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Research paper

Abnormal functional connectivity density in patients with major depressive disorder with comorbid insomnia

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ABSTRACT

Background: Insomnia is a common comorbidity symptom in patients with major depressive disorder (MDD). However, the brain functional alteration in MDD with higher level insomnia (MDD-HI) and lower level insomnia (MDD-LI) remains unclear. Here, we investigated the association of insomnia with global functional connectivity density (gFCD) in patients with MDD.

Methods: A total of 148 participants were recruited and underwent resting-state functional magnetic resonance imaging. A voxel-wise analysis of covariance was employed to explore group differences in gFCD among the MDD-HI, MDD-LI and healthy control (HC) groups.

Results: The gFCD in the bilateral parahippocampal/hippocampal gyri (PHG/HIP) was higher in the two MDD than in the HC group, and it was higher in the MDD-LI than in the MDD-HI group; the gFCD in the left fusiform area was lower in the MDD than in the HC group. The gFCD in the left inferior temporal gyrus (ITG) was higher in the MDD-HI than in the MDD-LI and HC groups. The gFCD in the left ITG and posterior PHG/HIP was associated with insomnia, while the gFCD in the left anterior PHG/HIP was correlated with non-insomnia depressive symptoms in the MDD group.

Limitations: The cross-sectional design and the use of brief/subjective insomnia assessments.

Conclusions: The present study showed that the abnormal brain features of MDD with different insomnia symptom. Importantly, the posterior and anterior parts of the hippocampus may play different roles in the presence or absence of insomnia in patients with MDD.

1. Introduction

Major depressive disorder (MDD) is considered the most prevalent mental disease worldwide, and will become the leading cause of global disease burden (Smith, 2014). However, as MDD is a heterogeneous disorder and characterized by various symptoms such as depressive mood, anhedonia, somatization, weight loss, cognitive disturbance, retardation, and sleep disruption (Association, 2013; Cleary and Guy, 1977; Sharpley and Bitsika, 2014), the etiology and neuropathology of MDD is complicated and remains largely obscure. Thus, there is substantial need to elucidate the underlying pathophysiology in patients with MDD with varying clinical characterizations (Sharpley and Bitsika, 2013). Sleep disturbances, especially insomnia, are observed in up to 90% of individuals with MDD (Geoffroy et al., 2018). In addition, the severity of insomnia is associated with the severity of depression, treatment response, suicidal ideation, and risk of recurrence (Li et al., 2012; Perlis et al., 1997; Pigeon et al., 2008). Therefore, research focused on the neural mechanisms of patients with MDD with different degrees of insomnia severity would advance our knowledge of the neuropsychopathology of patients with MDD with insomnia.

Resting state functional magnetic resonance imaging (R-fMRI) is a well-used, non-invasive tool to investigate functional organization in the human brain, and functional connectivity (FC) between regions could reflect spontaneous fluctuation in brain functional activities (Fox and Raichle, 2007). Unlike using previous hypothesis-based region of interest (ROI) for whole brain FC analysis, functional connectivity density (FCD) is a data-driven approach developed to identify the

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Table 1
Demographic and clinical characteristics for all participants.

Characteristic	HC (n = 38)	MDD-HI (n = 62)	MDD-LI (n = 48)	$F/T/\chi 2$ value	p value
Age	37.37 ± 10.47	41.12 ± 12.34	36.34 ± 10.04	2.63	0.08
Gender (male/female)	16/12	27/35	22/26	0.12	0.939†
Education (years)	12.39 ± 2.66	11.66 ± 3.42	11.35 ± 2.94	1.56	0.312
Duration (years)	–	7.11 ± 6.48	5.63 ± 7.68	1.09	0. 276#
Number of episode	–	3.47 ± 2.33	2.83 ± 2.68	1.04	0.301#
HAMD	1.26 ± 1.40	24.96 ± 3.51	16.60 ± 5.71	9.45	<0.001#
HAMD-S	0.28 ± 0.65	5.12 ± 0.84	1.78 ± 1.13	17.84	<0.001#
Adjusted HAMD	0.97 ± 1.07	19.83 ± 3.39	14.83 ± 5.55	5.83	<0.001#
HAMA	1.18 ± 1.62	18.20 ± 6.19	15.08 ± 6.35	2.59	0.011#
MoCA	28.00 ± 1.45	25.70 ± 3.14	25.43 ± 3.67	8.86	<0.001
Mean FD	0.05 ± 0.03	0.06 ± 0.04	0.05 ± 0.02	0.36	0.701

