Alterations of the amplitude of low-frequency fluctuations in treatment-resistant and treatment-response depression: A resting-state fMRI study

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ABSTRACT
Background: Patients with treatment-resistant depression (TRD) and those with treatment-response depression (TSD) respond to antidepressants differently and previous studies have commonly reported different brain networks in resistant and nonresistant patients. Using the amplitude of low-frequency fluctuations (ALFF) approach, we explored ALFF values of the brain regions in TRD and TSD patients at resting state to test the hypothesis of the different brain networks in TRD and TSD patients.

Methods: Eighteen TRD patients, 17 TSD patients and 17 gender-, age-, and education-matched healthy subjects participated in the resting-state fMRI scans.

Results: There are widespread differences in ALFF values among TRD patients, TSD patients and healthy subjects throughout the cerebellum, the visual recognition circuit (middle temporal gyrus, middle/inferior occipital gyrus and fusiform), the hate circuit (putamen), the default circuit (ACC and medial frontal gyrus) and the risk/action circuit (inferior frontal gyrus). The differences in brain circuits between the TRD and TSD patients are mainly in the cerebellum, the visual recognition circuit and the default circuit.

Conclusions: The affected brain circuits of TRD patients might be partly different from those of TSD patients.

1. Introduction

By the year 2020, major depressive disorder (MDD), clinically characterized by persistent and pervasive feelings of sadness, guilt, and worthlessness (American Psychiatric Association, 1994), will be the second leading cause of global disease burden. Despite the rapid progress made over the years in the development of antidepressants, still about one-third of depressed patients fail to respond to antidepressants (Petersen et al., 2001). Hence, treatment-resistant depression (TRD) remains a common therapeutic challenge for psychiatrists (Little, 2009; Bschor, 2010). Recent advances in imaging techniques make it possible to explore the structural and functional abnormalities associated with TRD and treatment-response depression (TSD). Thus imaging techniques may lead to a great understanding of the neuropathology as well as the development of effective antidepressants (Fagioli and Kupper, 2003).

Resting-state functional magnetic resonance imaging (fMRI) has attracted increasing attention since the study of Biswal et al. (1995).
They first reported that the spontaneous low frequency (0.01–0.08 Hz) fluctuations (LFF) in fMRI were highly synchronous among motor cortices in healthy subjects, concluding that the LFF was closely related to the spontaneous neural activities thus being physiologically meaningful. Since then, this new branch of fMRI has been well performed in psychiatric disorders, such as schizophrenia (Zhou et al., 2007), attention deficit hyperactivity disorder (ADHD) (Tian et al., 2006) and MDD (Anand et al., 2005, 2009; Cullen et al., 2009; Greicius et al., 2007; Guo et al., 2011a; Yao et al., 2009).

Most of these studies, however, have investigated LFF from the perspective of temporal synchronization and applied the functional connectivity analysis method. Detailed maps of complex functional systems have been generated by functional connectivity methods (Di Martino et al., 2008; Fox and Raichle, 2007; Margulies et al., 2007), which have proved to be reliable and reproducible over time (Deuker et al., 2009; He et al., 2009; Shehzad et al., 2009). Although functional connectivity has been verified as a powerful and efficient approach for neuroimaging studies of brain physiology and pathophysiology, and the result of abnormal functional connectivity between two remote areas can be comprehensive, it is uncertain which brain area is abnormal when one area shows abnormal functional connectivity with other areas. Thus, other approaches are required to be explored in future studies.

Although overlooked for years, other aspects of LFF may also be informative (Zuo et al., 2010). The amplitude of low-frequency fluctuations (ALFF) for the regional blood oxygen level-dependent (BOLD) signal is one of such approaches to explore the amplitude of LFF, not regional synchronization of LFF, during resting state. ALFF is an index in which the square root of the power spectrum was integrated in a low-frequency range, for detecting the regional intensity of spontaneous fluctuations in BOLD signal (Zang et al., 2007). Recent resting state fMRI studies in healthy subjects have indicated that ALFF was able to differentiate physiological states of the brain (Hoptman et al., 2010; Lui et al., 2009; Yan et al., 2009; Yang et al., 2007). Furthermore, ALFF has also been used in clinical studies including ADHD (Zang et al.,

