Disrupted regional homogeneity in treatment-resistant depression: A resting-state fMRI study

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A B S T R A C T

Background: Using a newly developed regional homogeneity (ReHo) approach, we were to explore the features of brain activity in patients with treatment-resistant depression (TRD) in resting state, and further to examine the relationship between abnormal brain activity in TRD patients and specific symptom factors derived from ratings on the Hamilton Rating Scale for Depression (HRSD).

Methods: 24 patients with TRD and 19 gender-, age- and education-matched healthy subjects participated in the fMRI scans.

Results:
1. Compared with healthy controls, decreased ReHo were found in TRD patients in the left insula, superior temporal gyrus, inferior frontal gyrus, lingual gyrus and cerebellum anterior lobe (culmen) (p<0.05, corrected).
2. Compared with healthy controls, increased ReHo were found in the left superior temporal gyrus, cerebellum posterior lobe (tuber), cerebellum anterior lobe (culmen), the right cerebellar tonsil and bilateral fusiform gyrus (p<0.05, corrected).
3. There was no correlation between the ReHo values in any brain region detected in our study and the patients’ age, years of education, illness duration, HRSD total score and its symptom factors.

Limitation: The influence of antidepressants to the brain activity in TRD patients was not fully eliminated.

Conclusions: The pathogenesis of TRD may be attributed to abnormal neural activity in multiple brain regions.

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1. Introduction

Major depressive disorder (MDD), the most common psychiatric disorder and the most important precursor of suicide (Montgomery, 2006), is characterized by a persistent depressed mood, anxiety and dysphoria, psychomotor changes, alterations of motivation and social behavior, and sleep abnormalities (American Psychiatric Association, 1994). Despite the progress made over the years in the development of antidepressants, about one-third of patients do not respond to antidepressants and result in significant social costs (Petersen et al., 2001). Hence, treatment-resistant depression (TRD) remains a common therapeutic challenge for psychiatrists (Tom, 2010). A patient is called a TRD patient, if he does not respond to two courses of antidepressants of different classes, even if he was administered adequate doses over an adequate period of time (Little, 2009). Recent advances in imaging techniques make it feasible to understand the neuropathology of MDD (Fagiolini and Kupfer, 2003). The pathogenesis of MDD, particularity TRD, however, remains unclear.

During the last decade, an increasing number of studies have investigated the neural correlates of TRD by means of functional magnetic resonance imaging (fMRI). An abnormality of the prefrontal–amygdalar–pallidostratal–mediothalamic mood regulating circuit is presumed to play an important part in the pathophysiology of TRD.

Abbreviations: fMRI, functional magnetic resonance imaging; ReHo, regional homogeneity; TRD, treatment-resistant depression; HRSD, Hamilton Rating Scale for Depression; MDD, major depressive disorder; ADHD, attention deficit hyperactivity disorder; BOLD, blood oxygen level-dependent; KCC, Kendall’s coefficient of concordance; GE, General Electric; TR, repetition time; TE, echo time; FOV, field of view; SPM, statistical parametric mapping; Hz, Hertz; PET, positron-emission tomography; SPECT, signal photon emission computed tomography; EEG, electroencephalograph.

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The findings have shown that TRD is associated with hyperintensity in subcortical gray matter (Steffens et al., 2001) and white matter (Hickie et al., 1995), and with atrophy in the right frontotemporal structures (Shah et al., 2002), the frontal lobe (Coffey et al., 1993), the temporal lobe (Shah et al., 1998) and the hippocampus (Axelson et al., 1993; Baldwin and Simpson, 1997; Fagiolini and Kupfer, 2003; Mervaala et al., 2000; Simpson et al., 1998). However, brain regions shown in these studies are different from each other, and the results are not consistent.

Recently, resting-state fMRI has attracted more attention 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 subjects, concluding that the low frequency fluctuation was closely related to the spontaneous neural activities. Since then, this new branch of fMRI has been well performed in patients with many psychiatric disorders, such as schizophrenia, depression, and attention deficit hyperactivity disorder (ADHD) (Tian et al., 2006; Yao et al., 2009; Greicius et al., 2007; Zhou et al., 2007). Most of these studies, however, have used functional connectivity analysis, using the correlation coefficients of all brain areas with a given region of interest (ROI). It is uncertain which brain area is abnormal when one area shows abnormal functional connectivity with other areas. Thus it is important to measure the regional activity.

