Brain Imaging and Behavior (2019) 13:1302–1310
https://doi.org/10.1007/s11682-018-9917-x

ORIGINAL RESEARCH

Aberrant interhemispheric functional connectivity in first-episode, drug-naïve major depressive disorder

Hong Yang[1] · Chengwei Wang[2,3] · Gongjun Ji[4] · Zhan Feng[1] · Jingfeng Duan[5] · Feng Chen[1] · Xiaohong Joe Zhou[6] · Yushu Shi[1] · Haiyan Xie[7]

Published online: 25 August 2018

Abstract

Many studies have indicated that depression is associated with impairment of the topological organization of the brain functional network, which may lead to disruption of mood and cognition in depressive patients. The abnormality of homotopic connectivity provides a basis for the clinical manifestations of depression, such as emotional and cognitive disorders. Several studies have investigated the abnormal imbalance of homotopic regions between the hemispheres in depressive patients. However, the reported findings are inconsistent. Additionally, the published studies have focused on only the grey matter when investigating functional connectivity abnormalities of the bilateral cerebral hemispheres in major depressive disorder (MDD). The aim of this study is to investigate functional connectivity abnormalities of the bilateral cerebral hemispheres in patients with first-episode, drug-naïve MDD using a voxel-mirrored homotopic connectivity (VMHC) method. Based on DSM-IV diagnostic criteria, 23 first-episode, drug-naïve MDD patients were recruited, together with 20 gender- and age-matched healthy normal controls. A Philips Achieva 3.0 T MRI scanner was used to acquire brain functional images at resting state as well as high-resolution structural images. The functional images were preprocessed by using Data Processing Assistant for Resting-State Functional MR Imaging toolkit and SPM8.VMHC between the bilateral hemispheres was computed and compared between the MDD and control groups. The correlation between the VMHC values of the abnormal homotopy function areas and the Hamilton Depression Rating Scale (HAMD) was evaluated in the MDD patients. Compared with the control group, the MDD patients showed significantly decreased VMHC values in the bilateral brain regions including the insular, putamen, and frontal white matter. The MDD patients did not exhibit increased VMHC values in any brain regions compared with the normal controls. In addition, a negative correlation was observed between the VMHC value in the frontal lobe white-matter and the HAMD in the MDD patients. Abnormalities in brain homotopic functional connectivity observed in this study may indicate abnormal neural circuits related to aberrant cognition and emotional processing in MDD. Although the physiological significance underlaying abnormal VMHC in white matter in the frontal lobe needs further research, our study new angle to investigate the role of white-matter abnormalities in MDD as well as other psychiatric disorders.

Keywords Major depressive disorder · Voxel-mirrored homotopic connectivity · Functional connectivity · Default mode network · Cognitive control network

✉ Haiyan Xie
1511861151@qq.com

[1] Department of Radiology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

[2] Department of CT/MRI, The First Affiliated Hospital of the Medical College, Shihezi University, Shihezi, China

[3] Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[4] Laboratory of Cognitive Neuropsychology, Department of Medical Psychology, Anhui Medical University, Hefei, China

[5] Department of Psychiatry, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

[6] Center for Magnetic Resonance Research and Departments of Radiology, Neurosurgery, and Bioengineering, University of Illinois at Chicago, Chicago, IL 60612, USA

[7] Department of Psychiatry, The Fourth Affiliated Hospital, College of Medicine, Zhejiang University, Yiwu, China

Introduction

The essential feature of major depressive disorder (MDD) is depressed mood or the loss of interest or pleasure in nearly all activities. MDD is associated with high mortality, much of which is accounted for by suicide. The World Health Organization projected that by 2020, MDD would be second only to coronary heart diseases in terms of disease burden socioeconomically (Sliz and Hayley 2012). However, neurophysiological mechanisms of MDD remain unclear despite considerable efforts in research.

A number of studies (Compton et al. 2005; Toro et al. 2008; Weissman and Banich 2000) have shown that communication between the left and right hemispheres of the human brain is a critical component of cognition and emotion processing. It is particularly important in the implementation of complex tasks that require coordination between the hemispheres. For example, the functional synchronicity of bilateral cerebral hemisphere areas—a spontaneous activity pattern in the homotopic region between both hemispheres—is one of the most prominent aspects of the functional structure of the brain (Salvador et al. 2005). The synchronicity of spontaneous activity between the hemispheres may represent coherence between cerebral hemispheres from communication to integration, and is a necessary process of cognitive and behavioral functions (Kelly et al. 2011).

Over the past decade, an increasing number of studies have targeted the pathogenesis of mental illness through the use of resting-state functional magnetic resonance imaging (rsfMRI). Many studies have focused on brain structures and functions related to depression. For example, one rsfMRI study showed that homotopic regions of the cerebral hemispheres of patients with depression exhibited unbalanced activities, especially in the prefrontal cortex (Grimm et al. 2008). Furthermore, rsfMRI provides a direct method for quantifying hemispheric interaction by identifying the temporal correlation of functional connectivity via recognition of the low-frequency blood oxygen level-dependent (BOLD) signals (Kelly et al. 2011). Voxel-mirrored homotopic connectivity (VMHC) is a method that measures the functional connection between the two voxels across the contralateral hemispheres in resting state, and can indicate functional connection strength between the two mirrored voxels (Zuo et al. 2010). A study on schizophrenia patients showed decreased VMHC in the precuneus, middle occipital gyrus, and superior temporal gyrus, suggesting homotopic abnormalities between the hemispheres at resting state. These findings indicate that interhemispheric resting-state functional connectivity is reduced in paranoid schizophrenia with clinical implications for psychiatric symptomatology, supporting the dysconnectivity hypothesis for schizophrenia (Guo et al. 2014). The VMHC method has also been applied to study autism (Anderson et al. 2010), cocaine addiction (Kelly et al. 2011), and more recently depression.

