



Research report

Frequency-dependent alterations in regional homogeneity in major depression

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H I G H L I G H T S

- We investigated spontaneous neural activity in MDD patients in the special frequency band.
- The MDD patients showed increased ReHo in the MOG in the slow-4 band.
- The MDD patients showed decreased ReHo in the ACC, IFG, SFG, and bilateral thalamus in the slow-4 band.
- The MDD patients showed increased ReHo in the mPFC in the slow-5 band.

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Previous studies using resting-state functional magnetic resonance imaging (fMRI) have found abnormal spontaneous neural activity in patients with major depressive disorder (MDD). Yet, the frequency-dependent neural activity in MDD is largely unknown. Here, we used resting-state fMRI and regional homogeneity (ReHo) methods to investigate spontaneous neural activity in specific frequency bands of 31 MDD patients and 31 age-, gender- and education-matched healthy controls. We examined spontaneous neural activity in three frequency bands: slow-4 (0.027–0.073 Hz), slow-5 (0.010–0.027 Hz), and the typical band (0.01–0.08 Hz). Compared to controls, MDD patients showed increased ReHo in the middle frontal gyrus (MFG) and decreased ReHo in the fusiform and postcentral gyrus at the typical band. Importantly, MDD patients showed increased ReHo in the middle occipital gyrus (MOG) and decreased ReHo in the anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), superior frontal gyrus (SFG) and the bilateral thalamus in the slow-4 band, while they showed increased ReHo in the medial prefrontal cortex (mPFC) in the slow-5 band. Our results suggest that the abnormality of ReHo in MDD is associated with the frequency band and that future studies should take frequency band effect into account when examining spontaneous neural activity.

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1. Introduction

Major depressive disorder (MDD) is a common mental disorder that is characterized by persistent depressed mood, anxiety and dysphoria, psychomotor changes, alterations of motivation and social behavior, and sleep abnormalities [3]. MDD is often accom-

panied by deficits in cognitive control and abnormal emotional processing [5]. Advanced noninvasive neuroimaging technology such as functional magnetic resonance imaging (fMRI), allows us to observe the functional brain abnormalities associated with MDD, and resting-state fMRI has been widely used in recent years to investigate abnormal spontaneous neural activity in MDD [6,9,11,19,29,40].

In contrast to task-based fMRI, resting-state fMRI does not require complex experimental designs that can remove some stimuli or task-related confounds. It provides a reliable measure of “baseline” brain activity and connectivity [14]. Regional homogeneity (ReHo) has been shown to be an effective index to measure

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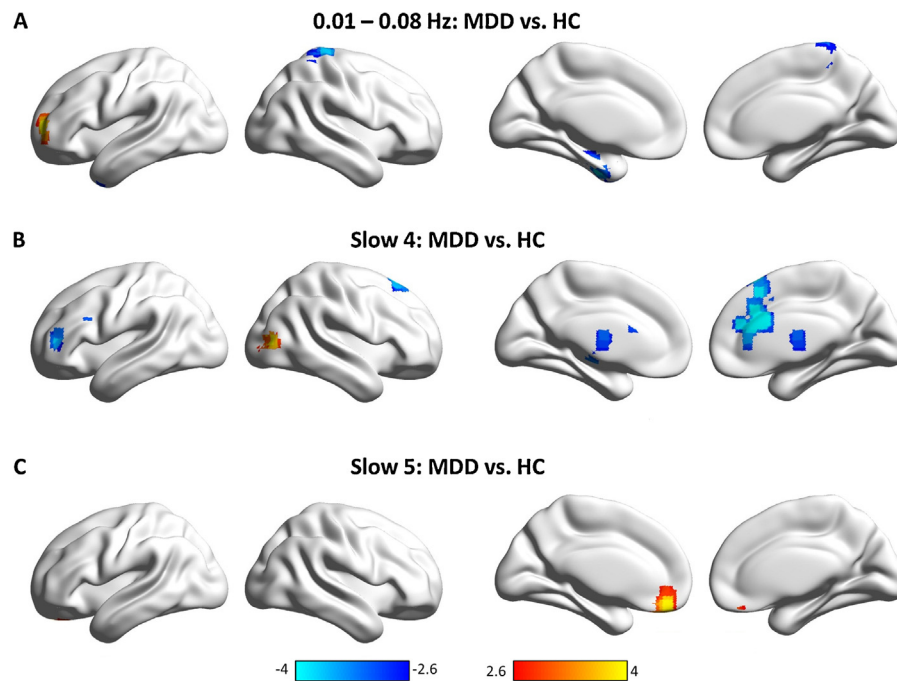