Regional homogeneity (ReHo), a newly developed method, reflects the temporal homogeneity of the regional blood oxygen level-dependent (BOLD) signal rather than its density. So abnormal ReHo may be relevant to the changes of temporal aspects of neural activity in the regional area, and can be used to find abnormal activity in the whole brain regions (Zang et al., 2004). Kendall’s coefficient of concordance (KCC) was used to measure the similarity of the time series of one given voxel with those of its nearest voxels in a voxel-wise analysis based 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 in the studies of other psychiatric disorders such as schizophrenia and ADHD (Liu et al., 2006; Cao et al., 2006). It might be helpful to understand the pathophysiology of TRD in the resting state by using the ReHo method, which can reflect the temporal homogeneity of neural activity. To our knowledge, only four papers were found to detect regional neural activity in depression in the resting state by using the ReHo method (Yuan et al., 2008; Yao et al., 2009; Liu et al., 2010; Wu et al., 2010). 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. Only one resting-state fMRI study was conducted on treatment-refractory depression (Wu et al., 2010). Wu et al. (2010) reported that treatment-refractory depression patients showed more abnormal cerebral regions with altered ReHo than did non-treatment-refractory depression and healthy subjects. Since the study of Wu et al. was performed by uncorrected P, the possibility of false positive findings should be considered. Second, the treatment-refractory depression patients in their study were picked out after the treatment trials, and they were not in the treatment resistant state at the scanning time. So it is meaningful to perform resting-state fMRI in TRD patients in the treatment resistant state.

To address these questions, in this resting-state study, we first used ReHo analysis (Zang et al., 2004) to examine the TRD patients just in the treatment resistant state at the corrected P < 0.05 level. We hypothesize that abnormal ReHo will be discovered in certain regions in TRD patients during resting state. These abnormalities may be a stable trait marker for the diagnosis of TRD. To test this hypothesis, we compared the ReHo of whole brain regions between TRD patients and healthy subjects.

2. Methods

2.1. Subjects

Twenty-four right-handed TRD patients took part in the whole study. Demographic data are presented in Table 1. The patients were originally recruited from the Mental Health Institute, 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). Exclusion criteria included bipolar disorder, any history of major illness, cardiovascular disease, and younger than 18 years or older than 50 years. The severity of depression was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) and to be eligible for the study, only patients who scored 18 or greater were included. All patients were taking at least two classes of antidepressants before participating in the study and treatment resistance was defined as non-responsiveness to at least two adequate trials (in terms of dosage, duration (6 weeks for each trial), and compliance) of different classes of antidepressants consistent with previous studies (Furtado et al., 2008; Shah et al., 2002). This non-responsiveness was defined as less than 50% reduction in HRSD score (Nierenberg and Amsterdam, 1990) after treatment at a minimum dose of 150 mg/day of imipramine equivalents (dose converted using a conversion table; Iidaka et al., 1997) for 6 weeks. Before MRI scan, there was a one-week period when the TRD patients were medication free. We chose a one-week period for patients to be off medication as the usual half-life of most antidepressants (except fluoxetine) is 12 to 24 h, and therefore most antidepressants should be washed off within a week.

Nineteen right-handed healthy subjects 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, non-patient edition (American Psychiatric Association, 1994). None of them had a history of neuropsychiatric illness or brain injury and were well matched with the patients for age, gender, years of education.

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) = 192/7.5 ms, 20 slices, 256 x 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 x 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.

Table 1

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>TRD patients (n = 24)</th>
<th>Healthy subjects (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>12/12</td>
<td>10/9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.88 (± 8.35)</td>
<td>24.37 (± 4.18)</td>
</tr>
<tr>
<td>Years of education (years)</td>
<td>13.38 (± 3.50)</td>
<td>15.05 (± 2.63)</td>
</tr>
<tr>
<td>HRSD score</td>
<td>24.50 (± 4.08)</td>
<td>–</td>
</tr>
<tr>
<td>Illness duration (months)</td>
<td>30.00 (± 4.43)</td>
<td>–</td>
</tr>
</tbody>
</table>

TRD = treatment resistant depression.
HRSD = Hamilton Rating Scale for Depression.
2.3. ReHo data analysis

Image preprocessing was conducted using statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, 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. None of the participants had more than 3 mm maximum displacement in x, y, or z and 3° of angular motion during the whole fMRI scan. After slice acquisition correction and head-motion correction, the fMRI images were normalized to the standard SPM8 echoplanar imaging template, resampling to 3°x3°x3 mm. 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://www.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.

