Research report

Abnormal amplitude low-frequency oscillations in medication-naive, first-episode patients with major depressive disorder: A resting-state fMRI study

Feng Liu [a,1], Wenbin Guo [b,c,1], Ling Liu [a], Zhiliang Long [a], Chaoqiong Ma [a], Zhimin Xue [b], Yifeng Wang [a], Jun Li [a], Maorong Hu [b], Jianwei Zhang [a], Handan Du [a], Ling Zeng [a], Zhening Liu [b], Sarah C. Wooderson [d], Changlian Tan [e], Jingping Zhao [b,*], Huafu Chen [a,*]

[a] Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, Sichuan 610054, China
[b] Mental Health Institute, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[c] Mental Health Center, the First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi 530021, China
[d] Department of Psychological Medicine, Institute of Psychiatry, King's College, London, United Kingdom
[e] Department of Radiology, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China

ARTICLE INFO

ABSTRACT

Background: Recent resting-state fMRI studies on major depressive disorder (MDD) have found altered temporal correlation between low-frequency oscillations (LFOs). However, changes on the amplitudes of these LFOs remain largely unknown.
Methods: Twenty-two medication-naive, first-episode patients with MDD and 19 age-, sex-, education-matched healthy controls were recruited. Resting-state fMRI was obtained by using an echo-planar imaging sequence and the fractional amplitude of low-frequency fluctuations (fALFF) was calculated to investigate the amplitude of LFOs in the resting state.
Results: Compared with control subjects, patients with MDD showed significantly decreased fALFF in right cerebellum posterior lobe, left parahippocampal gyrus and right middle frontal gyrus and increased fALFF in left superior occipital gyrus/cuneus ($p < 0.05$, corrected for multiple comparisons). Further receiver operating characteristic curves (ROC) analyses suggested that the alterations of fALFF in these regions might be used as markers to classify patients with MDD from healthy controls.
Conclusions: These findings indicated LFOs abnormalities in MDD and the fALFF analysis might be a potential approach in further exploration of this disorder.

1. Introduction

Major depressive disorder (MDD) is characterized by persistent depressed mood, anxiety and dysphoria, alterations of social behavior, and sleep abnormalities (APA, 1994). Although numerous efforts have been made in the past decades to the new treatment strategies, depressive symptoms continue to have a substantial impact at the individual and societal level. At present, the diagnosis of MDD is mainly dependent on clinical signs and symptoms. The exact neurobiologic mechanisms underlying MDD are still not fully understood.

Recently, increasing attention has been paid to resting-state fMRI. Numerous studies have demonstrated that functional brain abnormalities of depression can be examined by using resting-state fMRI (Bluhm et al., 2009; Chen et al., 2012; Guo et al., 2012a; Kenny et al., 2010; Liu et al., 2012b; Veer et al., 2010; Zhou et al., 2010). As early as 1995, Biswal et al. found that spontaneous low-frequency (0.01–0.08 Hz) oscillations (LFOs) are highly synchronous across motor cortices, concluding that LFOs are indeed a neurophysiologic index and relate to spontaneous neural activity. In addition, resting-state fMRI is relatively easy to obtain and asks patients nothing but to remain still, which is of more potential applications in clinical studies. Using resting-state fMRI, Greicius et al. (2007) report that resting-state functional connectivity between subgenual cingulate and thalamic is significantly increased in the depressed subjects. Besides, Lui et al. (2011) observe significantly decreased connectivity in prefrontal–limbic–thalamic areas in MDD groups. Moreover, Zeng et al.

(2012) demonstrate the whole-brain resting-state functional connectivity patterns could be used to discriminate depressive individuals from healthy controls, and find altered functional connections in limbic-cortical and visual cortical regions. However, these studies focus on the synchronization of LFOs (functional connectivity), not from the perspective of the amplitude of LFOs. Thus, it does not provide us information about regional spontaneous activity which is important for us to understand a disease completely. On the contrary, by examining the amplitude of LFOs, the regional information could be obtained.

