was defined as less than 50% reduction in HRSD scores (Nierenberg and Amsterdam, 1990) after an adequate trial. Only patients who scored 18 or greater on HRSD total score and have taken at least two types of antidepressants before participating in the study were included. Exclusion criteria for this group included any history of loss consciousness, substance use disorder within the six months prior to the scan, mental retardation, or any history of serious medical or neurological illness, any lifetime psychiatric disorder, and younger than 18 years or older than 60 years.

For patients with TSD, thirty-one right-handed, first-episode, treatment-naïve patients with MDD were initially recruited from the same hospital between July 2006 and August 2007. The exclusion criteria were similar to those of TRD patients, but the illness duration for this group was no more than 6 months. The patients were directed to take an antidepressant at a minimum dose of 150 mg/day of imipramine equivalents (dose converted using a conversion table) (Idak et al., 1997) for 6 weeks immediately after the fMRI scan. One of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor (SSRIs), or serotonin–norepinephrine reuptake inhibitor (SNRIs) was used. Treatment response was defined as more than 50% reduction in the HRSD total score after an adequate treatment, which was also consistent with previous studies (Furtado et al., 2008; Guo et al., 2011a; Shah et al., 2002).

For the control, twenty-three right-handed HS were recruited from the community through advertisement. The Structured Clinical Interview for DSM-IV, non-patient edition (First et al., 1997) was used to screen the HS. None of them had serious medical or
neuropsychiatric illness. There was no major psychiatric or neurological illness in their first-degree relatives. The controls were matched to the two groups of patients with age, gender and years of education.

Participants were given information about the study procedures. Written informed consent was obtained from all participants and the study was approved by the Ethics Committee of the Second Xiangya Hospital at the Central South University.

2.2. Scan acquisition

MRI data were acquired using a 1.5T GE scanner (General Electric, Fairfield, Connecticut, USA) equipped with high-speed gradients. A prototype quadrature birdcage head coil fitted with foam padding was applied to minimize head movement. Subjects were required to remain motionless, keep their eyes closed, and not think of anything in particular during image acquisition. After a localizer scan and conventional structural imaging was completed, functional images were acquired by using an echoplanar imaging sequence with the following parameters: TR/TE = 2000/40 ms, 20 slices, 64 x 64 matrix, 90° flip angle, 24 cm FOV, 5 mm section thickness and 1 mm gap.

2.3. Cohe-ReHo data analysis

The first 10 volumes of each subject were discarded to ensure steady state conditions during the analyzed portion of the data. Image preprocessing was performed by statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuro-science, London, UK). The steps included slice timing, head motion correction, and spatial normalization. Linear trend removing and band-pass (0.01–0.08 Hz) filtering were conducted by software REST (http://resting-fmri.sourceforge.net).

The algorithm for calculating the Cohe-ReHo included three steps. First, Welch’s modified periodogram averaging methods were used to estimate the power spectrums and cross spectrum in a given cluster. Second, the coherence across the low-frequency (0.01–0.08 Hz) band with the band-averaged estimates of the cross spectrum and power spectrum was calculated. Third, 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 the Cohe-ReHo of the cluster. Thus, we were able to obtain an individual Cohe-ReHo map in a voxel-wise way. All these steps were performed with software REST. The details of these steps were described in a previous study (Liu et al., 2010a).

2.4. Statistical analysis

Distributions of age and years of education among the three groups were compared with one-way analysis of variance (ANOVA). Chi-square test was used to compare gender distributions. A two-sample t-test was used to compare the illness duration and HRSD total scores between the two groups of patients with MDD.

Voxel-based comparison of entire brain Cohe-ReHo maps with ANOVA was conducted in REST with a significance threshold of p < 0.05 for multiple comparison. The age was used as a covariate to avoid any undetected age effect although age was not significantly different among three groups. Post hoc t-tests were performed to identify differences between each pair of groups. Illness duration was also used as a covariate in the post hoc t-test between TRD and TSD groups to minimize any potential influence of this variable. The resulting statistical map was set at p < 0.05 (corrected for multiple comparison, with a combined individual voxel p value of <0.05 and a cluster size > 10,503 mm³). Brain regions showing significant differences between TRD and TSD groups were identified as ROI from where the regional mean Cohe-ReHo values were extracted for further correlation analysis with HRSD total scores and illness duration.