Guo et al. (2013) reported decreased VMHC in the prefrontal cortex and precuneus of untreated MDD patients. Wang et al. (2013, 2015) also observed reduced VMHC in the orbitofrontal, parahippocampal, fusiform, and cuneus gyrus as well as the occipital regions in depressive patients. In addition, Marco et al. (2016) found decreased VMHC in the cuneus, precuneus, insula, superior temporal, and putamen regions. The abnormality of homotopic connectivity provides a possible basis for the clinical manifestations of depression, such as emotional and cognitive disorders. Although several studies have investigated the abnormal imbalance of homotopic regions between the hemispheres in depressive patients, the reported observations are inconsistent, possibly due to the differences in sample size, disease duration, severity, gender distribution, and/or treatment with different antidepressants.

In this study, we employ a VMHC analysis method to study the abnormality in both grey-matter and white-matter functional connectivity of hemispheric homotopic brain regions in first-episode, drug-naïve MDD patients. Additionally, based on previous functional imaging studies on depression, we hypothesize that functional coordination between the hemispheres is compromised in depressive patients. This compromised connectivity can be related to the pathogenesis of depression, and revealed by a decrease in homotopic connectivity at resting state.

Materials and methods

Participants

Under the approval by the local Medical Ethics Committee of the First Affiliated Hospital of Zhejiang University and with the written informed consent obtained from each subject, thisstudy enrolled 23 first-episode, drug-naïve MDD patients and 20 normal controls (NC). The patients were recruited from the Department of Psychiatry, the First Affiliated Hospital of Zhejiang University School of Medicine. The inclusion criteria were: (1) the symptoms complied with the diagnostic criteria for MDD according to the Structured Clinical Interview of the DSM-IV and by the consensus of two psychiatrists; (2) first episode of major depression experienced by the patient who had not yet received any treatment; and (3) a total score on the 17-item Hamilton Depression Rating Scale (HAMD) of no less than 17.

The 20 NC participants, matched for age, gender and educational level to the MDD patients, were recruited from hospital staff and students of the First Affiliated Hospital of Zhejiang University School of Medicine. The exclusion criteria were: (1) individuals with an HAMD score of more

than 7; (2) any current or lifetime psychiatric or neurological disorders; or (3) a family history of major psychiatric or neurological illness in their first-degree relatives.

Additional exclusion criteria for all participants were also applied, consisting of (1) age under 18 or above 45 years in order to avoid immature or possibly declined cognitive function (Lockwood et al. 2002), because patients with depression often suffer from cognitive executive function impairment (Lim et al. 2013); (2) a history of severe organic brain disease or brain trauma; (3) severe mental retardation; or (4) individuals with drug, alcohol or other psychoactive substance abuse.

Image acquisition

MRI data were collected on a Philips Achieva 3.0 T scanner at the First Affiliated Hospital of Zhejiang University School of Medicine. The participants were asked to lie down in the scanner with eyes closed, not to think about anything in particular, and not to fall asleep. An echo planar imaging (EPI) sequence was used for fMRI with the following parameters: repetition time (TR): 2000 ms, echo time (TE): 35 ms, flip angle: 90°, slice thickness/interval: 5.0/1.0 mm, and number of volumes (or time points): 200. A total of 24 transverse slices were used to cover the whole brain with all slices aligned in parallel to the anterior–posterior commissure. A gradient-echo sequence was also used to obtain high-resolution T1-weighted structural MRI images with the following parameters: TR/TE: 8/4 ms, flip angle: 8°, matrix size: 240 × 240, slice thickness: 1 mm, and field of view: 240 mm × 240 mm.

Data preprocessing

Functional images were preprocessed by using Data Processing Assistant for Resting-State Functional MR Imaging toolkit (Yan and Zang 2010), and SPM8 (www.fil.ion.ucl.ac.uk/spm). The first 5 images in the time series were excluded to ensure steady state longitudinal magnetization was achieved, followed by slice timing and head motion correction to ensure neither translation nor rotation in any given data set exceeded ±3 mm or ± 3 degree. The individual T1-weighted structural images were co-registered to the corresponding functional images. The T1-weighted images were segmented into grey matter, white matter, and cerebrospinal fluid, and normalized to the Montreal Neurologic Institute space. These transformation parameters were also applied to the functional images. Next, the normalized images were resampled to a voxel size of 3 × 3 × 3 mm^3. To account for differences in the geometric configuration of the cerebral hemispheres, the preprocessed functional images were further transformed to a symmetric space. Specifically, a group-specific symmetrical template was first generated by averaging the normalized grey matter with its left-right mirrored versions. Then, the normalized grey-matter images were registered to the symmetric template and a nonlinear transformation was applied to the normalized functional images. Finally, we spatially smoothed images with a 4-mm (full width at half maximum) isotropic Gaussian kernel.