Fig. 1. Brain regions with abnormal ReHo in MDD. Red represents higher ReHo in the MDD patients than in the healthy controls, whereas blue represents lower ReHo. (A) Brain regions showing abnormal ReHo in the typical band (0.01–0.08 Hz). (B) Brain regions showing abnormal ReHo in the slow-4 band. (C) Brain regions showing abnormal ReHo in the slow-5 band. All the clusters survived at $p < 0.05$, alphaSim corrected (individual voxel threshold $p < 0.01$ and a minimum cluster size of 40). More details about the brain regions are described in Tables 2–4. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

spontaneous neural activity in resting-state fMRI analysis [36]. ReHo reflects the neural coherence of a given voxel with its nearest voxels in a voxel-wise analysis, which has been interpreted as “localized connectivity” [17,19]. Numerous studies that have explored spontaneous brain activity in MDD using the ReHo method have provided some evidence of brain abnormalities in MDD during rest [10–12,19,20,22,29,31,35]. For example, Guo et al. [11] found abnormal ReHo in regions of limbic-cortical networks in MDD, while Liu et al. [22] found decreased ReHo in the insula and cerebellum in MDD. Wu et al. [29] found that MDD patients showed high ReHo within temporo-limbic regions and low ReHo in the frontal, parietal, and fusiform cortex and the caudate. Moreover, a meta-analysis by Iwabuchi et al. [17] found that the medial prefrontal cortex (mPFC) showed the most reliable abnormalities in MDD.

Previous resting-state studies have examined MDD-related neural activity in the typical low frequency band (0.01–0.08 Hz). However, whether the abnormal ReHo in MDD is related to a specific frequency band is largely unknown. The aim of the present study was to investigate frequency-dependent alterations in ReHo in MDD. The main reason why we focused on frequency-dependent alterations was that different neural signals within different frequency bands might be generated by distinct oscillators that have specific properties and physiological functions [4,24]. The low frequency band can be subdivided into several bands: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz) [4,24]. The slow-2 and slow-3 bands mainly reflect high-frequency physiological noise and white-matter signals, whereas the slow-4 and slow-5 bands reflect gray-matter signals [20,41]. Recently, Xue et al. [30] systematically explored the different characteristics of the slow-4 and slow-5 bands at regional and network levels. They found the slow-4 band exhibited higher ReHo in the superior frontal cortex, anterior cingulate cortex (ACC), the fusiform gyrus, and other areas, and the slow-5 band exhibited higher ReHo in the bilateral inferior frontal gyrus (IFG) and some midline structures, including the

medial frontal cortex (mPFC) and the supplementary motor area (SMA). In addition, Wei et al. (2014) found that low frequency fluctuations in specific bands were associated with personality traits, which might imply that spontaneous brain activity is frequency-dependent. On the other hand, using this approach to investigate the neural activity of specific frequency bands (slow-4 and slow-5 bands) has been successful in detecting local abnormalities in different psychiatric disorders, such as Alzheimer’s disease [21], schizophrenia [33,34], social anxiety [39], mild cognitive impairment [15], and Parkinson’s disease [16,39]. To the best of our knowledge, no study has investigated specific frequency bands in MDD. Therefore, it would be useful to differentiate the frequency band specificity associated with MDD.