### Table 1

<table>
<thead>
<tr>
<th>Variables (mean ± SD)</th>
<th>TRD</th>
<th>TSD</th>
<th>Healthy subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (M/F)</td>
<td>18 (11/7)</td>
<td>17 (10/7)</td>
<td>17 (10/7)</td>
<td>0.987 a</td>
</tr>
<tr>
<td>Age, years</td>
<td>27.39 ± 7.74</td>
<td>26.71 ± 7.73</td>
<td>24.24 ± 4.41</td>
<td>0.368 b</td>
</tr>
<tr>
<td>Education, years</td>
<td>13.56 ± 3.60</td>
<td>12.35 ± 2.12</td>
<td>13.82 ± 2.38</td>
<td>0.271 b</td>
</tr>
<tr>
<td>Illness duration, months</td>
<td>35.5 ± 49.89</td>
<td>2.59 ± 1.33</td>
<td>0.010 c</td>
<td></td>
</tr>
<tr>
<td>HRSD score</td>
<td>23.89 ± 3.69</td>
<td>25.58 ± 6.32</td>
<td></td>
<td>0.335 c</td>
</tr>
</tbody>
</table>

* The P value for gender distribution in the three groups was obtained by chi-square test.
* The P values were obtained by one-way analysis of variance tests.
* The P values were obtained by two sample t-test.

![Fig. 1](image-url)  
**Fig. 1.** Statistical maps showing ANOVA results of ALFF differences among the TRD, TSD patients and healthy subjects.
Anterior Cingulate Cortex.

Tables S1 and S2.

Table 2

Regions showing ALFF differences among the TRD, TSD groups and healthy subjects.

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>Voxel</th>
<th>MNI coordinates (mm)</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRD &gt; TSD (with illness duration correction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The posterior lobes of the cerebellum</td>
<td>1038</td>
<td>−9 −78 −21</td>
<td>4.65</td>
</tr>
<tr>
<td>ACC/medial frontal gyrus</td>
<td>128</td>
<td>−3 12 −12</td>
<td>3.58</td>
</tr>
<tr>
<td>TRD &gt; healthy subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The posterior lobes of the Cerebellum</td>
<td>889</td>
<td>−42 −42 −36</td>
<td>3.62</td>
</tr>
<tr>
<td>Medial fronto gyrus/ACC</td>
<td>64</td>
<td>6 33 −9</td>
<td>3.55</td>
</tr>
<tr>
<td>TRD &gt; healthy subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The anterior lobes of the cerebellum</td>
<td>172</td>
<td>−6 −39 −21</td>
<td>3.52</td>
</tr>
<tr>
<td>Lingual gyrus/cuneus</td>
<td>1204</td>
<td>−51 69 6</td>
<td>4.04</td>
</tr>
<tr>
<td>TSD &gt; healthy subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>66</td>
<td>54 9 −36</td>
<td>3.26</td>
</tr>
<tr>
<td>The anterior lobes of the cerebellum</td>
<td>67</td>
<td>21 −33 −39</td>
<td>2.99</td>
</tr>
<tr>
<td>TSD &gt; healthy subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The posterior lobes of the cerebellum</td>
<td>88</td>
<td>6 −75 −36</td>
<td>2.70</td>
</tr>
<tr>
<td>Middle temporal gyrus/middle occipital gyrus/inferior occipital gyrus/fusiform</td>
<td>653</td>
<td>−45 −60 −6</td>
<td>4.13</td>
</tr>
<tr>
<td>Putamen/caudate/medial fronto gyrus/ACC</td>
<td>881</td>
<td>18 27 −12</td>
<td>3.56</td>
</tr>
</tbody>
</table>

x, y, z, coordinates of primary peak locations in the MNI space; T statistical value of peak voxel showing ALFF differences among the TRD, TSD groups and healthy subjects. ACC, Anterior Cingulate Cortex. P<0.05, corrected for multiple comparisons.

In this study, we distinguished MDD patients according to treatment responsiveness, and examined the new clinical subtypes of TRD and TSD. Given that TRD and TSD patients respond to the antidepressants differently and previous studies have commonly reported different brain networks in resistant and nonresistant patients (Lui et al., 2011; Wu et al., 2011), we hypothesized that different brain circuits would be involved in the TRD and TSD patients using ALFF in resting state.