Several preprocessing steps were taken to remove the sources of possible spurious variance from the time series of each voxel, comprising (a) removing linear trends, (b) regressing out nuisance signals (global mean, white matter, cerebrospinal fluid signals, and 24 head-motion parameters), and (c) filtering with a temporal bandpass (0.01–0.08 Hz). Pearson's correlations were computed between the time series of every pair of mirrored interhemispheric voxels. The resulting correlations for each paired voxel produced a VMHC brain map (Fisher z transformed) and were used for subsequent group-level analyses. In addition, the frame-wise displacement (FD) (Power et al. 2012) was calculated for each subject and compared between groups.

Statistical analyses

Differences in VMHC between groups were evaluated by using a non-parametric test with Statistical non-Parametric Mapping software (https://warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/software/snpm). Briefly, the label ("patient" or "healthy control") of each subject was randomized for 5000 times. In each time, two-sample t test produced a t map. Based on the distribution of these 5000 t maps, the t value in real labeling condition could be inferred as significant or not. The resultant map was FWE-corrected at cluster level ($p < 0.05$) with cluster-defining threshold $p < 0.01$. To relate imaging findings with clinical symptoms, we extracted signal of sphere ROI (centered at peak voxel which showed the highest t-value from all the voxels in the same cluster, radius = 3 mm) in clusters showing abnormal VMHC, and performed Pearson's correlation with HAMD within the patient group.

Validation analyses

Additional tests were performed to investigate whether our main findings could survive three additional conditions. The first was keeping all pre-processing steps but not the regression of global brain signal. The second was keeping all pre-processes steps but not the regression of white matter signal. The third was censoring data according to each subject's FD. Specifically, image frames with a large FD (>0.5 mm) were identified as problematic time points (Yan et al. 2013). Centered around each problematic time point, one preceding and two following points were deleted to ensure exclusion of motion-related confounds. A subject would be excluded from the analyses if the remaining data contained less than 100 time points (or volume). Peak

voxels of significant regions from our main analysis were defined as ROIs in this validation analysis.

Results

Demographics and clinical characteristics

The demographic and clinical data of all participants are shown in Table 1. The two groups did not differ significantly in age, gender ratio, or educational level ($p > 0.05$). The HAMD score in the MDD group was significantly higher than that of the control group ($p < 0.05$). The FD was not significantly ($t = 0.76$, $p = 0.45$) different between the patient (mean ± SD, 0.18 ± 0.19) and control groups (mean ± SD, 0.16 ± 0.04).

VMHC differences between groups

The whole-brain distribution of VMHC within each group was illustrated in Fig. 1. Compared to the controls, the MDD patients showed significantly decreased VMHC in the insular cortex, putamen, and frontal white matter ($p < 0.05$, FWE corrected), as shown in Fig. 2 and Table 2.

Relationships between VMHC value and HAMD in MDD patients

Based on an ROI analysis in the frontal lobe white-matter region (peak voxel coordinate [−21 39 6]), a significant negative correlation was observed between the VMHC value and the HAMD score in the MDD patient group ($r = -0.44$, $P = 0.04$, Fig. 3).

Validation analysis

In all the three validation analyses, the ROI from main analysis showed significant VMHC decrease in patients as compared to controls (Table 2). In the data censoring condition, the remaining data length of all subjects was more than 100 time points. The results demonstrated that the difference between patients and healthy controls were not affected by preprocessing choices or subject motion, the results remain significant with changes in preprocessing.

Table 1 Demographics and clinical characteristics of the subjects

Variables (mean ± SD)	MDD ($n = 23$)	NC ($n = 20$)	P value
Age (years)	31.52 ± 6.86	30.10 ± 7.52	0.449[b]
Gender (male/female)	7/16	6/14	0.975[a]
Education (years)	12.13 ± 3.86	12.40 ± 3.13	0.741[b]
Illness duration (months)	11.87 ± 10.92		
HAMD score	25.09 ± 1.25	1.25 ± 1.682	$P < 0.001$[b]

Abbreviations: *MDD* major depressive disorder, *NC* normal control, *HAMD* Hamilton depression rating scale

[a] the P value was obtained by chi-square test

[b] the P values were obtained by Mann–Whitney U test

Discussion

The functional synergistic effects of the cerebral hemispheres ensure the harmony and unity of human activity. In this study, we found that the VMHC values in the insular cortex, putamen, and frontal white matter were significantly lower in depressive subjects than in healthy controls, suggesting that the synchronization of spontaneous neural activity in the homotopic functional regions of the bilateral hemispheres decreased and the functional connectivity was weakened. This finding is similar to those reported in previous studies (Marco et al. 2016; Guo et al. 2015; Lu et al. 2016).

VMHC methods have been employed in several prior studies on MDD at resting state. Guo et al. (2013) reported decreased homotopic connectivity in the medial prefrontal cortex and precuneus in first-episode, drug-naïve MDD patients; Wang et al. (2013) found decreased homotopic connectivity in the orbital-frontal gyrus, parahippocampal gyrus, fusiform gyrus, cuneus, and occipital regions in a similar patient population; Lai and Wu (2014) observed decreased homotopic connectivity in the medial prefrontal cortex, anterior cingulate, and posterior cerebellar lobe in MDD; Very recently, Marco et al. (2016) reported reduction in homotopic connectivity in the cuneus, precuneus, insula, superior temporal gyrus, and putamen. Our results in the current study were similar to those reported by Marco et al., however, considerable differences were also observed, likely due to the differences in the study cohorts. For example, Marco et al. studied a larger sample size. However, the subjects included both drug-naïve patients and patients receiving medication. As such, effects introduced by medication could confound the observation. The other three studies aimed at finding abnormal VMHC in first-episode, drug-naïve MDD patients. These studies followed the subjects for different disease durations at a shorter time (i.e., 5–6 months). In contrast, our study followed the subjects for an longer time (11 months on average). In addition, the ratio of male to female patients was close to 1 in their studies, while the ratio was nearly 1:2 in our study. Further studies are needed to systematically investigate the impact of these confounding factors on the observed results.