3. Results

3.1. Subjects

Data from 7 treatment-naive patients were excluded from further analysis due to treatment non-response; 3 HS were excluded due to withdrawal of the consents after structural fMRI scanning; and additional 4 subjects (1 TRD, 2 TSD, 1 HS) were excluded due to excessive head movement (more than 3 mm maximum displacement in x, y, z or 3° of angular motion during the scan) during the fMRI acquisition. Therefore, the data of 23 TRD patients, 22 TSD patients and 19 HS were available and used for all analyses. Demographic information, illness duration, and HRSD total scores were presented in Table 1. The three groups did not differ significantly in age, gender and years of education. There was no significant difference in HRSD total scores between the two groups of patients with MDD, however, the TRD group had longer illness duration than the TSD group.

3.2. Group differences in Cohe-ReHo

As shown in Fig. 1A, significant group differences in the Cohe-ReHo were detected in bilateral superior frontal gyrus, bilateral cerebellum, left inferior temporal gyrus (including left fusiform gyrus), left occipital cortex, and right fusiform gyrus by ANOVA. Using age as covariate, lower Cohe-ReHo values were observed in the TRD group in bilateral superior frontal gyrus and left cerebellum compared with HS (Table 2 and Fig. 1B). In contrast, lower Cohe-ReHo values were mainly found in bilateral superior frontal gyrus in the TSD group relative to HS (Table 2 and Fig. 1C). Compared to the TSD group, the TRD group showed significantly lower Cohe-ReHo in bilateral cerebellum and higher Cohe-ReHo in left fusiform gyrus. The comparison between the two groups of patients with MDD was performed with age and illness duration as covariates (Table 2 and Fig. 1D).

3.3. Correlations between Cohe-ReHo values and HRSD scores or illness duration

To investigate the relationship between the Cohe-ReHo values and HRSD scores or illness duration in patients with MDD, we computed the Pearson’s correlation coefficients between the Cohe-ReHo of the bilateral cerebellum or the left fusiform gyrus and HRSD scores or illness duration in the combined TRD and TSD groups.

Table 1

<table>
<thead>
<tr>
<th>Variables (Mean ± SD)</th>
<th>TRD</th>
<th>TSD</th>
<th>HS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (M/F)</td>
<td>23(11/12)</td>
<td>22(12/10)</td>
<td>19(10/9)</td>
<td>0.898*</td>
</tr>
<tr>
<td>Age, years</td>
<td>27.35 ± 7.26</td>
<td>28.09 ± 9.91</td>
<td>24.37 ± 4.18</td>
<td>0.269p</td>
</tr>
<tr>
<td>Education, years</td>
<td>13.13 ± 3.44</td>
<td>12.23 ± 2.62</td>
<td>13.11 ± 2.47</td>
<td>0.510p</td>
</tr>
<tr>
<td>Illness duration, months</td>
<td>27.43 ± 35.89</td>
<td>29.5 ± 17.3</td>
<td>25.89 ± 6.26</td>
<td>0.004*</td>
</tr>
<tr>
<td>HRSD score</td>
<td>24.52 ± 4.17</td>
<td>25.89 ± 6.26</td>
<td>25.89 ± 6.26</td>
<td>0.407*</td>
</tr>
</tbody>
</table>

TRD = treatment-resistant depression.
TSD = treatment-sensitive depression.
HS = healthy subjects.
* The P value for gender distribution in the three groups was obtained by chi-square test.
p The P values were obtained by one-way analysis of variance tests.
* The P values were obtained by two sample t-test.
groups. No correlation was found between the mean Cohe-ReHo values in the two brain regions and HRSD scores in the combined patients. However, there was a significant negative correlation between the mean Cohe-ReHo values in the left fusiform gyrus and illness duration in the pooled patients with MDD ($r = 0.480, p = 0.001$).

### 3.4. The cerebellum Cohe-ReHo analysis

As mentioned above, the bilateral cerebellum was a brain region where the significant difference in Cohe-ReHo existed between the two groups of patients with MDD, which provided a possibility that the Cohe-ReHo of the bilateral cerebellum might be used as a marker to differentiate TRD patients from TSD patients. To explore this possibility, we first obtained the mean Cohe-ReHo value of each patient within a cerebellum mask (Fig. 2) that was generated from areas of the cerebellum with significant between-group Cohe-ReHo differences. Then, the group difference was analyzed using t-test. As expected, a significant difference between the two groups was detected ($t = -4.048, p < 0.001$).