Notes: †, p value obtained using the chi-square test
#, p value obtained using the two-sample t-test between two MDD groups; other p values were obtained via one-way analysis of variance. Abbreviations: HC, healthy control; MDD-HI, major depressive disorder with high levels of insomnia; MDD-LI, major depressive disorder with low levels of insomnia; HAMD, Hamilton Rating Scale for Depression; Adjusted HAMD, HAMD scores after omission of the sleep subscale; HAMD-S, HAMD sleep subscale; HAMA, Hamilton Rating Scale for Anxiety; MoCA, Montreal Cognitive Assessment. FD, framewise displacement.

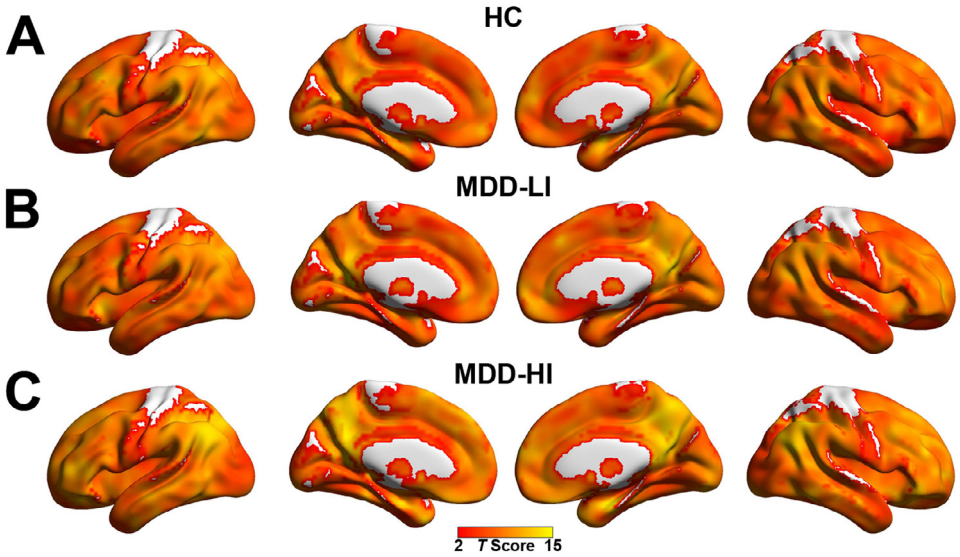

Fig.. 1. The gFCD distribution pattern maps in each of the three groups. Abbreviations: HC, healthy normal; MDD-LI, major depressive disorder group with lower insomnia; MDD-HI, MDD group with higher insomnia; gFCD, global functional connectivity density.

distribution of hubs at the voxel level in the human brain (Tomasi and Volkow, 2010; Sheline, 2011). Among these data-driven approaches, global FCD (gFCD) is more sensitive to individual differences in FC than local FCD (Tomasi and Volkow, 2011). gFCD has been widely used to explore the neuropathological basis of neuropsychiatric diseases and cognitive processing, including Alzheimer's disease, aging, MDD, and primary insomnia (Gong et al., 2017; Sui et al., 2015; Tomasi and Volkow, 2012; Yu et al., 2018). Previously, our group found that abnormal gFCD in patients with MDD was located in the sensorimotor network, superior temporal gyrus (STG), fusiform area (FFA), and ventrolateral prefrontal cortex, and abnormal gFCD in the STG was associated with the severity of depression (Gong et al., 2017). In primary insomnia, abnormal gFCD was observed in the default mode network (DMN), executive control network (ECN), salience network (SN) and FFA, and increased gFCD in the insula was associated with insomnia (Yu et al., 2018). Liu et al. investigated the brain regional activity difference between patients with MDD with high and low insomnia using the amplitude of low-frequency fluctuations (ALFF) and found that altered ALFF in the right inferior frontal gyrus and anterior insula was specific to insomnia and associated with the insomnia score (Liu et al., 2018). However, the ALFF primarily reflects concurrent local neuronal activity (Zuo et al., 2010), and how insomnia impacts gFCD in patients with MDD remains unclear.