In the present study, VMHC abnormalities in first-episode, drug-naïve MDD patients were observed in the insular cortex. As mentioned previously, the insular cortex is a brain area that is involved in interpretation of facial information. It also serves as an integrative hub between the sensory, interpretive

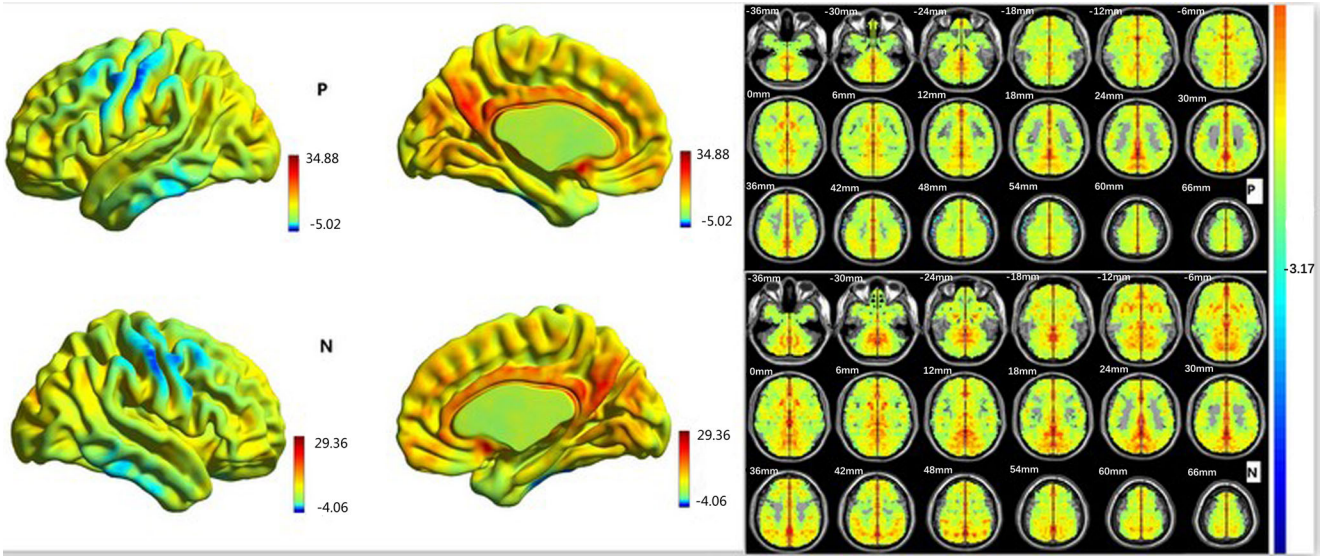

Fig. 1 The results of whole brain distribution of VMHC values in the patient group and in normal group respectively in the resting state, in the upper part of the figure is patients vs in the bottom part of the figure is normal controls. The warm colors indicate regions with more homotopic connectivity and the cold colors indicate regions with less homotopic connectivity. The color bar represents t-values. Left in the figure indicates the right side of the brain. Abbreviations: P = depressive patient; N = normal control

and cognitive regions involved in emotion processing (Avery et al. 2013; Manoliu et al. 2013; Sprengelmeyer et al. 2011). Decreased short-distance connectivity in the right insula in treatment-naïve MDD patients suggested impaired integration of emotion management (Guo et al. 2015). Craig (2009, 2011). Other studies (Chang et al. 2013; Menon and Uddin 2010) have suggested that the insular cortex utilizes sensory information from ascending homeostatic afferents together with contextual input from other cortical brain areas to form a conscious "feeling" or an emotional moment in time (Craig 2011). The posterior portion receives information on the physiological state of the body, which is integrated with information from higher order sensory cortices, as well as from the amygdala and the anterior cingulate cortex (ACC) in the