2. Methods

2.1. Subjects

Twenty right-handed TRD patients, originally recruited from the Mental Health Institute, the Second Xiangya Hospital, Central South University, China, took part in the whole study. Major depression was confirmed by two qualified psychiatrists (Dr. Zhao J and Dr. Liu Z) using the Structured Clinical Interview for DSM-IV Axis I Disorders (American Psychiatric Association, 1994). Exclusion criteria were bipolar disorder, any history of loss of consciousness, substance abuse within the six months prior to the scan, mental retardation, or any history of serious medical or neurological illness, any other psychiatric disorder, and being 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) at the day of the scan and to be eligible for the study, only patients who scored 18 or greater were included. All patients took at least two classes of antidepressants before participating in the study. Treatment resistance was defined as non-responsive 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). Non-responsiveness was defined as a 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. Data from two patients were excluded from further analysis due to excessive head motion (see ALFF data analysis). Detailed treatments and other clinical characters for TRD patients were exhibited in Supplementary Tables S1 and S2.

Twenty-six right-handed MDD, first-episode, treatment-naive patients were originally recruited from the same Hospital. Inclusion and exclusion criteria were similar to those of TRD patients. An additional exclusion criterion for these patients was that the current illness duration was no more than six months. Following the fMRI scan, all patients were directed to take antidepressants at a minimum dose of 150 mg/day of imipramine equivalents (dose converted using a conversion table) (Iidaka 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 more than a 50% reduction in the HRSD score after the antidepressant treatment, consistent with previous studies (Furtado et al., 2008; Gong et al., 2011; Nierenberg and Amsterdam, 1990; Shah et al., 2002). Data from nine patients were excluded from further analysis due to treatment non-response (7 patients) and excessive head motion (2 patients) (see ALFF data analysis).

Eighteen right-handed healthy subjects, recruited from the community, 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 all were well matched with the patients in terms of age, gender and years of education. Data from one subject was excluded from further analysis due to excessive head motion (see ALFF data analysis).

Clinical and demographic data from the remaining 52 participants were shown in Table 1. The three groups were well matched for age, gender and 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 1.5 T GE scanner (General Electric, Fairfield, Connecticut, USA) equipped with high-speed gradients just at the recruited day. To minimize head movement, a prototype quadrature birdcage head coil fitted with foam padding was used. The patients 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 echo-planar 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 scan lasted for 6 min and 180 volumes were obtained.

2.3. ALFF data analysis

Image preprocessing was conducted using statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). For each subject, the fMRI images were corrected for the acquisition delay between slices and for the head motion. None of the participants had more than 2 mm maximum displacement in x, y, or z and 2° of angular motion during the whole fMRI scan. The data of five subjects (two TRD patients, two TSD patients and one healthy subject) were discarded from further analysis because of excessive head movement. After slice acquisition correction and head-motion correction, the resulting images were spatially normalized to the Montreal Neurological Institute (MNI) EPI template in SPM8, and each voxel was resampled to $3 \times 3 \times 3$ mm$^3$. After this, the processed images were spatially smoothed with an 8 mm full width at half maximum Gaussian kernel. Finally, linear trend subtraction and temporal filtering (0.01–0.08 Hz) were performed on the time series of each voxel to reduce the effect of low-frequency drifts and physiological high frequency respiratory and cardiac noise for further ALFF analysis.

ALFF analysis was performed using the REST software (http://resting-fmri.sourceforge.net). The time series for each voxel was transformed to the frequency domain using a Fast Fourier Transform and the power spectrum was then obtained. Since the power of a given frequency was proportional to the square of the amplitude of this frequency component, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF (Zang et al., 2007).

To determine ALFF differences among the three groups, a one-way analysis of variance (ANOVA) was performed at each voxel, followed by post hoc t-tests to identify differences between each pair of groups. To remove the possible illness duration effect, post hoc t-tests were performed between TRD and TSD patients using illness duration as covariates. The resulting statistical maps were corrected for multiple comparisons to a significant level of $P<0.05$ by combining the individual voxel $P<0.05$ and cluster size $>389$ voxels using

![Fig. 2. Brain regions showing ALFF differences between the TRD patients and the TSD patients with illness duration correction. Red and blue denote higher and lower ALFF respectively and the color bars indicate the T value from post hoc analysis between each pair of groups. Of note, we showed the two-sample t-tests results within a mask showing significant group differences in the ANOVA analysis.](image-url)
Monte Carlo simulations in the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

3. Results

The demographic and clinical data are presented in Table 1. Gender, age and years of education did not differ significantly among the three groups. There was no significant difference in HRSD score between TRD and TSD groups. Illness duration was significantly longer in the TRD group relative to the TSD group \( (P = 0.010) \).