To date, several metrics have been developed to examine amplitude of LFOs by using resting-state fMRI, such as root mean square of LFOs (Biswal et al., 1995), resting state physiological fluctuation amplitude (Kannurpatti and Biswal, 2008), the power spectrum (Fransson, 2006), and the low-frequency spectral amplitude (Biswal et al., 2007). Recently, Zang et al. (2007) propose the amplitude of low frequency fluctuation (ALFF) by calculating the square root of the power spectrum in a frequency range to investigate the regional spontaneous activity. ALFF is subsequently used to represent different physiological states of the brain (Guo et al., 2012b, 2012c; Hoptman et al., 2010; Huang et al., 2010; Jiang et al., 2011; Wang et al., 2011). Although ALFF seems to be an effective method for detecting regional signals change of spontaneous activity, it is sensitive to the physiological noise. More recently, an improved ALFF method, fractional ALFF (fALFF) approach (Zou et al., 2008), measures the ratio of power spectrum of low-frequency range to that of the whole frequency range. Non-specific signal components could be effectively suppressed by this technology and the sensitivity and specificity in examining regional spontaneous brain activity could be significantly improved (Zou et al., 2008). By far, this method has been successfully used to investigate the brain function in healthy subjects (Kunisato et al., 2011b) and clinical populations (Hoptman et al., 2010; Kunisato et al., 2011a; Lai and Wu, 2012).

The aim of this study was to examine the amplitude of LFOs in MDD by using the fALFF approach. According to the aforementioned studies in MDD (Greicius et al., 2007; Lui et al., 2011; Zeng et al., 2012), we hypothesized that (1) patients with MDD may have significantly altered fALFF in prefrontal–limbic regions and visual cortical areas when compared with normal controls and that (2) the alterations of fALFF in these regions might be served as an index to differentiate patients from healthy subjects.

2. Methods

2.1. Subjects

Twenty-four right-handed patients with MDD were recruited from Mental Health Institute, the Second Xiangya Hospital, Central South University, China. The patients were partially from our previous study (Guo et al., 2012a). Patients were recruited consecutively and the diagnosis of MDD was made with the Structured Clinical Interview for DSM-IV criteria (First et al., 1997). All patients were medication-naive and at their first episode. Exclusion criteria were age younger than 18 years or older than 60 years, history of loss consciousness, mental retardation, cardiovascular disease, bipolar disorder, neurological illness, use of vasoactive medications, and alcohol or drug abuse. An additional exclusion criterion was that the current illness duration was more than 6 months. Severity of depression was quantified by using the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967). To be eligible for the study, only patients who scored 18 or more were included.

Twenty right-handed healthy controls partially from the same previous study were included for this analysis (Guo et al., 2012a).

They were screened by the same psychiatrists using the non-patient edition of the Structured Clinical Interview for DSM-IV. None of them had a history of serious medical or neuropsychiatric illness or history of major psychiatric illness in their first-degree relatives.

This study was approved by the local ethical committee, and written informed consent was obtained from each subject.

2.2. Data acquisition

The MR images were acquired on a GE 1.5-T MR system (General Electric, Fairfield, Connecticut, USA). Foam padding and headphones were used to minimize head movement and reduce scanner noise. During scanning, the participants were instructed to hold still, relax with their eyes closed but not fall asleep. Functional images were obtained with an echo-planar imaging (EPI) sequence. Sequence parameters were as follows: repetition time/echo time (TR/TE)$=2000/40$ ms, slices$=20$, thickness$=5$ mm, gap$=1$ mm, field of view (FOV)$=24$ cm, flip angle (FA)$=90°$, data matrix$=64 \times 64$. For each participant, the fMRI scanning lasted for 6 min and 180 volumes were obtained.

2.3. Data preprocessing

Preprocessing and statistical analysis of functional images were carried out using the statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of each subject were discarded due to the signal reaching equilibrium and the participants adapting to the scanning noise. The remaining 170 volumes were corrected for the acquisition delay between slices and for the head motion (a least squares approach and a 6-parameter spatial transformation). Only participants with head motion less than 1.5 mm in the x, y or z direction and less than 1.5° rotation about each axis were included. The resulting images were spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template in SPM8 and resampled to $3 \times 3 \times 3$ mm^3. After this, the normalized images were spatially smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

After preprocessing in SPM, linear trend was removed and fALFF analysis was performed by using the Resting-State fMRI Data Analysis Toolkit (http://resting-fmri.sourceforge.net). The analysis procedure for fALFF was carried out according to previous study (Zou et al., 2008). Briefly, the time course of each voxel was first converted to the frequency domain without band-pass filtering by using a Fast Fourier Transform (FFT) and the power spectrum was obtained. Since the power of a given frequency was proportional to the square of the amplitude of its 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. The sum of amplitude across 0.01–0.08 Hz was divided by that across the entire frequency range. For standardization purpose, the fALFF of each voxel was divided by the global mean fALFF value within a brain mask.