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**Table 2**

Regions showing Cohe-ReHo difference among the TRD, TSD groups and HS.

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>Cluster size (mm$^3$)</th>
<th>MNI coordinates</th>
<th>$T$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRD &lt; healthy subjects</td>
<td>40,446</td>
<td>$x = -18$, $y = -12$, $z = 72$</td>
<td>5.30</td>
</tr>
<tr>
<td>Left cerebellum</td>
<td>16,362</td>
<td>$x = -9$, $y = -39$, $z = 39$</td>
<td>4.27</td>
</tr>
<tr>
<td>TSD &lt; healthy subjects</td>
<td>34,020</td>
<td>$x = -9$, $y = 0$, $z = 72$</td>
<td>8.45</td>
</tr>
<tr>
<td>TRD &lt; TSD</td>
<td>19,710</td>
<td>$x = -39$, $y = -66$, $z = -42$</td>
<td>4.56</td>
</tr>
<tr>
<td>Left fusiform gyrus</td>
<td>12,177</td>
<td>$x = -30$, $y = 93$, $z = 0$</td>
<td>4.00</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 difference among the TRD, TSD groups and HS. $p < 0.05$, corrected for multiple comparisons.

TRD = treatment-resistant depression.

TSD = treatment-sensitive depression.

HS = healthy subjects.
To explore the sensitivity and specificity of using cerebellar Cohe-ReHo values to differentiate TRD from TSD, receiver operating characteristic curves (ROC) was created. As shown in Fig. 2, at the cut-off point of the Cohe-ReHo value of 0.95, the Cohe-ReHo of the cerebellum could correctly classify 19 of 23 TRD patients and 19 of 22 TSD patients. Consequently, at this cut-off point, the sensitivity and specificity of differentiating TRD from TSD were 83% and 86%, respectively. The area under the ROC curve was 0.819 (95% confidence intervals from 0.693 to 0.946).

The ROC of the sensitivity and specificity of using the left fusiform gyrus Cohe-ReHo values to differentiate TRD from TSD was also plotted. However, the Cohe-ReHo values of the left fusiform gyrus failed to differentiate TRD from TSD (data not shown).

4. Discussion

To our knowledge, this is the first study of using the Cohe-ReHo of RS-fMRI signals to explore the regional brain activity in patients with TRD or TSD and HS. There were significant differences in Cohe-ReHo values of widespread brain regions among patients with TRD, patients with TSD and HS. These brain regions included bilateral superior frontal gyrus, bilateral cerebellum, left inferior temporal gyrus (including left fusiform gyrus), left occipital cortex, and right fusiform gyrus. Compared with HS, the TRD group had lower Cohe-ReHo values in bilateral superior frontal gyrus and left cerebellum; however, the TSD group only had lower Cohe-ReHo values in bilateral superior frontal gyrus. In the comparison of the two groups of patients with MDD, the TRD group exhibited lower Cohe-ReHo values in bilateral cerebellum and higher Cohe-ReHo values in left fusiform gyrus than the TSD group. These results suggest that the Cohe-ReHo measurement of regional brain activity might be a useful method to study the pathogenesis of TRD and TSD.

The finding of the lower Cohe-ReHo values in the left cerebellum in patients with TRD has provided further evidence that the cerebellum is involved in the mood regulation although it is traditionally believed as a region for motor coordination. The involvement of cerebellum in emotional and cognitive process has been reported in a large body of studies (Lekeu et al., 2002; Schmahmann and Sherman, 1998). Patients with cerebellar damage exhibited cognitive–affective symptoms (Parvizi et al., 2001, 2007; Schmahmann and Sherman, 1998). However, the mechanism of the cerebellum in mood regulation and cognitive processing remains unknown. The cerebellum is bi-directionally connected to multiple regions of the prefrontal cortex and the limbic regions, such as the amygdala, the hippocampus, and the septal nuclei. Since the prefrontal cortex and the limbic system are the key areas for mood regulation and cognition, it is likely that the effects of the cerebellum on emotion and cognitive process are through these connections.