In the present study, we aimed to investigate group differences between patients with MDD with higher insomnia symptom (MDD-HI), patients with MDD with lower insomnia symptom (MDD-LI), and matched healthy control (HC) subjects using gFCD based on R-fMRI data. Further, the gFCD values in the group difference ROIs were extracted to explore the clinical significance of abnormal gFCD regions in the MDD group, as the DMN and hippocampus play important roles in sleep and emotion (Horovitz et al., 2009; Phelps, 2004), and dysfunction in these brain regions has also been reported by previous insomnia and depression studies (Kaiser et al., 2016; O'Byrne et al., 2014; Zhu et al., 2012). We hypothesized that insomnia would influence gFCD in the DMN and hippocampus, and these alterations would be associated with insomnia in patients with MDD.

2. Methods

2.1. Participants

A total of 120 patients with MDD and 40 age-, sex-, and years of education-matched HCs were enrolled in the present study. The third affiliated hospital of Anhui Medical University Research Ethical

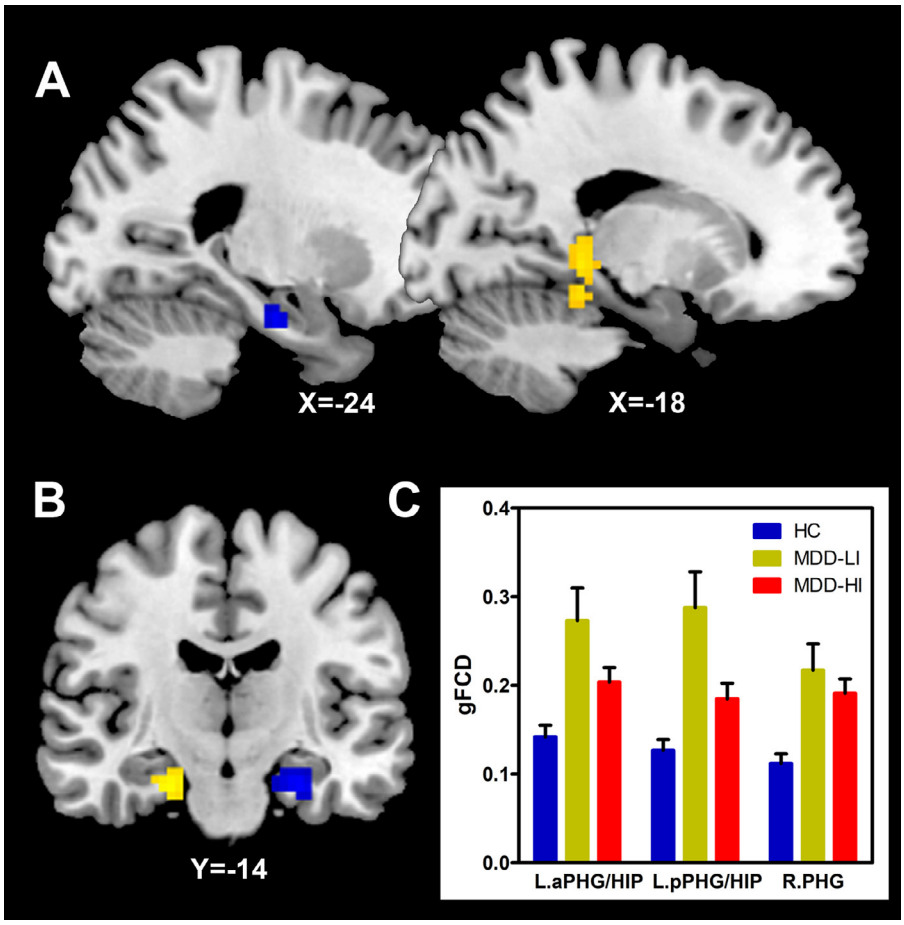

Fig.. 2. The group difference in gFCD in the PHG/HIP showed an inverse U shape distribution (3dClustSim correction, $p < 0.001$). Abbreviations: L.aPHG/HIP, left anterior parahippocampal/hippocampal gyrus; L.pPHG/HIP, left posterior parahippocampal/hippocampal gyrus; R.PHG, right parahippocampal gyrus. HC, healthy control; MDD-LI, major depressive disorder group with lower insomnia; MDD-HI, MDD group with higher insomnia; gFCD, global functional connectivity density.