2.4. Statistical analysis

Two-sample t-tests were performed to assess the differences in age and education, and chi-square test was performed to assess the difference in gender. As described in previous study, micro-movements can significantly influence measures and results derived from the resting-state fMRI scan (Power et al., 2012). Hence, we also examined the group differences of head motion by using two-sample t-tests according to framewise displacement (FD) measurement (Power et al., 2012). In addition, two-sample

t-test was performed to determine fALFF differences between two groups. The resulting statistical map was corrected for multiple comparisons to a significant level of $p < 0.05$ by combining the individual voxel $p < 0.005$ and cluster size > 49 voxels. This correction was confined within a whole brain mask and was determined by Monte Carlo simulations using the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

To identify the relationship of the fALFF values in regions with significant group differences and the severity of depression, linear correlation analyses were performed. Correlations between the mean fALFF values from the significant clusters of the comparison and HRSD total scores were analyzed. Furthermore, we plotted receiver operating characteristic curves (ROC) to examine whether these clusters could be used as markers to discriminate patients with MDD from healthy controls.

3. Results

3.1. Participants

Data from two patients and one healthy control were excluded for further analysis due to excessive head motion. Twenty-two patients with MDD and 19 healthy subjects completed the whole study. The two groups were matched for gender (12 males for MDD group and 10 males for control group; $\chi^2 = 0.02$, df $= 1$, $p = 0.902$), age (mean $\pm$ SD) (28.09 $\pm$ 9.91 years for MDD group; 24.37 $\pm$ 4.18 years for healthy controls; $t = 1.52$, df $= 39$, $p = 0.136$), the years of education (12.23 $\pm$ 2.62 years for MDD group; 13.11 $\pm$ 2.47 years for healthy controls; $t = 1.10$, df $= 39$, $p = 0.278$) and the mean FD (0.0889 $\pm$ 0.0349 mm for MDD group; 0.0993 $\pm$ 0.0432 mm for healthy controls; $t = -0.84$, df $= 39$, $p = 0.400$). Mean duration of illness was 2.95 $\pm$ 1.73 months and mean total score of HRSD was 25.89 $\pm$ 6.26 in the MDD group.

3.2. Differences in fALFF values between patients with MDD and controls

Group differences are shown in Table 1 and Fig. 1. Compared with healthy controls, the MDD group exhibited significantly reduced fALFF in right cerebellum posterior lobe, left parahippocampal gyrus and right middle frontal gyrus. Significantly increased fALFF was found in left superior occipital gyrus/cuens.

Table 1
fALFF differences between the patients with MDD and control groups.

Brain regions	BA	Voxels	MNI coordinates (mm)			t Value
			x	y	z	
Right cerebellum posterior lobe	–	77	48	−54	−48	−4.08
Right middle frontal gyrus	10/11	82	30	48	−12	−4.40
Left superior occipital gyrus, cuneus	17/18	90	−12	−96	3	3.84
Left parahippocampal gyrus	35	153	−42	−21	−24	−3.97

x, y, z, coordinates of primary peak locations in the MNI space; t statistical value of peak voxel showing fALFF differences between the patients with MDD and healthy subjects (negative values: patients with MDD < healthy subjects; positive values: patients with MDD > healthy subjects). MDD, major depressive disorder; BA, Brodmann's area.
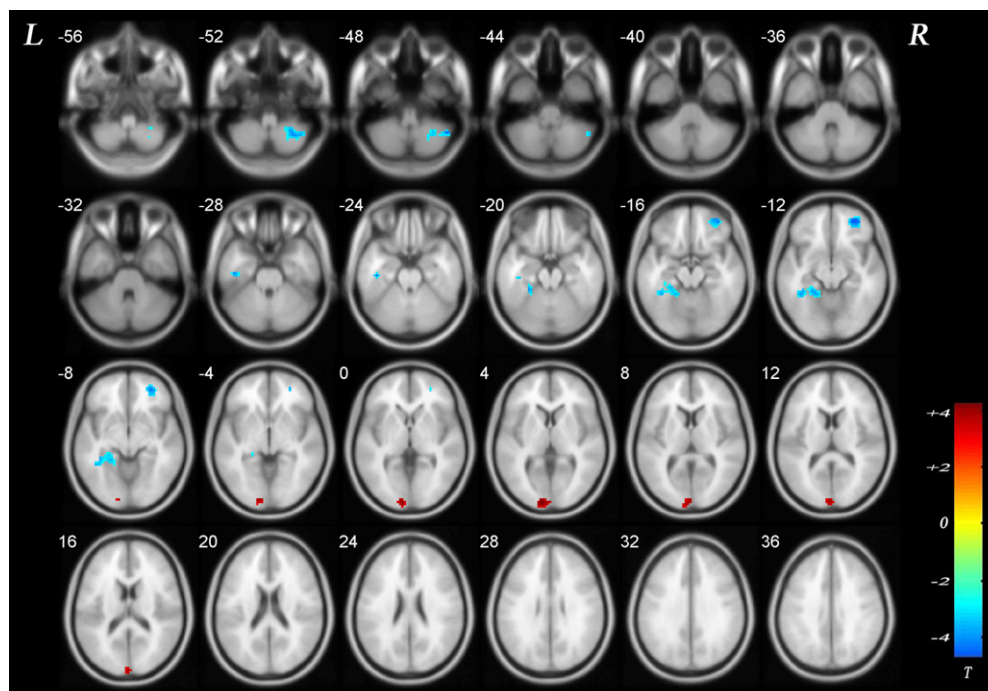