We sought to address this issue by examining the frequency-dependent neural activity in MDD during the resting-state. This is the first study, to our knowledge, to use ReHo as an index to investigate the spontaneous neural activity of specific frequency bands (slow-4 and slow-5 band) in MDD. We hypothesized that MDD patients would show abnormal ReHo in regions associated with cognitive control and emotional processing, and that these abnormalities would be associated with specific frequency bands. In addition, we also investigated ReHo in the typical frequency band (0.01–0.08 Hz) to identify potential frequency-dependent changes [34].

2. Materials and methods

2.1. Participants

This investigation recruited thirty-one depressed patients (eighteen female) who were outpatients at a Chongqing Medical University affiliated hospital. Thirty-one age-, gender-, and education-matched healthy subjects were recruited from students, government retirees, hospital staff, logistics staff, and other persons. Detailed demographic and clinical characteristics of the samples are shown in Table 1. All patients were diagnosed as suffer-

Table 1
Demographic information and clinical characteristics.

Characteristic	Depressed patients (n = 31)	Healthy controls (n = 31)	p value
Age (years)	33.8 ± 9.2	34.7 ± 12.5	0.756
Education (years)	12.4 ± 3.3	12.2 ± 3.3	0.879
Duration of illness (months)	34.1 ± 46.8		N. A.
HAMD	22.7 ± 5.0		N. A.
BDI	21.1 ± 7.4		N. A.

HAMD = Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory. N. A., not applicable. Values given as mean with standard deviation.

ing from MDD using the following criteria: (1) they did not have any brain lesions; (2) their symptoms met the criteria for MDD according to the DSM-IV; (3) they scored higher than 20 on the Hamilton Depression Scale; and (4) they did not have other psychotic diseases, drug/tobacco abuse, or other types of personality disorders. Sixteen depressed patients in the current sample were medication naive; 11 patients took SSRIs (e.g., Fluoxetine or Paroxetine); 3 patients took an SNRI (e.g., Venlafaxine); 1 patient took a TCA (e.g., Amitriptyline). A semi-structured interview was conducted with each healthy control to verify that they did not have any psychiatric problems or a history of psychiatric illness, such substance abuse or a personality disorder. All patients and healthy controls had normal eyesight or corrected eyesight, did not have color blindness (tested using a seven-color board), and were right-handed, as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971). All the participants provided their written informed consent to the participate the current study, and the study protocol was approved by a local ethics committee.

2.2. Image acquisition

MRI scanning was conducted with a Siemens 3T scanner (MAGENTOM Trio, a Tim system) with an eight-channel phased array coil. A total of 242 functional images were acquired for each participant with a gradient echo type Echo Planar Imaging (EPI) sequence: echo time (TE) = 30 ms; repetition time (TR) = 2000 ms; flip angle = 90°; slices = 32; slice thickness = 3.0 mm; slice gap = 1 mm; field of view (FOV) = 220 × 220 mm²; resolution matrix = 64 × 64; in-plane resolution = 3.4 × 3.4 mm²; interslice skip = 0.99 mm. In addition, a high-resolution T1 weighted magnetization prepared gradient echo sequence (MPRAGE: TR/TE/TI = 1900/2.52/900 ms, flip angle = 9°, matrix = 256 × 256) anatomical scan also was acquired for registration purposes and anatomically localized the functional regions. One hundred and seventy-six contiguous sagittal slices were obtained with a 1 × 1 mm in-plane resolution and a 1 mm slice thickness. The participants were instructed to keep their eyes closed during image acquisition, while keeping their head as still as possible without falling asleep.