Group statistical analysis was performed using SPM8. The resulting fMRI data were then spatially smoothed with a Gaussian kernel of 8×8×8 mm³ full-width at half-maximum.

The resulting statistical map was set at p<0.05 (corrected for multiple comparison, with a combined threshold of P=0.005 and a minimum continuous cluster number of 46).

We also performed a voxel-based correlational analysis between mean ReHo values of the clusters and the patients’ age, years of education, illness duration, HRSD total score and its symptom factors. P<0.05 was used to determine significant correlation.

3. Results

3.1. Subjects

24 TRD patients and 19 healthy subjects completed the whole study. The results of HRSD rating are shown in Table 2. The TRD group and the control group did not differ significantly in age, gender and years of education.

3.2. ReHo: TRD patients versus control subjects

As shown in Tables 3, 4 and Fig. 1, the TRD group showed a significant ReHo decrease in the left insula, superior temporal gyrus, inferior frontal gyrus, lingual gyrus and cerebellum anterior lobe (culmen) (p<0.05, corrected). A significant ReHo increase was found in the left superior temporal gyrus, cerebellum posterior lobe (tuber), cerebellum anterior lobe (culmen), the right cerebellar tonsil and bilateral fusiform gyrus (p<0.05, corrected).

3.3. The correlations between ReHo values and symptom and related factors

There was no correlation between the ReHo values in any brain region detected in our study and the patients’ age, years of education, illness duration, HRSD total score and its symptom factors.

4. Discussion

To the best of our knowledge, this is the first resting-state fMRI study to examine TRD in treatment resistant state using the ReHo method. We found disrupted regional homogeneity in the TRD group relative to the control group in several brain regions. The TRD group showed a significant ReHo decrease in the left insula, superior temporal gyrus, inferior frontal gyrus, lingual gyrus and cerebellum anterior lobe (culmen). A significant ReHo increase was found in the left superior temporal gyrus, cerebellum posterior lobe (tuber), cerebellum anterior lobe (culmen), the right cerebellar tonsil and bilateral fusiform gyrus in TRD patients.

There is one outstanding finding that abnormal ReHo was detected in a large number of cerebellum regions. As far as we know, this point is not reported in MDD yet, let alone in TRD.

During the last decade, neuroimaging studies with MDD have consistently demonstrated regional blood flow and metabolic abnormalities. Most studies have shown decreased metabolic activity in prefrontal, temporal, parietal cortex and cingulated regions in patients with MDD (Biver et al., 1994; Mayberg, 1997; Greicius et al., 2007). Further structural MRI studies indicated that treatment resistance of depression was associated with the abnormality of the prefrontal–amygdalar–pallidostriatal–mediothalamic mood regulating circuit, which is presumed to play an important role in the pathophysiology of TRD (Sheline, 2003). Positron-emission tomography (PET) and signal photon emission computed tomography (SPECT) studies also identified the engagement of regions in that circuit in TRD (Mayberg, 2003; Soares and Mann, 1997). Our study is a cross-sectional study. We also find the widely abnormal brain activity in TRD patients. The brain regions with abnormal ReHo in the TRD group in our study are included in the prefrontal–amygdalar–pallidostriatal–mediothalamic mood regulating circuit. So our results provide additional information for the abnormality of the prefrontal–amygdalar–pallidostriatal–mediothalamic mood regulating circuit in TRD.

Compared with the study of Wu et al. (2010), our study showed that abnormal ReHo in widespread brain regions was found in TRD patients. At this point, the two studies are consistent. Unlike the Wu et al. study, abnormal ReHo in a large number of cerebellum regions such as tuber, culmen and tonsil was detected in our study. The uncorrected P in the Wu et al. study might be partially contributed to the difference between the two studies. The possibility of false positive findings should be seriously considered at the uncorrected P.
level. Take the Wu et al. study itself for example, a great number of correlations between the altered regional ReHo and measures of clinical severity were found in the study when P was uncorrected. Only one correlation survived at the corrected P<0.05 threshold. TRD patients in a different state might be the second factor to the difference. The TRD patients in the Wu et al. study were picked out after clinical trials and they were not in a treatment resistant state at the scanning time. Meanwhile the patients in our study were already in a treatment resistant state before taking part in the study. A week of being medication free before the scans might not exclude the effect of medication thoroughly though the antidepressants they took were not so effective to the disease. The patients were actually in the treatment resistant state at the scanning time, and the results from such TRD patients might speak louder than those from the Wu et al. study.