There were widespread differences in ALFF values among the TRD patients, TSD patients and healthy subjects throughout the cerebellum, the visual recognition circuit, the hate circuit, the default circuit and the risk/action circuit by ANOVA analysis (Fig. 1).

Several brain circuits exhibited significant ALFF differences (illness duration correction) when comparing TRD and TSD patients mainly in TRD patients in the posterior lobes of the cerebellum and the default circuit (ACC and medial frontal gyrus) with higher ALFF values, and in the visual recognition circuit (lingual gyrus and cuneus) with lower ALFF values (Table 2 and Fig. 2).

Higher ALFF values were observed in TRD patients in the posterior lobes of the cerebellum and the default circuit (ACC and medial frontal gyrus), while lower ALFF values were seen in the visual recognition circuit (lingual gyrus, middle occipital gyrus, middle temporal gyrus and cuneus) compared with healthy subjects (Table 2 and Fig. 3).

Moreover, higher ALFF values were mainly found in TSD patients in the anterior lobes of the cerebellum and the visual recognition circuit (inferior temporal gyrus), while lower ALFF values were speculated in the posterior lobes of the cerebellum, the visual recognition circuit (middle temporal gyrus, middle/inferior occipital gyrus and fusiform), the hate circuit (putamen), the default circuit (ACC and medial frontal gyrus) and the risk/action circuit (inferior frontal gyrus) (Table 2 and Fig. 4).

4. Discussion

The ALFF approach adopted here to identify altered brain circuits of MDD patients has proved to be very informative. However, the exact biological mechanisms behind ALFF remain uncertain to date. Recent resting-state fMRI studies imply that the ALFF of BOLD signals may represent a potentially meaningful and stable property of the brain. In animal studies, LFF was closely related to task-induced BOLD signal (Logothetis et al., 2001), and gamma band of electrophysiological recordings (Shmuel and Leopold, 2008) in monkeys. In rats, the LFF was associated with the delta band activity with electrophysiological recordings (Lu et al., 2007). In human healthy subjects,
Biswal et al. (1995) found that LFFs (0.01–0.08 Hz) were highly synchronous among motor cortices, and concluded that LFF was closely related to spontaneous neural activities. Moreover, the LFF in the visual cortex was highly related to alpha band power in humans (Goldman et al., 2002; Moosmann et al., 2003). Several physiological factors can impact LFF amplitudes. LFF amplitudes are found to be sensitive to carbon dioxide (CO2) level, with amplitudes suppressed by hypercapnia (Biswal et al., 1997; Wise et al., 2004). Some studies suggest that the different resting states, such as eyes open vs. eyes closed, impact the LFF amplitude in visual cortex (McAvoy et al., 2008; Yang et al., 2007). Several clinical studies have demonstrated altered baseline brain activity by measuring the amplitude of ALFF in ADHD (Zang et al., 2007), early Alzheimer’s disease (He et al., 2007), amnestic mild cognitive impairment (Han et al., 2011) and schizophrenia (Hoptman et al., 2010; Huang et al., 2010; Zhou et al., 2007). These converging lines of evidences indicate that ALFF may reflect spontaneous neural activity of the brain with physiological meaning.

The main findings of the present study were that TRD patients show higher ALFF values in the default circuit (ACC and medial frontal gyrus), and lower ALFF values in the visual recognition circuit (lingual gyrus and cuneus) compared with TSD patients. The simple role of the cerebellum in motor coordination and motor behavior has been traditionally recognized for years, but this issue has been greatly challenged. Increasing attention has been paid to the involvement of the cerebellum in emotional and cognitive processing (Lekeu et al., 2002; Schmahmann and Sherman, 1998). The cerebellar cognitive-affective syndrome was identified in patients with cerebellar damage (Parvizi et al., 2001; Schmahmann and Sherman, 1998). However, the mechanism of the cerebellum affecting mood and cognitive processing remains uncertain. The cerebellum is connected with the frontal cortex and the limbic regions, such as the amygdala, the hippocampus and the septal nuclei. Decreased regional homogeneity (ReHo) in the cerebellum was found in MDD patients and their first-degree relatives in a recent study (Liu et al., 2010). Also, our previous studies exhibited increased/decreased ReHo in a large number of cerebellum regions in TRD patients (Guo et al., 2011b), and decreased ReHo in TSD patients (Guo et al., 2011a). In addition, cerebellum volume reduction has been reported in MDD patients (Pillay et al., 1997). The relation between cerebellar volume reduction and higher ALFF values in the cerebellum is unclear due to lack of structural analysis in the present study. Our findings, in line with the above studies, indicate that TRD patients had abnormal spontaneous neural activity in the cerebellum, which might partially underlie the pathogenesis of TRD.