Fig. 1. fALFF differences between patients with MDD and healthy controls. The color bars represent the t value of the group analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
ROC analysis between patients with MDD and healthy controls.

Brain regions	Area under the curve	Cut-off value	Sensitivity	Specificity
Right cerebellum posterior lobe	0.823	0.94[a]	86.4% (19/22)	68.4% (13/19)
Right middle frontal gyrus	0.854	1.06	90.9% (20/22)	68.4% (13/19)
Left superior occipital gyrus, cuneus	0.792	1.02	81.8% (18/22)	73.3% (14/19)
Left parahippocampal gyrus	0.880	0.93	81.8% (18/22)	94.7% (18/19)

ROC: receiver operating characteristic curves; MDD: major depressive disorder.

[a] Using this cut-off value, the mean fALFF value of the right cerebellum posterior lobe could correctly classify 19 of 22 patients with MDD and 13 of 19 healthy controls, yielding a sensitivity of 86.4% and a specificity of 68.4%. The means of other cut-off points were similar.
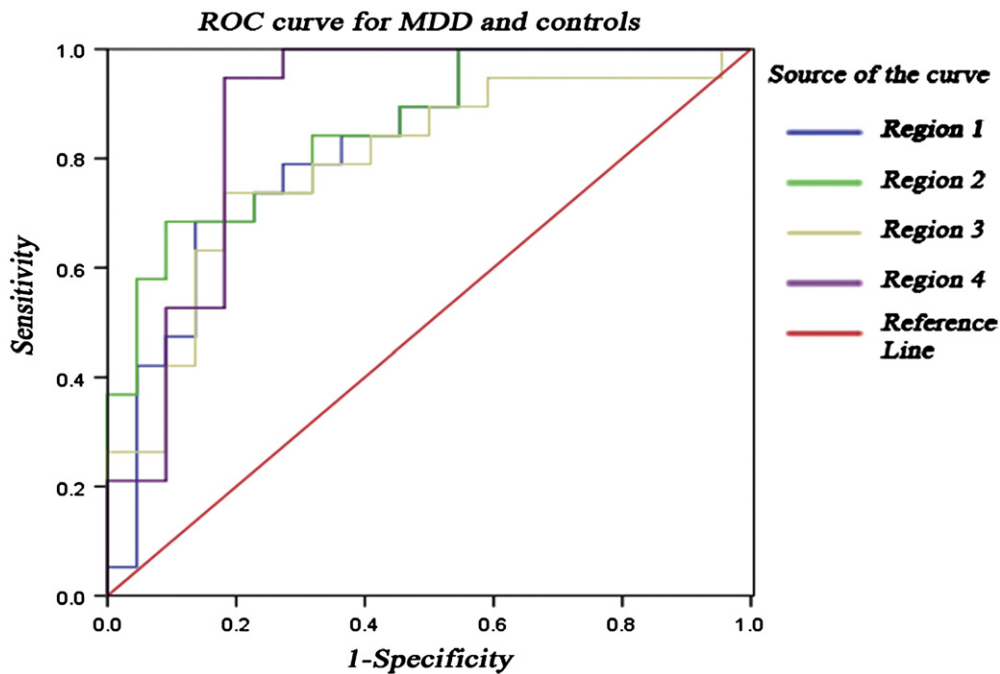

Fig. 2. Receiver operating characteristic (ROC) curves for patients with MDD and healthy controls. *Region 1*: right cerebellum posterior lobe; *Region 2*: right middle frontal gyrus; *Region 3*: left superior occipital gyrus, cuneus; *Region 4*: left parahippocampal gyrus.