Increased/decreased ReHo in a large number of cerebellum regions, such as tuber, culmen and tonsil, was an unexpected finding in the present study. The role of the cerebellum in motor coordination and motor behavior has been recognized for years. Recently, more attention was paid to the involvement in emotional and cognitive processing in the cerebellum. The cerebellar cognitive-affective syndrome was raised in a large body of studies in patients with cerebellar damage (Schmahmann and Sherman, 1998; Parvizi et al., 2001). The mechanism of the region affecting mood processing, however, remains unclear. The cerebellum is connected with limbic regions, including the amygdala, the hippocampus and the septal nuclei. Recently, Liu et al. (2010) found decreased ReHo in the

**Table 4**

<table>
<thead>
<tr>
<th>Brain regions of ReHo decreased patients vs controls (TRD-HS)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>T</th>
<th>Voxels</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula</td>
<td>−42</td>
<td>−24</td>
<td>18</td>
<td>−2.72</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>−45</td>
<td>15</td>
<td>−12</td>
<td>−2.71</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>−36</td>
<td>15</td>
<td>−9</td>
<td>−2.74</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>−27</td>
<td>−45</td>
<td>−3</td>
<td>−2.71</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Culmen</td>
<td>−12</td>
<td>−33</td>
<td>−18</td>
<td>−2.71</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

AlphaSim corrected, T>2.70, p<0.005.
TRD = treatment resistant depression.
HS = Healthy subjects.

![Fig. 1.](image)

Fig. 1. Brain regions with increased/decreased ReHo in TRD patients are superimposed on a T1W template (patients vs controls, two-sample T test). These regions included the left superior temporal gyrus, cerebellum posterior lobe (tuber), cerebellum anterior lobe (culmen), the right cerebellar tonsil and bilateral fusiform gyrus with increased ReHo, and the left insula, superior temporal gyrus, inferior frontal gyrus, lingual gyrus, and cerebellum anterior lobe (culmen) with decreased ReHo. The color bar signifies the T value of the group analysis.
cerebellum in MDD patients and in their first-degree relatives. Cerebellar volume reduction has been reported in MDD (Pillay et al., 1997). Our study also showed a large number of cerebellum regions exhibiting abnormal ReHo. Although the relation between cerebellar volume reduction and abnormal ReHo in the cerebellum is unclear due to lack of structural analysis in the present study, our results suggest that TRD patients had abnormal neural activity in a great number of cerebellum regions.

The inferior frontal gyrus is likely important for cognition, which is implicated in the go/no go task and risk aversion (Aron et al., 2004; Christopoulos et al., 2009). The hyperfrontality (Walter et al., 2007; Fitzgerald et al., 2008; Fu et al., 2004) and hypofrontality (Lee et al., 2008; Mittersichthaler et al., 2003; Elliott et al., 2002) of the inferior frontal gyrus have been reported in MDD patients. Hypo- and hyperfrontality in the inferior frontal gyrus at the same time may be interpreted as ReHo having decreased in the left inferior frontal gyrus in TRD patients in our study. Neural activity in the inferior frontal gyrus of TRD is not synchronous, which may be related to cognitive bias and implies the abnormality of the inferior frontal gyrus involved in the pathogenesis of TRD. As well, one electroencephalographic (EEG) literature (Coan and Allen, 2004) found greater alpha activity over the left than the right frontal regions in MDD, which is believed to reflect relatively greater right frontal and attenuated left frontal activity and also suggested that neural activity in the frontal gyrus of MDD is asymmetric and asynchronous.