2.3. Image preprocessing

Image preprocessing was performed using statistical parametric mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). Briefly, the first ten images were discarded for each subject because of the instability of the initial MRI signal and participants' adaptation to the situation. The remaining 232 images were slice-acquisition corrected and aligned to the first image for head-motion correction (a least-squares approach and a 6-parameter spatial transformation). None of the subjects had more than 3 mm maximum displacement in the x, y, or z translation and 3° of the angular motion during the entire fMRI scan. Then, the corrected images were spatially normalized to the Montreal Neurological Institute (MNI) EPI template in SPM8 and resampled to 3 × 3 × 3 mm³ voxels, and the linear drift was removed. Finally,

the data were filtered to reduce the influences of low frequency drift and high-frequency noise, using typical temporal bandpass (0.01–0.08 Hz), slow-5 bandpass (0.01–0.027 Hz), and slow-4 bandpass (0.027–0.073 Hz), separately [4,41].

2.4. ReHo analysis

ReHo analysis was performed by the Resting-State fMRI Data Analysis Toolkit (REST, <http://www.restfmri.net>). The ReHo value was calculated to measure the similarity of the time series of a given voxel with those of its nearest neighbors (26 voxels) in a voxel-wise analysis. Individual ReHo maps were generated by calculating the Kendall's coefficient of concordance (KCC) of the time series of a given voxel to its nearest 26 voxels. The formula and details of calculating the KCC value have been described in a previous study [36]. For standardization purposes, the individual ReHo map was divided by its own mean KCC within the mask made from the normalization step [35]. Then, the resulting data were spatially smoothed with a Gaussian kernel (full-width at half-maximum [FWHM] = 6 mm).

2.5. Statistical analysis

ReHo differences between the groups were examined in the typical frequency band (0.01–0.08 Hz) using a two-sample *t*-test on the individual normalized ReHo maps in a voxel-by-voxel manner. Then, a two-way repeated-measures analysis of variance (ANOVA) was performed to examine the effects of group and frequency band on the ReHo. Group (the MDD patients vs. healthy controls) served as a between-subject factor and frequency band (the slow-4 vs. the slow-5) served as a within-subject factor. The resulting statistical map was set at *p* < 0.05 (AlphaSim corrected for multiple comparisons, with a combined individual voxel *p* value < 0.01 with a cluster size > 40 voxels).

3. Results

3.1. ReHo analysis in the typical frequency band (0.01–0.08 Hz)

The MDD patients showed significantly higher ReHo in the typical frequency band (0.01–0.08 Hz), relative to the healthy controls in the dorsal lateral prefrontal cortex (dlPFC), while lower ReHo was observed in the fusiform and postcentral gyrus (Table 2 and Figs. 1 a and 2).

3.2. Main effect of groups and frequency bands

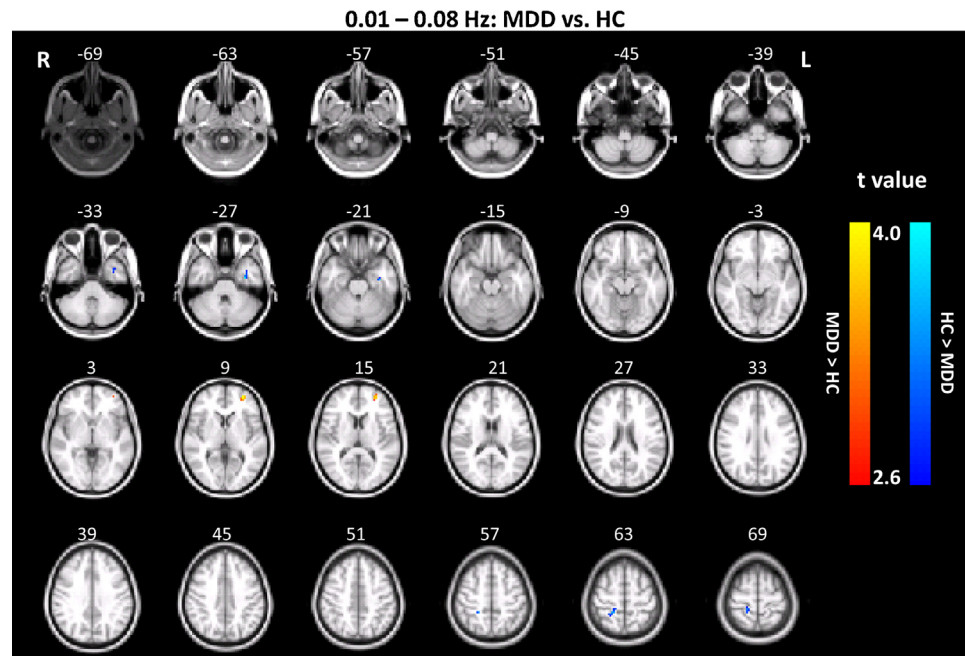
The ANOVA found a main effect of groups on ReHo, which is shown in Table S1 and Fig. S1. Compared to the controls, the MDD patients exhibited significantly higher ReHo in the middle occipital gyrus (MOG), medial frontal gyrus, angular gyrus, cerebellum supramarginal gyrus, and the middle frontal gyrus (MFG), while lower ReHo was observed in the anterior cingulate cortex (ACC), bilateral thalamus, brainstem, and the superior frontal gyrus (SFG). There was no significant interaction between frequency band and group.