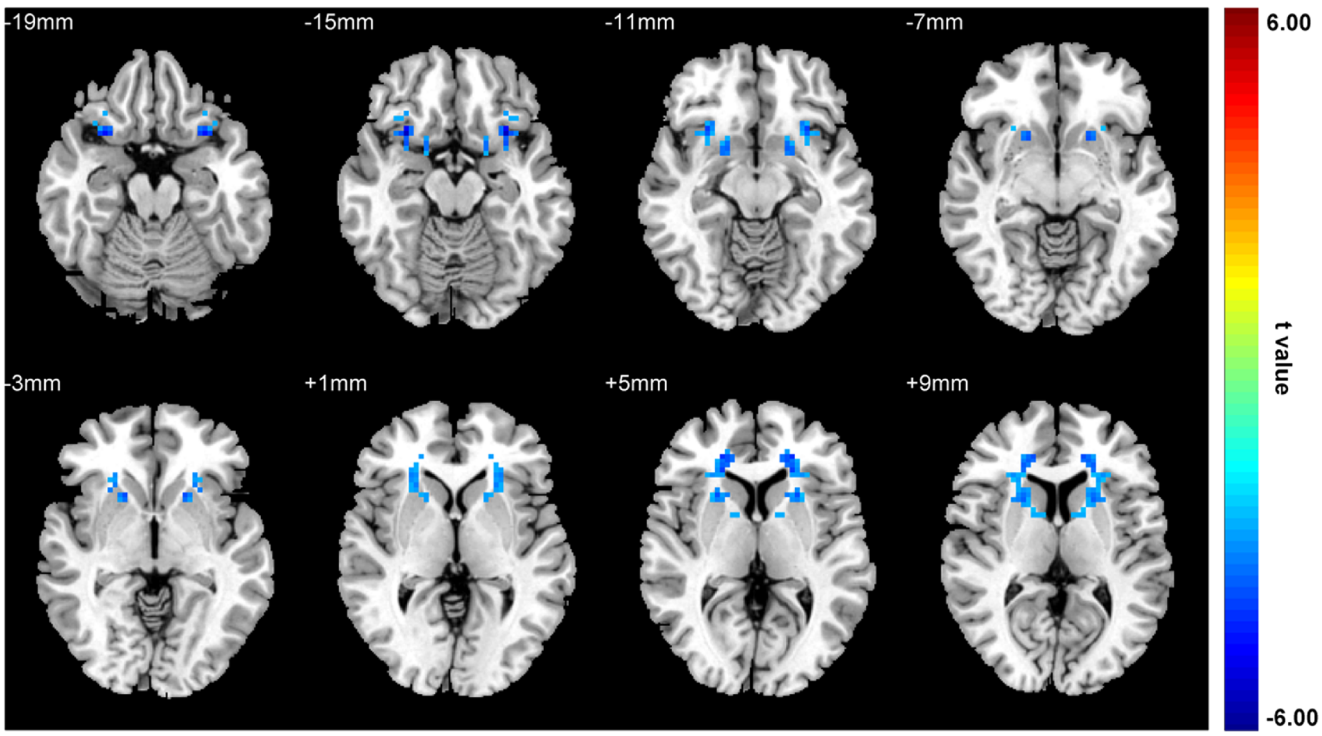

Fig. 2 Regions showing significant differences in VMHC between MDD patients and healthy controls ($P < 0.05$, FWE corrected). Blue colors indicate reduced VMHC in patients compared to the controls. The color bar represents t-values. Left in the figure indicates the right side of the brain

Table 2 Regions showing significant differences in VMHC between MDD patients and healthy controls

Main analysis				Validation analysis (t value)		
Brain area	Peak t value	Brodmann area	MNI coordinates (x,y,z)	No global signal regression	No WM signal regreesion	Data scrubbing
Insular/putamen	5.29	47	−30 15–15	4.49***	4.88***	4.83***
White matter	3.97	NA	−21 39 6	3.29*	3.11*	4.11*
White matter	3.87	NA	−21 30 6	3.49**	3.12*	3.96**

Main analysis and validation analysis showing the difference between patients and healthy controls were not affected by preprocessing choices or subject motion, the results remain significant with changes in preprocessing

The peak t value and coordinates were reported by SnPM; * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$, uncorrected

middle and anterior portion of the insular cortex where emotion awareness, self-recognition and other functions are represented (Craig 2010; Nieuwenhuys 2012).

As part of the striatum, the putamen composes of the limbic (the ventral putamen), associative (the dorsorostral putamen), and sensorimotor (the dorsocaudal putamen) sub-regions (Postuma and Dagher 2006). Some studies have shown that the ventral striatum, temporal lobe (including hippocampus and amygdala), dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex (OFC) play a major role in emotional/motivational functions and reward processing (Kumar et al. 2008; Lacerda et al. 2004; Redgrave et al. 2010), and are involved in the fronto-striatal or fronto-limbic networks (Keating et al. 2012; Vai et al. 2015). These regions have also been found to be associated with anhedonia and dejection (Heller et al. 2009), which are two core symptoms of MDD. Additionally, the sensorimotor striatum and the primary and supplementary motor cortices were implicated in motor output (Bracht et al. 2012; Redgrave et al. 2010), and related to psychomotor retardation (Walther et al. 2012), a key feature of MDD. Moreover, cognitive impairment was also found in MDD patients (Culpepper 2015). This can be related to the associative striatum and DLPFC, which play an essential role in the integration of cognitive functions and in the prefrontal cortex–basal ganglia circuit (Levy and Dubois 2006). Therefore, based on these studies, it is plausible to hypothesize that different regions of the putamen may have connections with the related cortices and constitute different networks that contribute to the related symptoms in MDD. The decreased VMHC in putamen, which was observed in our study, appears to be consistent with the hypothesis of abnormality in the limbic-cortico-striatal-thalamic-cortical (LCSTC) circuits (Yeh et al. 2010) or limbic-cortico-striatal-pallidal-thalamic (LCSPT) network (Drevets et al. 2008; Sheline 2000) in MDD. Further research is needed to provide more evidence to support this hypothesis. Interestingly, the insula and putamen are part of the "hate circuit" (Zeki and Romaya 2008), which can also be regarded as a network implicated in emotion regulation (Ochsner et al. 2012) and reported as aberrant in patients with MDD (Tao et al. 2013).