The decreased ReHo in the cerebellum in patients with MDD was also observed in other neuroimaging studies. Using KCC-ReHo method, Liu and colleagues found decreased KCC-ReHo in the cerebellum of patients with MDD patients and their first-degree relatives (Liu et al., 2010b). Similarly, in our previous studies, we found decreased KCC-ReHo in the cerebellum of patients with TRD or TSD (Guo et al., 2011a, 2011b). However, the finding of the lower Cohe-ReHo values of the cerebellum in patients with TRD relative to healthy controls, but not in patients with TSD in present study were somewhat unexpected since one of previous studies found that patients with TSD had significantly lower KCC-ReHo in the left cerebellum posterior lobe (Guo et al., 2011a). This discrepancy might be caused by multiple factors. First, methodologically, since coherence is not susceptible to random noise induced by phase delay among the time courses to be measured, the Cohe-ReHo method applied to the present study can be regarded to be superior to KCC-ReHo (Liu et al., 2010a). Our previous studies revealed that there were greater numbers of regions in the cerebellum with lower KCC-ReHo in patients with TRD than those in TSD patients (voxel size, 303 vs. 70). For patients with TRD, the Cohe-ReHo method found fewer regions with lower ReHo values in the cerebellum than the KCC-ReHo. It is possible that the insensitivity to random noises of the Cohe-ReHo method might neglect the small alterations in the cerebellum of patients with TSD. In addition, in the present study, we adopted a relatively large cluster size (>10,503 mm³) for AlphaSim correction. The criteria of large cluster size would also exclude relatively small voxel sizes with lower KCC-ReHo values in the cerebellum of patients with TSD. Second, different sample sizes in our present and previous studies might also attribute to the difference. Third, no correlation was seen between the mean Cohe-ReHo values in the cerebellum and HRSD scores or illness duration in the pooled patients, suggesting that the Cohe-ReHo values in the cerebellum might be independent of the disease severity and illness duration. Taken these findings together, it is suggested that the abnormal Cohe-ReHo in the cerebellum may be a stable alteration of patients with TRD and may be used as a marker to differentiate TRD patients from TSD patients with...
a high sensitivity (83%) and specificity (86%). However, due to the nature of post hoc analyses, large sample size, prospective studies on the sensitivity and specificity of the Cohe-ReHo in the cerebellum in differentiating TRD patients from TSD patients are warranted.

The fusiform gyrus is presumed to play a role in facial processing (Kanwisher et al., 1997). Accurate facial processing is important to social interaction which may be in turn affect individual emotion. The association between negative emotional bias and the right fusiform was reported in patients with MDD (Surguladze et al., 2005). In this study, depressed patients showed positive response to sad expressions and neutral response to happy expressions. The positive response to sad expressions was correlated to the activation in the right fusiform gyrus. In contrast, HS demonstrated positive response to happy expressions which was correlated to the activation of the bilateral fusiform gyrus. In a study using KCC–ReHo method, Yao and colleagues found that decreased KCC–ReHo in the right fusiform gyrus of patients with MDD was associated with a cluster of depressive symptoms related to negative cognitive patterns (Yao et al., 2009). In contrast, the present study revealed higher Cohe-ReHo in the left fusiform gyrus in the TRD group relative to the TSD group, suggesting that the involvement of the fusiform gyrus in the recognition of facial expressions in TRD group may be different from that in the TSD group. Higher Cohe-ReHo in the left fusiform gyrus can be interpreted as the temporal synchronization of the neural activity in this area. The increased Cohe-ReHo has been considered as a compensatory mechanism in previous studies (Alalade et al., 2011; Chantiluke et al., 2012). However, compared with HS, both patients with TRD and those with TSD did not differ significantly in the Cohe-ReHo of the fusiform gyrus. Moreover, there was a negative correlation between Cohe-ReHo in the left fusiform gyrus and illness duration in the combined patients with MDD. These data and the result of the ROC analysis suggest that the Cohe-ReHo in the left fusiform gyrus may not be a good marker to discriminate TRD from TSD. More importantly, the role of fusiform gyrus in different types of MDD is worthy of further exploration with large sample studies.