3.3. Correlations between fALFF and the severity of depression

Linear correlation analyses showed no significant correlation between the mean fALFF values and HRSD total scores.

3.4. ROC analysis

As shown in Table 2 and Fig. 2, the areas under the curves (AUC) of the above-mentioned four clusters were relatively high, hereby suggesting that the mean fALFF values of these regions might be used as markers for the diagnosis of MDD.

4. Discussion

To the best of our knowledge, this is the first study using fALFF method to examine the amplitude of LFOs in medication-naive, first-episode patients with MDD. A major strength of the present study is the recruitment of a well-defined group of patients. The antidepressants have been shown to have an effect on making the brain function of patients with depression similar to that of healthy controls (Fu et al., 2007; Lui et al., 2011). In the present study, we found that patients with MDD had lower fALFF in right cerebellum posterior lobe, left parahippocampal gyrus and right middle frontal gyrus, and higher fALFF in left superior occipital gyrus/cuens. Our findings indicated that there were abnormalities in LFOs in patients with MDD.

Significantly decreased fALFF were observed in middle frontal gyrus and parahippocampal gyrus in MDD after multiple comparisons correction. These two regions are important regions in the cortical–limbic dysregulation model in MDD. Previous studies document that alterations in cortical–limbic circuits are implicated in the mechanisms underlying emotional dysfunction (Drevets, 2000; Liu et al., 2010; Tekin and Cummings, 2002). Disrupted fronto-limbic connectivity, which leads to the loss of prefrontal cortex control over limbic regions, is considered to be at the root of the pathogenesis of emotional, cognitive and behavioral changes in depression (Savitz and Drevets, 2009). Moreover, decreased fronto-limbic connectivity has been found in both task (Siegle et al., 2002) and resting-state conditions (Anand et al., 2009). Thus, abnormalities of LFOs amplitude in middle frontal gyrus and parahippocampal gyrus may lead to a disconnection syndrome, which partly contribute to emotional dysregulation exhibited by patients with MDD.

The visual area, including superior occipital gyrus and cuneus was found to show higher fALFF value in patients with MDD. These two regions are thought as the key regions related to visual recognition circuit (Tao et al., 2011). As all the participants were scanned with eyes closed, thus the visions between the two groups are not significantly different. By using a working memory

task, previous study find that the non-psychotic depressed groups showed greater activation than the healthy comparison in the superior occipital gyrus (Garrett et al., 2011). Moreover, there is an altered activity in the occipital cortex in remitted geriatric depression during rest (Yuan et al., 2008). Consistent with these studies, the abnormal fALFF values in the occipital gyrus may be linked with impaired working memory and aberrant visual recognition processing in major depression.

The lower fALFF in the cerebellum was unexpected in the current study. In contrast to the large number of neuroimaging studies investigating cerebral cortex in MDD, little attention has been paid to the abnormalities in cerebellum. Traditionally, the emphasis of studies on cerebellum function has been on the acquisition of motor coordination and motor behavior (Stein and Glickstein, 1992). However, the notion that cerebellum is involved in emotional control and probably plays a role in the perception of emotional stimuli has gained popularity (Schmahmann, 2010). Up to now, both structural and functional studies have found alterations in the cerebellum in patients with MDD. Gray matter changes have been found in the cerebellum in depressed group (Liu et al., 2012a; Peng et al., 2011), and decreased regional homogeneity of the cerebellum is found in patients with MDD by using resting-state fMRI (Guo et al., 2011). In the present study, significantly reduced fALFF in the cerebellum provided additional evidence for the involvement of cerebellar abnormality in MDD, and may result in the emotional dysregulation and cognitive dysfunction that widely exist in patients with MDD.