The fusiform gyrus is thought to be involved in facial processing (Kanwisher et al., 1997). Surguladze et al. (2005) reported a negative emotional bias in the activity in the right fusiform gyrus in MDD, that depressed patients 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. Decreased ReHo of the right fusiform gyrus in MDD during resting state indicated a participation of dysfunction of the fusiform gyrus in the negative cognitive models (Yao et al., 2009; Beck, 1976). Our study showed the increased ReHo of the bilateral fusiform gyrus in TRD patients during resting-state, compared with the earlier study, indicating that the involvement of the fusiform gyrus in recognizing facial expressions in TRD patients might be different from that in MDD patients. Increased ReHo in the bilateral fusiform gyrus suggested that the activity of the fusiform gyrus is temporally synchronous, and may interpret the persistent negative emotional models in TRD. Therefore, our results also provide further support for abnormal neural activity of the fusiform gyrus in TRD.

The abnormal neural activity in the insula in MDD has been documented in PET and fMRI studies (Manes et al., 1999; Cannon et al., 2007). ReHo in the right insula is reported to be positively correlated with the severity of anxiety, retardation and hopelessness (Yao et al., 2009). Reiman et al. (1997) also reported the involvement of the insula in the emotional response to potentially distressing thoughts or interoceptive sensory stimuli. Our study showed a decreased ReHo in the left insula in TRD patients, which is similar with the former studies in MDD patients. The role of the insula in the emotional response may be partially attributed to the pathogenesis in TRD.

In addition, TRD patients showed decreased ReHo in the left superior temporal gyrus and the left lingual gyrus, and increased ReHo in the left superior temporal gyrus. The superior temporal gyrus has been involved in the perception of emotions in facial stimuli (Radua et al., 2010). The lingual gyrus of the occipital lobe continued on to the tentorial surface of the temporal lobe in front, and joins the hippocampal gyrus. The two regions were associated with the prefrontal—amygdalar—palilodosrinal—medialbithalamic mood regulating circuit. Our results provide additional evidence for the involvement of the superior temporal gyrus and the lingual gyrus in the pathogenesis in TRD.

Unfortunately, no correlation was found between the abnormal ReHo in any brain region detected in our study in TRD patients and the patients’ age, years of education, illness duration, HRSD total score and its symptom factors, indicating that abnormal ReHo cannot be used as a quantitative marker for the assessment of clinical symptom severity in TRD patients, although it can be used to help locate functional aberrant brain regions. Something else, such as self-focus, rumination, automatic thoughts, treatment response, etc., which are not well covered in HDRS, might be related to the abnormal ReHo. These need to be evaluated in future studies.

5. Study limitations

All TRD patients in the present study received at least two classes of antidepressants before taking part in the study. Although the antidepressants were not so effective to the disease and there was a one-week period for patients to be off medication, the effects of medication should be not ignored in interpreting the differences between the patients and healthy subjects. Recent studies (Anand et al., 2005; Fu et al., 2007) suggested that antidepressants seemed to normalize brain function and to make the brain function of patients with MDD more similar to that of healthy subjects. Therefore, our results were likely because of the disease rather than the medication, although we could not eliminate completely the medication effects.

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). In the future, a more rigorous approach should be explored to remove such physiological noises.

6. Conclusions

Patients with TRD showed a significant ReHo decrease in the left insula, superior temporal gyrus, inferior frontal gyrus, lingual gyrus and cerebellum anterior lobe (culmen). A significant ReHo increase was found in the left superior temporal gyrus, cerebellum posterior lobe (tuber), cerebellum anterior lobe (culmen), the right cerebellar tonsil and bilateral fusiform gyrus. There was no correlation between the ReHo values in any brain region detected in our study and the patients’ age, years of education, illness duration, HRSD total score and its symptom factors. Taking together, the pathogenesis of TRD may be attributed to abnormal neural activity in multiple brain regions.

Contributors

Dr. Zhao J designed the study along with Drs. Sun X and Chen H. Drs. Liu Z, Wu R and Tan C collected the original imaging data. Drs. Guo W, Liu L and Xu Q managed and analyzed the imaging data. Drs. Liu Z, Wu R and Tan C contributed to and have approved the final manuscript. Dr. Zhao J designed the study along with Drs. Sun X and Chen H. Drs. Liu Z, Wu R and Tan C collected the original imaging data. Drs. Guo W, Liu L and Xu Q managed and analyzed the imaging data. Dr. Guo W 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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References


Wiley InterScience; 2010.