Compared with HS, the superior frontal gyrus was the only region where both TRD and TSD groups had lower Cohe-ReHo values. As an important part of the prefrontal cortex, the superior frontal gyrus, was reported to play a key role in self-awareness, emotional regulation, and cognitive processing (Goldberg et al., 2006; Price, 1999; Zald and Kim, 2001). Prefrontal impairments are believed to be related to the cognitive and emotional dysfunction in MDD. Structural MRI studies have revealed reduced volume in prefrontal lobe in patients with MDD (Kumar et al., 1998). The reduction of volume occurred in both gray matter (Coffey et al., 1993; Drevets et al., 1997; Kumar et al., 1998) and white matter (Bell-McInty et al., 2002; Korgaonkar et al., 2010). Moreover, fMRI studies have shown lower glucose metabolism and cerebral blood flow in prefrontal cortex in patients with MDD (Baxter et al., 1989; Mayberg et al., 1999; Nobler et al., 2000). The finding of the lower Cohe-ReHo in the bilateral superior frontal gyrus in the present study is consistent with previous studies, in which the results support the involvement of the superior frontal gyrus in the pathogenesis of depression. The lower Cohe-ReHo in this brain region in both TRD and TSD patients suggest that both groups may share some identical neural substrates. This may explain why patients with TRD or TSD share some common core symptoms of depression, such as sadness, helplessness/hopelessness, anhedonia, and distorted cognition.

In contrast, none of limbic areas was observed to have abnormal Cohe-ReHo in the present study. Since limbic region is commonly believed to play an important role in the pathogenesis of MDD (Yao et al., 2009), the negative finding in the present study might result from a relatively strict statistical threshold was used. For example, when we loosened our statistical threshold to the significant level of combining an uncorrected individual voxel p < 0.05 and cluster size > 1350 mm³, patients with TRD did exhibit lower Cohe-ReHo in left anterior cingulate cortex (ACC) and higher Cohe-ReHo in right posterior cingulate cortex (PCC) relative to patients with TSD.

5. Study limitations

This study is limited by a relatively small sample size. Therefore, the results from this study may not be generalizable to other patients with MDD. Since the TRD patients in the present study were not sequentially determined, some cases of TRD might not be true TRD. For instance, a patient might not respond to one antidepressant, but could respond to a different antidepressant. Consequently, the TRD group might represent a heterogeneous group with different pharmacological response profiles. The heterogeneity of the sample might confound our findings. Future studies should use sequential methodology to determine treatment response. Previous studies have shown that antidepressants seemed to normalize aberrant brain activity and to make brain activity of MDD patients more similar to that of HS (Anand et al., 2005; Fu et al., 2007). Since in our study, the TRD group took at least two types of antidepressants before the fMRI was acquired, the findings in the TRD group were more likely due to the nature of illness instead of the effect from medications. The TRD group had longer illness duration than the TSD group. Although we used the illness duration as a covariate to minimize the influence of illness duration on the difference between the two groups, there is no way to know if this was adequate. A longitudinal study is necessary to establish whether these altered neural activities in TRD or TSD are the consequences of disease development or an inherent biomarker of each type of MDD. Additionally, cerebellar volume reduction has been reported in MDD patients (Pillay et al., 1997). Due to lack of structural analysis in the present study, the relationship between cerebellar volume reduction and lower Cohe-ReHo is unclear.

6. Conclusions

The Cohe-ReHo of RS-fMRI signals in the present study showed that there were significant differences in Cohe-ReHo values of widespread brain regions among patients with TRD, patients with TSD and HS. Compared with HS, both the TRD group and TSD group had lower Cohe-ReHo values in the superior frontal gyrus. However, the TRD group exhibited lower Cohe-ReHo values in the bilateral cerebellum and higher Cohe-ReHo values in the left fusiform gyrus than the TSD group. The Cohe-ReHo in the cerebellum might be used as a marker to differentiate the TRD from TSD.

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Contributors

Dr. Zhao J designed the study along with Drs. Sun X and Chen H. Drs. Chen J, Liu Z, Xue Z, Xu X, Tan C and Wu R collected the original imaging data. Drs. Guo W and Liu F managed and analyzed the
image data, and Drs. Guo W and Gao K wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict of interest declared.

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