Unfortunately, no significant correlation was found between the areas with abnormal fALFF and HRSD total scores. In spite of the fact that the current findings might be confounded by the small sample size, it is also possible that abnormal fALFF in these regions might be a trait change for MDD regardless of the severity of symptoms. In addition, as presented in Table 2, the sensitivity and specificity of ROC analysis in right cerebellum are 86.4% and 68.4%, and the sensitivity and specificity of ROC analysis in right middle frontal gyrus are 90.9% and 68.4%. The specificity of ROC analysis in cerebellum and middle frontal gyrus seems relatively low and thus may not be used for the diagnosis of MDD. However, the sensitivity of ROC analysis in these two regions was relatively high. This characteristic of possessing high sensitivity may be advantageous for the purpose of diagnosis, because the cost is different for misclassifying a patient with MDD into a healthy control (with sensitivity reduced in this case) and misclassifying a healthy control into a patient with MDD (with specificity reduced in this case), and the former cost is much higher than the latter. It is well known that misclassifying a healthy person to be a patient might be troublesome; however, misclassifying a patient to be a healthy subject might cause severe consequences. If a patient with MDD is misdiagnosed as a healthy subject, necessary therapy to delay or cure the disease might not be provided on time. This may accelerate the progression of disease from mild to severe, eventually leading to death of patient. Therefore, it is important to alleviate this circumstance by providing high sensitivity to the disease. Moreover, the AUC of cerebellum and middle frontal gyrus were relatively high (0.823 and 0.854), indicating good diagnostic accuracy. Furthermore, by using support vector machine (SVM), Gong et al. (2011) obtained a significantly diagnostic accuracy of gray matter was 67.39% ($p=0.01$; 69.57% specificity, 65.22% sensitivity). From these, we speculated that these regions might be used as trait alteration for the diagnosis of MDD.

5. Study limitations

Several limitations should be considered in explaining the results. First, we used a relatively low sampling rate (TR=2 s) for multislice acquisitions. Under this sampling rate, respiratory and cardiac fluctuations were reduced but could not completely be eliminated. A more rigorous approach should be used to correct such physiological noises in future studies. Second, all subjects were instructed to close their eyes during the resting-state data acquisition. Recent study reported that there are statistically significant differences in the spontaneous brain activity between the conditions of eyes-closed and eyes-open (Yan et al., 2009). Thus, it would be interesting to examine which condition could be more sensitive for detecting the changes in the amplitude of LFOs. Third, no significant correlations between HRSD and fALFF were found in this study. Although the AUC of the four regions were relatively high, no significant correlations may limit our findings to some extent. Larger sample size will be necessary to confirm the current results or refute them in the future studies. Finally, although fALFF is regarded as reflecting regional signal dynamics, the exact physiological nature of fALFF is not fully understood. The exact basis remains to be fully characterized.

6. Conclusion

Taken together, the current findings suggested that fALFF was abnormal in patients with MDD. This finding might have already existed in the initial stage of MDD, because our case group only included medication-naive, first-episode patients with MDD. The abnormal amplitude of LFOs in these regions may have implications for the understanding of the pathophysiology of MDD. Further analysis should be conducted to investigate the progression of these changes by longitudinal studies.

Conflict of interest

No conflict of interest declared.

References

Anand, A., Li, Y., Wang, Y., Lowe, M.J., Dzemidzic, M., 2009. Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. Psychiatry Research 171, 189–198.

APA, 1994. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. American Psychiatric Publishing, Inc.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magnetic Resonance in Medicine 34, 537–541.

Biswal, B.B., Kannurpatti, S.S., Rypma, B., 2007. Hemodynamic scaling of fMRI-BOLD signal: validation of low-frequency spectral amplitude as a scalability factor. Magnetic Resonance Imaging 25, 1358–1369.

Bluhm, R., Williamson, P., Lanius, R., Theberge, J., Densmore, M., Bartha, R., Neufeld, R., Osuch, E., 2009. Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: decreased connectivity with caudate nucleus. Psychiatry and Clinical Neurosciences 63, 754–761.

Chen, J.D., Liu, F., Xun, G.L., Chen, H.F., Hu, M.R., Guo, X.F., Xiao, C.Q., Wooderson, S.C., Guo, W.B., Zhao, J.P., 2012. Early and late onset, first-episode, treatment-naive depression: same clinical symptoms, different regional neural activities. Journal of Affective Disorders , http://dx.doi.org/10.1016/j.jad.2012.05.025.

Drevets, W.C., 2000. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Progress in Brain Research 126, 413–431.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). American Psychiatric Press, Washington, DC.

Fransson, P., 2006. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia 44, 2836–2845.

Fu, C.H., Williams, S.C., Brammer, M.J., Suckling, J., Kim, J., Cleare, A.J., Walsh, N.D., Mitterschiffthaler, M.T., Andrew, C.M., Pich, E.M., Bullmore, E.T., 2007. Neural responses to happy facial expressions in major depression following antidepressant treatment. American Journal of Psychiatry 164, 599–607.

Garrett, A., Kelly, R., Gomez, R., Keller, J., Schatzberg, A.F., Reiss, A.L., 2011. Aberrant brain activation during a working memory task in psychotic major depression. American Journal of Psychiatry 168, 173–182.