Medial frontal gyrus and ACC are recognized as the core regions associated with the brain’s default mode network (DMN) (Buckner...
et al., 2008; Greicius et al., 2007; Raichle et al., 2001). Medial frontal gyrus is assumed to play an important role in emotional processing, such as attention to emotion, identification, or regulation of emotion (Phillips et al., 2003; Teasdale et al., 1999). The abnormal spontaneous neural activity in the medial frontal gyrus may result in the dysfunction of this region, and lead to a loss of top-down regulation, which is thought to be the basis of the pathogenesis of emotional, behavioral, cognitive, and endocrine changes in depression (Savitz and Drevets, 2009a, 2009b). Also, medial frontal gyrus appears to be important in dysfunctional emotional behavior in schizophrenia (Takahashi et al., 2004). ACC plays a critical role in the cognition and emotional regulation (MacDonald et al., 2000; Mayberg et al., 2002). Decreased ReHo was found in this region in MDD patients (Yao et al., 2009). Abnormal spontaneous neural activity in the two brain regions of the DMN might partly contribute to the emotional and cognitive symptoms seen in MDD patients. Therefore higher ALFF values in the two regions in TRD patients might indicate that impaired default circuit might partly be contributed to the pathogenesis of TRD.

Interestingly, occipital gyrus, including lingual gyrus and cuneus, was found to show lower ALFF value in resting state in TRD patients than that in TSD patients. Lingual gyrus and cuneus were regarded as the key regions related to visual recognition circuit (Tao et al., 2011). Reductions in occipital cortex γ-aminobutyric acid (GABA) levels have been shown in MDD patients in previous studies (Epperson et al., 2006; Sanacora et al., 2002), and the reductions could be reversed by selective serotonin reuptake inhibitors (SSRIs) by magnetic resonance spectroscopy (Sanacora et al., 2002). Fernandez et al. (2005) reported that treatment-naïve MDD patients had increased occipital delta dipole density by magnetoencephalography. In a resting-state fMRI study, Yuan et al. (2008) revealed that abnormal activity of the occipital cortex was involved in the pathophysiology in remitted geriatric depression. These studies suggested the impaired visual recognition circuit participating in the neuropsychology of MDD. Consistent with these studies, the lower ALFF values in the occipital gyrus (including lingual gyrus and cuneus) provided a neural basis for disrupted visual recognition processing in TRD.

Other significantly affected circuits in TSD patients were those associated with risk and action, hate circuits. The inferior frontal gyrus, a core region of the risk/action circuit, was related to response inhibition (Aron et al., 2004; Tao et al., 2011). Reduced size of the putamen, a member of hate circuit (Tao et al., 2009), was reported in MDD patients (Husain et al., 1991). Increased dopamine D2 receptor binding and oxidative stress (Michel et al., 2010) were also found in this region of MDD. Lower ALFF values in these two regions in TSD patients might partially entail the emotion and cognitive symptoms seen in these patients.

5. Study limitations

In addition to the relatively small sample size, several limitations should be considered in explaining the results.

First, 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 effective in the treatment of the disease, the effect of medication should be not ignored in interpreting the difference between the TRD 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 to be due to the disease rather than the medication, although we could not eliminate completely the medication effects.

Second, the current study is 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. Future studies might benefit from the clinical intervention of a single antidepressant with a fixed dose.

Third, the TRD group had longer illness duration than the TSD group. Although the illness duration was applied as a covariate in the present study, we could not eliminate the possible influence of this variable.

6. Conclusions

Despite these limitations, our study first demonstrated that there are widespread differences in ALFF values among TRD patients, TSD patients and healthy subjects throughout the cerebellum, the visual recognition circuit, the hate circuit, the default circuit and the risk/action circuit. Although the TRD and TSD groups appear to share some identical brain networks, the brain circuits between the TRD and TSD patients might be partly different, mainly in the cerebellum, the visual recognition circuit and the default circuit.

Contributors

Dr. Zhao J designed the study along with Drs. Sun X and Chen H. Drs. Chen J, Liu Z, Xue Z, Xu X, Wu R and Tan C collected the original imaging data. Drs. Guo W, Liu F, Ma C and Xiao C managed and analyzed the imaging data. Dr. Guo W and Wooderson SC 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.pnpbp.2012.01.011.

References