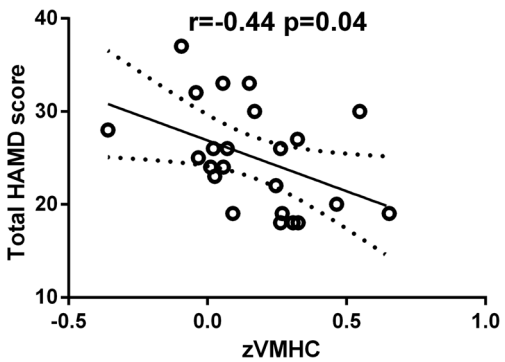

Fig. 3 Significantly negative correlations between the VMHC values and the HAMD score in the frontal lobe white-matter in patient group

Similar to many other functional MRI (fMRI) studies on MDD, existing literature on MDD using VHMC focuses almost exclusively on the grey matter without analyzing signals from the white matter. Recently, increasing evidences emerged to indicate that the low-frequency BOLD fluctuations in the brainwhite matter are more than just noise. They may reflect the neurobiological aspect of the low-frequency BOLD signals in the white matter (Ji et al. 2017; Gawryluk et al. 2014). One study suggested the existence of 12 symmetrical white-matter functional networks, corresponding to combinations of white-matter tracts identified by diffusion tensor imaging. Six of the networks included interhemispheric commissural bridges traversing the corpus callosum, such as forceps minor. Meanwhile, signals in white-matter networks can be correlated with signals from the grey-matter functional networks. In particular, superficial frontotemporal and frontoparietal white-matter networks are highly correlated to default mode network (DMN), frontoparietal control network, and ventral attention and dorsal attention networks, suggesting a role of white-matter networks in communication between the distant regions of these networks (Peer et al. 2017). This raises an important issue – whether the observed white-matter signals reflect neuronal-related activity in the white matter. This possibility can be masked by three confounding factors: random noise artifacts (such as head motion), nonrandom factors affecting the signals such as differential distribution of

blood vessels across the white-matter, and contamination from the grey-matter signals to the observed networks due to smoothing and/or partial volume effects. Therefore, to rigorously substantiate the finding of decreased functional homotopic connectivity in the frontal lobe white matter in depressive patients, further research is necessary to rule out the possible influence from these confounding factors. The negative correlation between the VMHC value of the white-matter and the HAMD also require further investigations to reveal the underlying mechanism. Notice that the correlation between the VMHC disturbance and HAMD could be affected by voxel selection, as the peak voxel was selected by its ability to differentiate between the patient and control groups. Although this does not affect the results, this correlation should therefore not be taken as additional proof to the role of prefrontal white-matter in depression. Nevertheless, the observation of abnormal VMHC in the white-matter of MDD patients may provide a new angle to explore the possible role of white-matter in elucidating the mechanisms of MDD.

Limitations and conclusion

There are several limitations in the present study. First, the sample size was relatively small. Thus, the findings should be considered preliminary and need to be replicated with a larger cohort of patients. Second, a symmetrical standard template was applied with smoothed imaging data to improve the functional correlations between mirrored regions. In general, the human brain is not symmetrical. Although morphometric asymmetry could not account for the reduced VMHC (Kelly et al. 2011), the effects of methodological symmetry should not be overlooked. Third, due to the use of smoothing in data processing, activities in the grey matter may be related to activities in the adjacent white matter, and vice versa. Fourth, although our findings suggest that functional networks are involved in the abnormalities of neural circuits in depressive disorders, we did not study these abnormal functional networks comprehensively to reveal their possible interrelationships. Independent component analysis or graph-based brain network analysis can be used for future investigations. In conclusion, abnormalities in brain homotopic functional connectivity were observed in both grey and white matter in this study. This observation may indicate abnormal neural circuits related to aberrant cognition and emotion processing in MDD. Although the physiological significance underlying abnormal VMHC in the white matter requires further research, our study suggests a new angle to investigate the role of white-matter abnormalities in MDD as well as in other psychiatric disorders.

Acknowledgments This study was supported in part by The Science Technology Department of Zhejiang Province (Grant No. 2017C33096) and The Health and Family Planning Commission of Zhejiang Province (Grant No. 2015107509).

References

Anderson, J. S., Druzgal, T. J., Froehlich, A., DuBray, M. B., Lange, N., Alexander, A. L., et al. (2010). Decreased interhemispheric functional connectivity in autism. *Cerebral Cortex, 21*, 1134–1146. https://doi.org/10.1093/cercor/bhq190.

Avery, J. A., Drevets, W. C., Moseman, S. E., Bodurka, J., Barcalow, J. C., & Simmons, K. (2013). Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biological Psychiatry, 76*, 258–266. https://doi.org/10.1016/j.biopsych.2013.11.027.

Bracht, T., Federspiel, A., Schnell, S., Horn, H., Höfle, O., Wiest, R., et al. (2012). Cortico-cortical white matter motor pathway microstructure is related to psychomotor retardation in major depressive disorder. *PLoS One, e52238*, 7. https://doi.org/10.1371/journal.pone.0052238.

Chang, L. J., Yarkoni, T., Khaw, M. W., & Sanfey, A. G. (2013). Decoding the role of the insula in human cognition: Functional parcellation and large-scale reverse inference. *Cerebral Cortex, 23*, 739–749. https://doi.org/10.1093/cercor/bhs065.

Compton, R. J., Feigenson, K., & Widick, P. (2005). Take it to the bridge: an interhemispheric processing advantage for emotional faces. *Brain Research. Cognitive Brain Research, 24*, 66–72. https://doi.org/10.1016/j.cogbrainres.2004.12.002.

Craig, A. D. (2009). How do you feel–now? The anterior insula and human awareness. *Nature Reviews Neuroscience, 10*, 59–70. https://doi.org/10.1038/nrn2555.

Craig, A. D. (2010). The sentient self. *Brain Structure & Function, 214*, 563–577. https://doi.org/10.1007/s00429-010-0248-y.