Gong, Q., Wu, Q., Scarpazza, C., Lui, S., Jia, Z., Marquand, A., Huang, X., McGuire, P., Mechelli, A., 2011. Prognostic prediction of therapeutic response in depression using high-field MR imaging. Neuroimage 55, 1497–1503.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biological Psychiatry 62, 429–437.

Guo, W.B., Liu, F., Chen, J.D., Gao, K., Xue, Z.M., Xu, X.J., Wu, R.R., Tan, C.L., Sun, X.L., Liu, Z.N., Chen, H.F., Zhao, J.P., 2012a. Abnormal neural activity of brain regions in treatment-resistant and treatment-sensitive major depressive disorder: a resting-state fMRI study. Journal of Psychiatric Research 46, 1366–1373.

Guo, W.B., Liu, F., Xue, Z.M., Xu, X.J., Wu, R.R., Ma, C.Q., Wooderson, S.C., Tan, C.L., Sun, X.L., Chen, J.D., Liu, Z.N., Xiao, C.Q., Chen, H.F., Zhao, J.P., 2012b. Alterations of the amplitude of low-frequency fluctuations in treatment-resistant and treatment-response depression: a resting-state fMRI study. Progress in Neuro-Psychopharmacology and Biological Psychiatry 37, 153–160.

Guo, W.B., Liu, F., Xue, Z.M., Yu, Y., Ma, C.Q., Tan, C.L., Sun, X.L., Chen, J.D., Liu, Z.N., Xiao, C.Q., Chen, H.F., Zhao, J.P., 2011. Abnormal neural activities in first-episode, treatment-naive, short-illness-duration, and treatment-response patients with major depressive disorder: a resting-state fMRI study. Journal of Affective Disorders 135, 326–331.

Guo, W.B., Liu, F., Xun, G.L., Hu, M.R., Guo, X.F., Xiao, C.Q., Chen, H.F., Wooderson, S.C., Chen, J.D., Zhao, J.P., 2012c. Reversal alterations of amplitude of low-frequency fluctuations in early and late onset, first-episode, drug-naive depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry , http://dx.doi.org/10.1016/j.pnpbp.2012.08.014.

Hamilton, M., 1967. Development of a rating scale for primary depressive illness. British Journal of Social and Clinical Psychology 6, 278–296.

Hoptman, M.J., Zuo, X.N., Butler, P.D., Javitt, D.C., D'Angelo, D., Mauro, C.J., Milham, M.P., 2010. Amplitude of low-frequency oscillations in schizophrenia: a resting state fMRI study. Schizophrenia Research 117, 13–20.

Huang, X.Q., Lui, S., Deng, W., Chan, R.C., Wu, Q.Z., Jiang, L.J., Zhang, J.R., Jia, Z.Y., Li, X.L., Li, F., Chen, L., Li, T., Gong, Q.Y., 2010. Localization of cerebral functional deficits in treatment-naive, first-episode schizophrenia using resting-state fMRI. Neuroimage 49, 2901–2906.

Jiang, G.H., Qiu, Y.W., Zhang, X.L., Han, L.J., Lv, X.F., Li, L.M., Lin, C.L., Zhuo, F.Z., Hu, S.Y., Tian, J.Z., 2011. Amplitude low-frequency oscillation abnormalities in the heroin users: a resting state fMRI study. Neuroimage 57, 149–154.

Kannurpatti, S.S., Biswal, B.B., 2008. Detection and scaling of task-induced fMRI-BOLD response using resting state fluctuations. Neuroimage 40, 1567–1574.

Kenny, E.R., O'Brien, J.T., Cousins, D.A., Richardson, J., Thomas, A.J., Firbank, M.J., Blamire, A.M., 2010. Functional connectivity in late-life depression using resting-state functional magnetic resonance imaging. American Journal of Geriatric Psychiatry 18, 643–651.

Kunisato, Y., Okamoto, Y., Okada, G., Aoyama, S., Demoto, Y., Munakata, A., Nomura, M., Onoda, K., Yamawaki, S., 2011a. Modulation of default-mode network activity by acute tryptophan depletion is associated with mood change: a resting state functional magnetic resonance imaging study. Neuroscience Research 69, 129–134.

Kunisato, Y., Okamoto, Y., Okada, G., Aoyama, S., Nishiyama, Y., Onoda, K., Yamawaki, S., 2011b. Personality traits and the amplitude of spontaneous low-frequency oscillations during resting state. Neuroscience Letters 492, 109–113.

Lai, C.H., Wu, Y.T., 2012. Patterns of fractional amplitude of low-frequency oscillations in occipito-striato-thalamic regions of first-episode drug-naive panic disorder. Journal of Affective Disorders , http://dx.doi.org/10.1016/j.jad.2012.04.021.