Table 2

In the typical frequency band (0.01–0.08 Hz), brain regions showing differences in ReHo between groups.

Anatomical region	BA	Side	Cluster size (#voxels)	Peak voxel			
				T	x	y	z
MDD > HC							
Dorsolateral Prefrontal Cortex	10	L	46	4.88	–30	51	6
HC > MDD							
Fusiform	20/21	L	47	–4.18	–33	9	–33
Postcentral Gyrus	3/4	R	80	–3.80	21	–42	57

All the coordinates are donated by Montreal Neurological Institute (MNI) space coordinates. All the clusters survived $p < 0.05$, Alphasim corrected (individual voxel threshold $p < 0.01$ and a minimum cluster size of 40).

**Fig. 2.** Detailed slice showing abnormal ReHo in the typical band (0.01–0.08 Hz).

The main effect of frequency bands on ReHo is shown in Table S2 and Fig. S2. Several brain regions showed higher ReHo in the slow-4 band compared to the slow-5 band, including the middle frontal gyrus (MFG), superior frontal gyrus (SFG), precuneus, anterior cingulate cortex (ACC), and the cerebellum, and some regions showed higher ReHo in the slow-5 band compared to the slow-4 band, including the medial frontal gyrus, middle occipital gyrus (MOG), supramarginal gyrus, angular gyrus, middle frontal gyrus (MFG), inferior parietal lobule (IPL), and the supplementary motor area (SMA).

3.3. Frequency-dependent alterations in ReHo in MDD patients

Next, we examined ReHo between the groups in the slow-4 band and slow-5 band. Compared with the controls, the MDD patients exhibited significantly higher ReHo in the middle occipital gyrus (MOG) in the slow-4 band, and lower ReHo in the anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), superior frontal gyrus (SFG), and the bilateral thalamus in the slow-4 band (Table 3, Figs. 1 b, and 3).

The MDD patients also showed significantly higher ReHo in the medial prefrontal cortex (mPFC) in the slow-5 band, but did not show significantly lower ReHo in any brain region in the slow-5 band (Table 4, Figs. 1 c, and 4).

4. Discussion

The present study used the ReHo method to explore spontaneous neural activity during the resting state in three different frequency bands (the slow-4, slow-5, and typical bands). Our results showed that MDD patients exhibited abnormal ReHo in the frontal and temporal regions in the typical band. We also found that widespread brain regions showed significant differences in ReHo between MDD patients and healthy controls, and between the slow-4 and slow-5 bands. Importantly, we found that many brain regions showed significant group differences in the slow-4 band, and that some other brain regions showed significant group differences in the slow-5 band, which suggests that abnormal ReHo in MDD patients might be associated with specific frequency bands.