Craig, A. D. (2011). Significance of the insula for the evolution of human awareness of feelings from the body. *Annals of the New York Academy of Sciences, 1225*, 72–82. https://doi.org/10.1111/j.1749-6632.2011.05990.x.

Culpepper, L. (2015). Impact of untreated major depressive disorder on cognition and dailyfunction. *The Journal of Clinical Psychiatry, 76*, 901. https://doi.org/10.4088/JCP.13086tx4c.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities inmood disorders: Implications for neurocircuitry models of depression. *Brain Structure & Function, 213*, 93–118. https://doi.org/10.1007/s00429-008-0189-x.

Gawryluk, J. R., Mazerolle, E. L., & D'Arcy, R. C. (2014). Does functional MRI detect activation in white matter? A review of emerging evidence, issues, and future directions. *Frontiers in Neuroscience, 8*, 239. https://doi.org/10.3389/fnins.2014.00239 eCollection 2014.

Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., et al. (2008). Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biological Psychiatry, 63*, 369–376. https://doi.org/10.1016/j.biopsych.2007.05.033.

Guo, W. B., Liu, F., Dai, Y., Jiang, M. L., Zhang, J., Yu, L. Y., et al. (2013). Decreased interhemispheric resting-state functional connectivity in first-episode, drug-naive major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 41*, 24–29. https://doi.org/10.1016/j.pnpbp.2012.11.003.

Guo, W. B., Xiao, C. Q., Liu, G. Y., Wooderson, S. C., Zhang, Z. K., Zhang, J., et al. (2014). Decreased resting-state interhemispheric coordination in first-episode, drug-naive paranoid schizo -phrenia.

Progress in Neuro-Psychopharmacology & Biological Psychiatry, 48, 14–19. https://doi.org/10.1016/j.pnpbp.2013.09.012.

Guo, W., Liu, F., Xiao, C., Zhang, Z., Liu, J., Yu, M., et al. (2015). Decreased insular connectivity in drug-naive major depressive disorder at rest. *Journal of Affective Disorders, 179*, 31–37. https://doi.org/10.1016/j.jad.2015.03.028.

Heller, A. S., Johnstone, T., Shackman, A. J., Light, S. N., Peterson, M. J., Kolden, G. G., et al. (2009). Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. *Proceedings of the National Academy of Sciences, 106*, 22445–22450. https://doi.org/10.1073/pnas.0910651106.

Ji, G. J., Liao, W., Chen, F. F., Zhang, L., & Wang, K. (2017). Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise. *Science Bulletin, 62*, 656–657. https://doi.org/10.1016/j.scib.2017.03.021.

Keating, C., Tilbrook, A. J., Rossell, S. L., Enticott, P. G., & Fitzgerald, P. B. (2012). Reward processingin anorexia nervosa. *Neuropsychologia, 50*, 567–575. https://doi.org/10.1016/.neuropsychologia.2012.01.036.

Kelly, C., Zuo, X. N., Gotimer, K., Cox, C. L., Lynch, L., Brock, D., et al. (2011). Reducedinterhemispheric resting state functional connectivity in cocaine addiction. *Biological Psychiatry, 69*, 684–692. https://doi.org/10.1016/j.biopsych.2010.11.022.

Kumar, P., Waiter, G., Ahearn, T., Milders, M., Reid, I., & Steele, J. (2008). Abnormal temporal difference reward-learning signals in major depression. *Brain, 131*, 2084–2093. https://doi.org/10.1093/brain/awn136.

Lacerda, A. L., Keshavan, M. S., Hardan, A. Y., Yorbik, O., Brambilla, P., Sassi, R. B., et al. (2004). Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. *Biological Psychiatry, 55*, 353–358. https://doi.org/10.1016/j.biopsych.2003.08.021.

Lai, C. H., & Wu, Y. T. (2014). Decreased inter-hemispheric connectivity in anterior sub-network of default mode network and cerebellum: significant findings in major depressive disorder. *International Journal of Neuropsychopharmacology, 17*, 1935–1942. https://doi.org/10.1017/S1461145714000947.

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. *Cerebral Cortex, 16*, 916–928. https://doi.org/10.1093/cercor/bhj043.

Lim, J., Oh, I. K., Han, C., Huh, Y. J., Jung, I. K., Patkar, A. A., et al. (2013). Sensitivity of cognitive tests in four cognitive domains in discriminating MDD patients from healthy controls: a meta-analysis. *International Psychogeriatrics, 25*, 1543–1557. https://doi.org/10.1017/S1041610213000689.

Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *The American Journal of Psychiatry, 159*, 1119–1126. https://doi.org/10.1176/appi.ajp.159.7.1119.

Lu, Y., Liang, H., Han, D., Mo, Y., Li, Z., Cheng, Y., et al. (2016). The volumetric and shape changes of the putamen and thalamus in first episode, untreated major depressive disorder. *NeuroImage Clinical, 11*, 658–666. https://doi.org/10.1016/j.nicl.2016.04.008.

Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., et al. (2013). Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Frontiers in Human Neuroscience, 7*, 930. https://doi.org/10.3389/fnhum.2013.00930.

Marco, H., Benedikt, S., Stephan, F., Wolfram, S., Jens, M., Arolt, V., et al. (2016). Major depressive disorder: findings of reduced homotopic connectivity and investigation of underlying structural mechanisms. *Human Brain Mapping, 37*, 1209–1217. https://doi.org/10.1002/hbm.23097.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function, 214*, 655–667. https://doi.org/10.1007/s00429-010-0262-0.