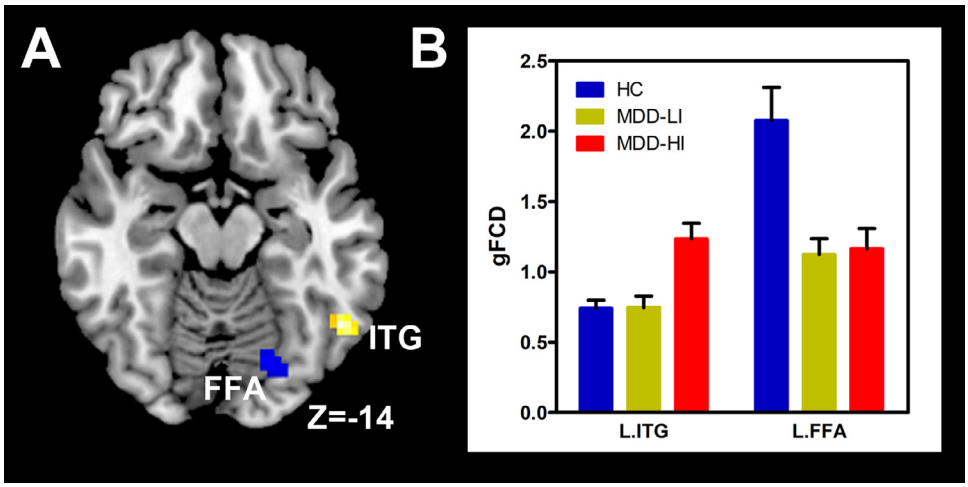

Fig.. 3. The group difference in gFCD in the left ITG and FFA (3dClustSim correction, $p < 0.001$). Abbreviations: ITG, inferior temporal gyrus; FFA, fusiform area; HC, healthy control; MDD-LI, major depressive disorder group with lower insomnia; MDD-HI, MDD group with higher insomnia; gFCD, global functional connectivity density.

Committee approved the study. All participants signed informed consent. Ten MDD and two HC participants were excluded for excessive head motion artifacts (the head motion exceed 2.5 mm or 2.5° of angular motion relative to the first volume) and/or incomplete EPI images after normalized data artificial checking (See Section 2.3). Finally, the data of the remaining 38 HC and 110 MDD subjects were entered into the final analysis. The inclusion criteria for MDD were: (1) the diagnosis criteria for MDD according to the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) were met; (2) the score of 17 items of the Hamilton Depression Rating Scale (HAMD) was ≥ 17; (3) the subjects were naïve to antidepressant medication or had undergone a washout period of at least five half-lives of previously prescribed medicine; (4) age between 18 and 59 years and age at onset younger than 55 years. The exclusion criteria for MDD were: (1) history of other neuropsychiatric disorders; (2) substance abuse (caffeine, nicotine, and alcohol); (3) contraindication to MRI scanning. HCs were required to have a HAMD score ≤ 7. The exclusion criteria for HCs were: history of neurological and psychiatric disease, seizures, head injury, stroke or transient ischemic attack; caffeine, drug, or alcohol abuse; any brain lesions found on T2 MRI.

2.2. Assessments

The HAMD was employed for depression severity, the Hamilton

Table 2
Brain areas exhibiting significant group differences in global functional connectivity density.

Brain regions	Brodmann area	Cluster size (voxels)	MNI coordinates (*x*, *y*, *z*)	Peak *F*-score
L.aPHG/HIP	27	61	−16, −35, −6	9.12
L.pPHG/HIP	27	37	−45, −39, −18	29.64
L. ITG	37	60	−54, −54, −21	7.24
L.FFA	38	36	−54, 3, −9	18.92
R.PHG	28	35	21, −15, −24	6.51

Abbreviations: L.aPHG/HIP, left anterior parahippocampal/hippocampal gyrus; L.pPHG/HIP, left posterior parahippocampal/hippocampal gyrus; L.ITG, left inferior temporal gyrus; L.FFA, left fusiform area; R.PHG, right parahippocampal gyrus.