4.1. Differential ReHo between groups in the typical frequency band (0.01–0.08 Hz)

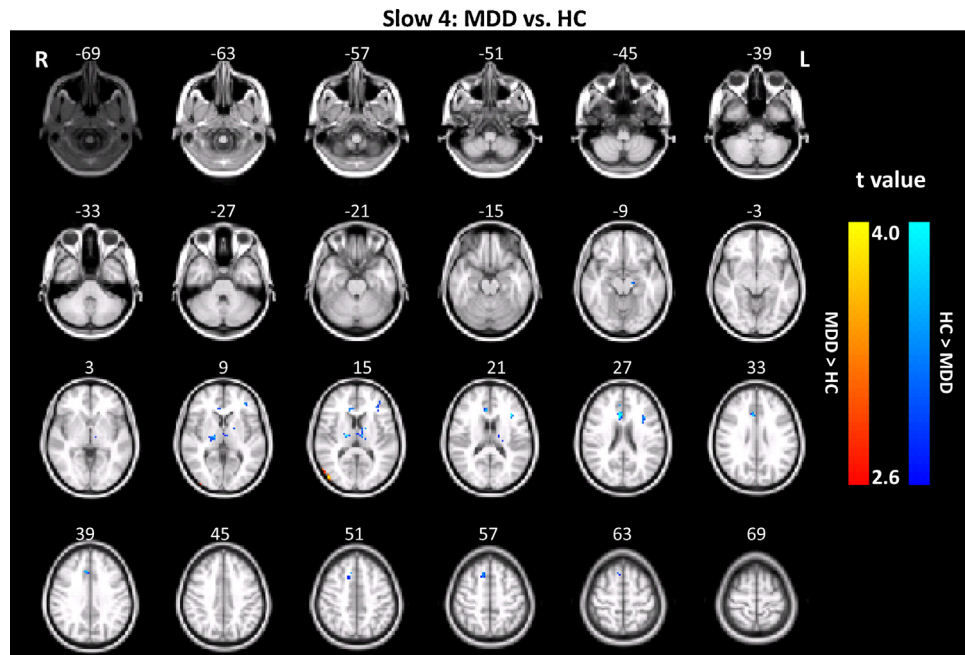
Compared with healthy controls, the MDD patients showed significantly decreased ReHo in the fusiform gyrus and postcentral gyrus, and increased ReHo in the dorsal lateral prefrontal cortex (dlPFC) in the typical frequency band (0.01–0.08 Hz). The dlPFC, which is a key region in the cognitive control network, is involved in working memory and cognitive control [5], and it is closely associated with the cognitive symptoms of depression [26]. In addition, abnormal ReHo in the sensory processing region (post-

Table 3

In the slow-4 (0.027–0.073 Hz), brain regions showing differences in ReHo between groups.

Anatomical region	BA	Side	Cluster size (#voxels)	Peak voxel			
				T	x	y	z
MDD > HC							
Middle Occipital Gyrus	19	R	44	4.21	48	–81	9
HC > MDD							
Anterior Cingulate Cortex	24/32	R	95	–4.87	6	21	24
Inferior Frontal Gyrus	10	L	68	–4.33	–36	21	15
Thalamus	–	R	42	–4.21	18	–12	9
Thalamus	–	L	99	–4.13	–15	–3	12
Superior Frontal Gyrus	8	R	57	–3.93	9	24	48

All the coordinates are donated by Montreal Neurological Institute (MNI) space coordinates. All the clusters survived $p < 0.05$, Alphasim corrected (individual voxel threshold $p < 0.01$ and a minimum cluster size of 40).

**Fig. 3.** Detailed slice showing abnormal ReHo in the slow-4 band (0.027–0.073 Hz).**Table 4**

In the slow-5 (0.01–0.027 Hz), brain regions showing differences in ReHo between groups.