Nieuwenhuys, R. (2012). The insular cortex: a review. *Progress in Brain Research, 195*, 123–163. https://doi.org/10.1016/B978-0-444-53860-4.00007-6.

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences, 1251*, E1–E24. https://doi.org/10.1111/j.1749-6632.2012.06751.x.

Peer, M., Nitzan, M., Bick, A. S., Levin, N., & Arzy, S. (2017). Evidence for functional networks within the human Brain's white matter. *The Journal of Neuroscience, 37*, 6394–6407. https://doi.org/10.1523/JNEUROSCI.3872-16.2017.

Postuma, R. B., & Dagher, A. (2006). Basal ganglia functional connectivity based on a meta analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cerebral Cortex, 16*, 1508–1521. https://doi.org/10.1093/cercor/bhj088.

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. https://doi.org/10.1016/j.neuroimage.2011.10.018.

Redgrave, P., Coizet, V., Comoli, E., McHaffie, J. G., Leriche, M., Vautrelle, N., et al. (2010). Interactions between the midbrain superior colliculus and the basal ganglia. *Frontiers in Neuroanatomy, 4*, 132. https://doi.org/10.3389/fnana.2010.00132.

Salvador, R., Suckling, J., Schwarzbauer, C., & Bullmore, E. (2005). Undirected graphs of frequency -dependent functional connectivity in whole brain networks. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 360*, 937–946. https://doi.org/10.1098/rstb.2005.1645.

Sheline, Y. I. (2000). 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. *Biological Psychiatry, 48*, 791–800. https://doi.org/10.1016/S0006-3223(00)00994-X.

Sliz, D., & Hayley, S. (2012). Major depressive disorder and alterations in insular cortical activity: a review of current functional magnetic imaging research. *Frontiers in Human Neuroscience, 6*, 323. https://doi.org/10.3389/fnhum.2012.00323.

Sprengelmeyer, R., Steele, J. D., Mwangi, B., Kumar, P., Christmas, D., Milders, M., et al. (2011). The insular cortex and the neuroanatomy of major depression. *Journal of Affective Disorders, 133*, 120–127. https://doi.org/10.1016/j.jad.2011.04.004.

Tao, H., Guo, S., Ge, T., Kendrick, K. M., Xue, Z., Liu, Z., et al. (2013). Depression uncouples brain hate circuit. *Molecular Psychiatry, 18*, 101–111. https://doi.org/10.1038/mp.2011.127.

Toro, R., Fox, P. T., & Paus, T. (2008). Functional coactivation map of the human brain. *Cerebral Cortex, 18*, 2553–2559. https://doi.org/10.1093/cercor/bhn014.

Vai, B., Poletti, S., Radaelli, D., Dallaspezia, S., Bulgarelli, C., Locatelli, C., et al. (2015). Successful antidepressant chronotherapeutics enhance fronto-limbic neural responses and connectivity in bipolar depression. *Psychiatry Research: Neuroimaging, 233*, 243–253. https://doi.org/10.1016/j.pscychresns.2015.07.015.

Walther, S., Hügli, S., Höfle, O., Federspiel, A., Horn, H., Bracht, T., et al. (2012). Frontalwhite matter integrity is related to psychomotor retardationin major depression. *Neurobiology of Disease, 47*, 13–19. https://doi.org/10.1016/j.nbd.2012.03.019.

Wang, L., Li, K., Zhang, Q. E., Zeng, Y. W., Jin, Z., Dai, W. J., et al. (2013). Interhemispheric functional connectivity and its relationships with clinical characteristics in major depressive disorder: a resting state fMRI study. *PLoS One, 8*, e60191. https://doi.org/10.1371/journal.pone.0060191.

Wang, Y., Zhong, S., Jia, Y., Zhou, Z., Wang, B., Pan, J., et al. (2015). Interhemispheric resting state functional connectivity abnormalities

in unipolar depression and bipolar depression. *Bipolar Disorders, 17*, 486–495. https://doi.org/10.1111/bdi.12315.

Weissman, D. H., & Banich, M. T. (2000). The cerebral hemispheres cooperate to perform complex but not simple tasks. *Neuropsychology, 14*, 41–59. https://doi.org/10.1037/0894-4105.14.1.41.

Yan, C. G., & Zang, Y. F. (2010). A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience, 4*, 13. https://doi.org/10.3389/fnsys.2010.00013.

Yan, C. G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R. C., DiMartino, A., et al. (2013). A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage, 76*, 183–201. https://doi.org/10.1016/j.neuroimage.2013.03.004.

Yeh, P. H., Zhu, H., Nicoletti, M. A., Hatch, J. P., Brambilla, P., & Soares, J. C. (2010). Structuralequation modeling and principal component analysis of gray matter volumes inmajor depressive and bipolar disorders: differences in latent volumetric structure. *Psychiatry Research: Neuroimaging, 184*, 177–185. https://doi.org/10.1016/j.pscychresns.2010.07.007.

Zeki, S., & Romaya, J. P. (2008). Neural correlates of hate. *PLoS One, 3*, e3556. https://doi.org/10.1371/journal.pone.0003556.

Zuo, X. N., Kelly, C., Di Martino, A., Mennes, M., Margulies, D. S., Bangaru, S., et al. (2010). Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *The Journal of Neuroscience, 30*, 5034–5043. https://doi.org/10.1523/JNEUROSCI.2612-10.2010.