Liu, F., Guo, W., Yu, D., Gao, Q., Gao, K., Xue, Z., Du, H., Zhang, J., Tan, C., Liu, Z., Zhao, J., Chen, H., 2012a. Classification of different therapeutic responses of major depressive disorder with multivariate pattern analysis method based on structural MR scans. PLoS One 7, e40968.

Liu, F., Hu, M., Wang, S., Guo, W., Zhao, J., Li, J., Xun, G., Long, Z., Zhang, J., Wang, Y., Zeng, L., Gao, Q., Wooderson, S.C., Chen, J., Chen, H., 2012b. Abnormal regional spontaneous neural activity in first-episode, treatment-naive patients with late-life depression: a resting-state fMRI study. Progress in Neuro-Psychopharmacology and Biological Psychiatry 39, 326–331.

Liu, X., Wang, Y., Liu, H., Liu, Z., Zhou, W., 2010. Diffusion tensor imaging and resting state functional magnetic resonance imaging on young patients with major depressive disorder. Zhong Nan Da Xue Xue Bao Yi Xue Ban 35, 25–31.

Lui, S., Wu, Q., Qiu, L., Yang, X., Kuang, W., Chan, R.C., Huang, X., Kemp, G.J., Mechelli, A., Gong, Q., 2011. Resting-state functional connectivity in treatment-resistant depression. American Journal of Psychiatry 168, 642–648.

Peng, J., Liu, J., Nie, B., Li, Y., Shan, B., Wang, G., Li, K., 2011. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: a voxel-based morphometry study. European Journal of Radiology 80, 395–399.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.

Savitz, J.B., Drevets, W.C., 2009. Imaging phenotypes of major depressive disorder: genetic correlates. Neuroscience 164, 300–330.

Schmahmann, J.D., 2010. The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychology Review 20, 236–260.

Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, V.A., Carter, C.S., 2002. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biological Psychiatry 51, 693–707.

Stein, J.F., Glickstein, M., 1992. Role of the cerebellum in visual guidance of movement. Physiological Reviews 72, 967–1017.

Tao, H., Guo, S., Ge, T., Kendrick, K.M., Xue, Z., Liu, Z., Feng, J., 2011. Depression uncouples brain hate circuit. Molecular Psychiatry , http://dx.doi.org/10.1038/mp.2011.127.

Tekin, S., Cummings, J.L., 2002. Frontal–subcortical neuronal circuits and clinical neuropsychiatry: an update. Journal of Psychosomatic Research 53, 647–654.

Veer, I.M., Beckmann, C.F., van Tol, M.J., Ferrarini, L., Milles, J., Veltman, D.J., Aleman, A., van Buchem, M.A., van der Wee, N.J., Rombouts, S.A., 2010. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Frontiers in Systems Neuroscience 4, 41.

Wang, Z., Yan, C., Zhao, C., Qi, Z., Zhou, W., Lu, J., He, Y., Li, K., 2011. Spatial patterns of intrinsic brain activity in mild cognitive impairment and alzheimer's disease: a resting-state functional MRI study. Human Brain Mapping 32, 1720–1740.

Yan, C., Liu, D., He, Y., Zou, Q., Zhu, C., Zuo, X., Long, X., Zang, Y., 2009. Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. PLoS One 4, e5743.

Yuan, Y., Zhang, Z., Bai, F., Yu, H., Shi, Y., Qian, Y., Liu, W., You, J., Zhang, X., Liu, Z., 2008. Abnormal neural activity in the patients with remitted geriatric depression: a resting-state functional magnetic resonance imaging study. Journal of Affective Disorders 111, 145–152.

Zang, Y.F., He, Y., Zhu, C.Z., Cao, Q.J., Sui, M.Q., Liang, M., Tian, L.X., Jiang, T.Z., Wang, Y.F., 2007. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain & Development 29, 83–91.

Zeng, L.L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., Zhou, Z., Li, Y., Hu, D., 2012. Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. Brain 135, 1498–1507.

Zhou, Y., Yu, C., Zheng, H., Liu, Y., Song, M., Qin, W., Li, K., Jiang, T., 2010. Increased neural resources recruitment in the intrinsic organization in major depression. Journal of Affective Disorders 121, 220–230.

Zou, Q.H., Zhu, C.Z., Yang, Y., Zuo, X.N., Long, X.Y., Cao, Q.J., Wang, Y.F., Zang, Y.F., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. Journal of Neuroscience Methods 172, 137–141.