Rating Scale for Anxiety (HAMA) was used for anxiety evaluation, and the HAMD sleep disorder subscale (HAMD-S) was used to evaluate symptoms of insomnia in patients with MDD. Then, the adjusted HAMD scores were calculated, i.e., the HAMD scores after omission of the Sleep subscale. Following, according to the HAMD-S score, the MDD group was divided into the MDD-HI (HAMD-S score > 3) and the MDD-LI (HAMD-S score ≤ 3) (Liu et al., 2018; Park et al., 2013). We also used the Montreal cognitive assessment to evaluate cognitive performance in all participants (Smith et al., 2007).

2.3. Imaging acquisition and preprocessing

Imaging was performed using a Siemens Verio 3.0 Tesla scanner (Siemens, Erlangen, Germany) at the third affiliated hospital of Anhui Medical University. Structural images were acquired with high resolution spoiled gradient-recalled echo, with parameters: repetition time/echo time (TR/TE); 1900/2.48 ms; flip angle (FA), 9°; acquisition matrix, 256 × 256; field of view (FOV), 240 × 240 mm; thickness, 1.0 mm; gap, 0 mm; voxel size, 1 × 1 × 1 mm^3; number of slices, 176, and number of excitations (NEX), 1.0. The resting-state fMRI (R-fMRI) datasets were obtained in an 8-min gradient-recalled echo-planar imaging pulse sequence, and the parameters included TR/TE, 2000/25 ms; FA, 90°; acquisition matrix, 64 × 64; FOV, 240 × 240 mm; thickness, 4.0 mm; gap, 0 mm; voxel size, 3.75 × 3.75 × 4 mm^3; number of slices, 36; and number of volumes, 240. During the data scans, all subjects were instructed to relax and maintain their eyes closed, and stabilizers were used to immobilize the heads of the subjects. All participants were checked for wakefulness following the scan and they all claimed to have been awake during the scanning.

The R-fMRI data were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and DPABI 3.0 (Data Processing & Analysis of Brain Imaging; http://rfmri.org/dpabi) on MATLAB 8.0 (The MathWorks, Inc., Natick, MA, USA). We removed the first five volumes to account for the magnetization equilibrium and the subjects' adaptation to the experimental environment. The remaining 235 images were then slice-time corrected, reoriented, realigned, and co-registered to the T1-weighted structural images, which were segmented with DARTEL (Ashburner, 2007). Images from all subjects were normalized into the standard stereotactic Montreal Neurological Institute (MNI) space and smoothed with a Gaussian kernel (FWHM = 6 mm). After normalization, manual quality inspection of the normalized images was conducted to ensure that all main brain regions were integrated and properly located. The images were resampled to 3 × 3 × 3 mm^3 voxels. The voxel time series were further detrended and temporally filtered (0.01–0.1 Hz). We normalized the variance of each time series to control for fluctuations in signal intensity. The noise of white matter (WM), and cerebrospinal fluid (CSF) and six head motion vector-related covariates were regressed out. The global signal was not regressed out for its controversial application to resting-state fMRI data (Chai et al., 2012; Murphy et al., 2009). We also calculated the correlation between the maximal framewise displacement (FD) value and severity of depression (Power et al., 2012).

2.4. Global FCD calculation

We calculated the gFCD map of each participant using an in-house script according to the method described by Tomasi and Volkow (2010, 2011). The gFCD at a given voxel (x_0) was computed as the global number of functional connections between x_0 and all other voxels using Pearson's liner correlation, and two voxels with an absolute correlation coefficient value > 0.6 were considered functionally connected (Tomasi et al., 2016; Tomasi and Volkow, 2011). In addition, the calculation of the gFCD was restricted to the gray matter regions with a signal-to-noise ratio > 50% to minimize undesired effects from susceptibility-related signal-loss artifacts (Tomasi and Volkow, 2010). To increase the normality of the distribution, grand mean scaling of gFCDs was performed by dividing by the mean value of the qualified voxels of the whole brain. Finally, the normalized gFCD maps were spatially smoothed with an 8 × 8 × 8 mm^3 Gaussian kernel. Because the threshold of the Pearson correlation coefficient (r = 0.6) was arbitrarily selected, we also validated the reliability of our results using two other thresholds of r > 0.5 and r > 0.7.