Anatomical region	BA	Side	Cluster size (#voxels)	Peak voxel			
				Z	x	y	z
MDD > HC							
Medial Frontal Gyrus	11	L	49	4.48	–6	45	–18

All the coordinates are donated by Montreal Neurological Institute (MNI) space coordinates. All the clusters survived $p < 0.05$, Alphasim corrected (individual voxel threshold $p < 0.01$ and a minimum cluster size of 40).

central gyrus) and the visual processing region (fusiform gyrus) might contribute to perceptual impairments in patients with major depression, which is consistent with previous resting-state fMRI studies [20,27].

4.2. Main effect of groups and frequency bands

The main effect of groups in the ANOVA indicated that widespread brain regions showed significant differences in ReHo between the MDD patients and the healthy controls. We observed decreased ReHo in MDD patients in the ACC, thalamus, and SFG. These results are consistent with previous studies that have demonstrated abnormalities in the thalamus in MDD patients during the resting state [8] and emotion-processing tasks [1], as well as abnor-

mal structural volume [23,32]. The ACC is considered to be critical to cognitive control [5]. The involvement of the ACC in emotional processing and the interaction between emotion and cognition have been reported in a large number of studies [6,7]. These results imply that decreased ReHo in these regions could be associated with abnormal emotional processing and emotional control. Additionally, we observed increased ReHo in MDD patients in brain regions involved in language processing and visual processing, including the angular gyrus, supramarginal gyrus, and the MOG, which might contribute to cognitive dysfunction in MDD [37].

The present results showed that higher ReHo in the slow-4 band was located mainly in the middle frontal gyrus (MFG), superior frontal gyrus (SFG), precuneus, anterior cingulate cortex (ACC), and the cerebellum. In contrast, higher ReHo in the slow-5 band was

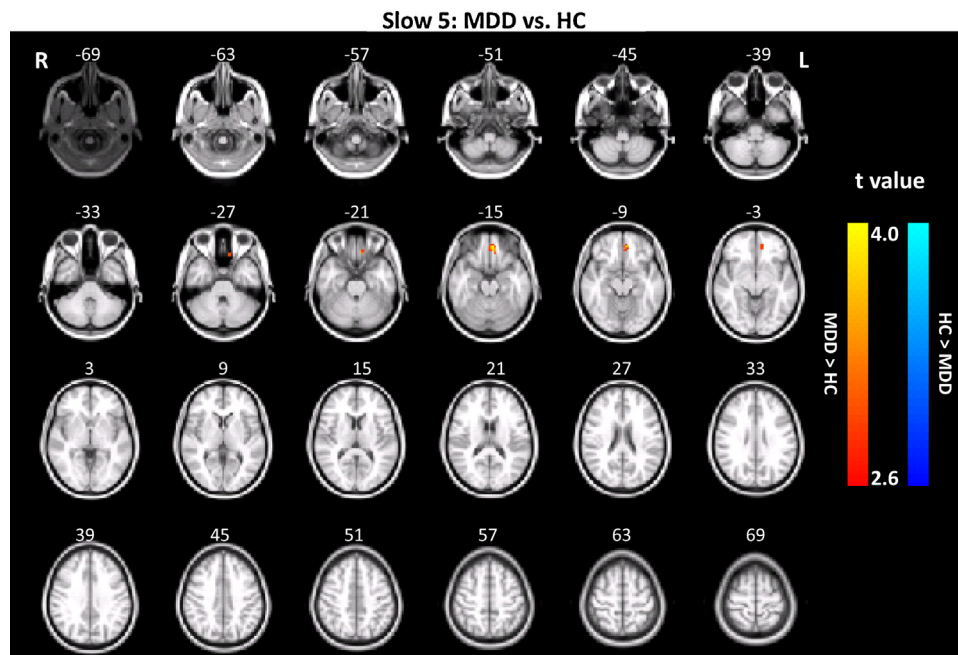


Fig. 4. Detailed slice showing abnormal ReHo in the slow-5 band (0.01–0.027 Hz).

located mainly in the middle occipital gyrus (MOG), supramarginal gyrus, angular gyrus, inferior parietal lobule (IPL), medial prefrontal cortex (mPFC), and the supplementary motor area (SMA). These results are similar to those of previous studies that used the ReHo method to detect different neural patterns between the slow-4 and slow-5 bands, which implied that the slow-4 and slow-5 bands might represent different psychophysiological states or functions [30,34].