2.5. Demographic and behavioral analyses

One-way analysis of variance (ANOVA), two sample t-tests, and chi-square tests were conducted to compare the demographic and behavioral data among groups (SPSS 20, IBM Corp., Armonk, NY, USA). The

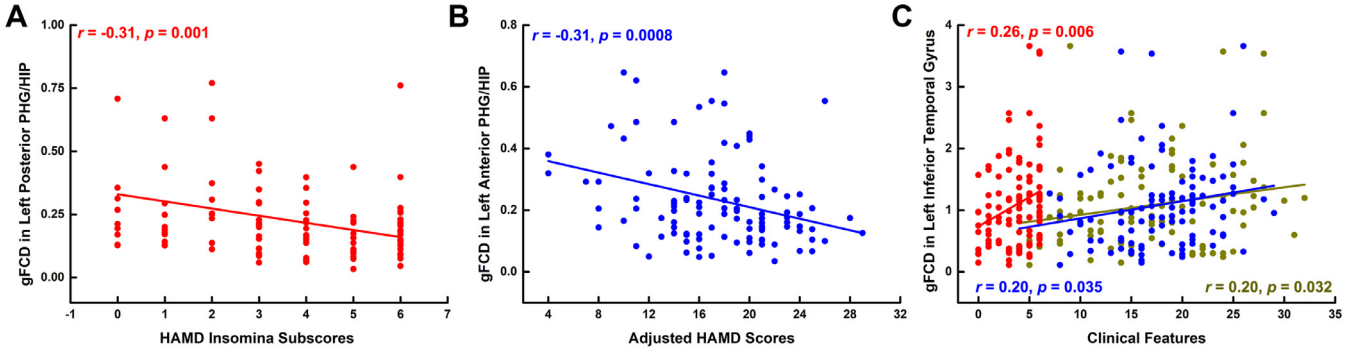

Fig.. 4. The clinical significance of abnormal gFCD in the pooled MDD group.
Note, the red dots represent the HAMD subscores of insomnia, the blue dots mean the adjusted HAMD scores, while the olivine dots represent the HAMA scores. Abbreviations: gFCD, global functional connectivity density; PHG/HIP, parahippocampal/hippocampal gyrus; MDD, major depressive disorder; HAMD, Hamilton Rating Scale for Depression; Adjusted HAMD, HAMD scores after omission of sleep subscale; HAMA, Hamilton Rating Scale for Anxiety. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Pearson correlation was employed to examine the relationships between the HAMD and adjusted HAMD scores, HAMD-S scores, and HAMA scores in the pooled MDD group. The statistical significance was set at $p < 0.05$.

2.6. Group differences in gFCD and clinical significance

First, a voxel-wise based one sample *t*-test was conducted to acquire the gFCD spatial distribution pattern in each group using the Resting-State fMRI Data Analysis Toolkit (REST V1.8, http://restfmri.net/forum/REST_V1.8), The voxel level significant threshold was set at a $p < 0.001$, corrected for multiple comparisons at the cluster level with 3dClustSim in AFNI_ 18.3.03 (gray matter mask correction (67,541 voxels), voxel level $p < 0.05$, cluster level $\alpha < 0.001$, $\kappa > 256$, cluster size > 6942 mm^3; https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html).

Second, group differences in gray matter gFCD mapping were examined using a voxel-wise ANOVA with age, sex, and years of education as nuisance covariates (REST), corrected with 3dClustSim (gray matter mask correction (67,541 voxels), voxel level $p < 0.001$, cluster level $\alpha < 0.001$, $\kappa > 35$, cluster size > 945 mm^3). Then, post-hoc analysis was conducted by comparing the average gFCD value in the significant regions between each two groups.