4.3. Frequency-dependent alterations in ReHo in MDD patients

It is important that the abnormalities in brain spontaneous activity in the MDD patients were associated with specific frequency bands. Specifically, our results showed that MDD patients exhibited increased ReHo in the MOG and decreased ReHo in the ACC, thalamus, IFG, and the SFG in the slow-4 band. Previous studies suggest that the slow-4 band has less power and is localized more with subcortical structures, such as the thalamus and basal ganglia [4,42]. Our results implied that the slow-4 band might be more sensitive for detecting abnormal intrinsic brain activity in subcortical regions (e.g., thalamus) in MDD. This pattern is consistent with related findings in other disorders. For example, Zhang et al. (2013) found the slow-4 band was sensitive to abnormal thalamus activity in PD [38]. Similar to the group effects we found, we observed decreased ReHo in the ACC, thalamus, and SFG, and increased ReHo in the MOG in the slow-4 band. These similar patterns imply that the slow-4 band might be more sensitive for detecting abnormalities in intrinsic brain activity in MDD patients. Furthermore, our MDD patients showed decreased ReHo in the IFG, which is considered to be a key region involved in the control of inhibition [2]. Previous studies have indicated that abnormalities in the IFG in MDD patients were linked to impaired executive function during emotion-related tasks [28]. These results suggest that abnormal ReHo in MDD patients in the slow-4 band might be associated with impaired cognitive control and abnormal perceptual and emotional processing.

Compared with the slow-4 band, the lower frequency slow-5 band has higher power and is localized mainly within the prefrontal and parietal cortex, especially within some default mode

regions, such as the mPFC [42]. Our results showed higher ReHo in the slow-5 band in mPFC, which replicates previous research. Specifically, MDD patients, compared to healthy controls, showed increased ReHo in the mPFC in the slow-5 band. These results implied that the slow-5 band might be more sensitive for detecting abnormal intrinsic brain activity in the mPFC. The mPFC is a key region in the default mode network (DMN), which is involved in self-referential processing [13]. Previous studies suggested that depression is characterized by self-focus and pathological functioning of the DMN [18,25]. We think the abnormal ReHo in the mPFC in the present study might be linked to dysregulation of self-referential activity. In addition, on the neural network level, previous studies suggest that lower frequency bands are associated with long distance connectivity and large-scale networks [4,33]. This might indicate that abnormalities in the slow-5 band of the mPFC are associated with abnormal long distance connectivity and dysregulation of large-scale neural networks in MDD [43]. Thus, our findings implied that specific frequency bands could have specific pathophysiological significance, and that further research should examine spontaneous brain activity in different frequency bands.

4.4. Limitations

Several limitations of this study are worth mentioning. First, the present study was limited by a relatively small sample size. Therefore, the results of the current study should be replicated with a larger sample. Second, we were unable to completely exclude the effect of medication on neural activity, which might limit the translational value of our findings [11]. Third, physiological noise, such as respiratory and cardiac fluctuations, could not be entirely removed because of the low-sampling rate (TR=2s), although we tried to correct for such noise.

5. Conclusions

This is the first study to examine differences in spontaneous neural activity in specific frequency bands between MDD patients and healthy controls. Our results indicate that abnormal ReHo in MDD may be associated with these frequency bands. The findings

implied that future studies should take frequency band effects into account when examining spontaneous neural activity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bbr.2016.03.012>.

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