Third, to investigate the behavioral significance of gFCD, a partial correlation analysis was used to explore these association between the abnormal gFCDs and clinical traits (including the HAMD-S, adjusted HAMD, and HAMA scores) in the pooled MDD group, controlling for the effects of age, sex, and years of education. Significance was set at $p < 0.05$ after correcting for multiple comparisons with false discovery rate (FDR) correction. The results were reported using the xjview toolbox (https://www.alivelearn.net/xjview/).

3. Results

3.1. Demographic and behavioral information

As showed in Table 1, there were no significant differences in age, sex, years of education and mean FD among the three groups ($p > 0.05$), and no difference in duration of disease and number of episodes between the two MDD groups ($p > 0.05$). Compared to the MDD-HI group, the MDD-LI group showed lower HAMD, adjusted HAMD, and HAMA scores ($p < 0.05$). Both MDD groups showed lower cognitive performance (MocA) than the HC group ($F = 8.86$, $p > 0.001$). In the pooled MDD group, the HAMD-S score was significant positively associated with the HAMD score ($r = 0.71$, $p = 5.91 \times 10^{-13}$) and adjusted HAMD score ($r = 0.47$, $p = 1.69 \times 10^{-5}$), and not associated with the HAMA score ($r = 0.16$, $p = 0.129$). The HAMD score was positively associated with the HAMA score in the pooled MDD group ($r = 0.36$, $p = 0.001$).

3.2. gFCD patterns in the three groups

As illustrated in Fig. 1, the gFCD spatial distributed pattern in the three groups was similar. Notably, greater gFCD was found in the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, and inferior parietal lobe (IPL), dorsolateral prefrontal cortex (dlPFC), anterior insula, and anterior cingulate cortex, while gFCD was weaker in the sensorimotor network, basal ganglia, anterior temporal cortex, and posterior insula. No significant association between mean FD and depressive symptoms was found in the MDD group.

3.3. Group differences in gFCD

The voxel-wise ANOVA results revealed a five-cluster group difference in gFCD in the whole gray matter, as shown in Figs. 2 and 3 and Table 2, including the left anterior parahippocampal/hippocampal gyrus (PHG/HIP), posterior PHG/HIP, right PHG, left fusiform area (FFA), and left inferior temporal gyrus (ITG). The post-hoc analysis revealed a different alteration pattern in the two MDD groups compared with the HC group. In the bilateral PHG/HIP, gFCD was greater in the MDD than in the HC group and greater in the MDD-LI than in MDD-HI group. In the left ITG, gFCD was higher in the MDD-HI that in the HC and MDD-LI groups. In the left FFA, gFCD was greater in the HC than in the two MDD groups. In the validation analyses, the group difference was similar with that of the other two connection thresholds ($r = 0.5$ and $r = 0.7$) (Figure S1).

3.4. Clinical significance of abnormal gFCD between the groups

The partial correlation analyses revealed that the gFCD in the left posterior PHG/HIP was significant negatively correlated with the HAMD subscore of insomnia ($r = -0.31$, $p = 0.001$), the gFCD in left anterior PHG/HIP was significant negatively correlated with the adjusted HAMD score ($r = -0.31$, $p = 0.0008$), and the gFCD in the left ITG was positively correlated with the HAMD-S ($r = 0.26$, $p = 0.006$), adjusted HAMD ($r = 0.20$, $p = 0.035$), and HAMA ($r = 0.20$, $p = 0.032$) scores in the pooled MDD group Fig 4. After FDR correction, the associations between gFCD in left ITG and the adjusted HAMD and HAMA scores were not significant. No other significant association between gFCD and clinical features was found in the MDD group.

4. Discussion

In the present study, we investigated the neuropathological characteristics of insomnia in patients with MDD using a data-driven approach. Our findings indicated that, in the PHG/HIP, gFCD was higher in the MDD-LI group than in the MDD-HI group, while gFCD in the left ITG was higher in the MDD-HI group than in the HC and MDD-LI groups. Furthermore, in the MDD group, abnormal gFCD in the left anterior PHG/HIP was associated with non-insomnia symptoms of depression, while that in the left ITG and posterior PHG/HIP was associated with insomnia symptoms. Our findings suggest that the anterior and posterior PHG/HIP play different roles in generating insomnia and non-insomnia symptoms in patients with MDD. As the ITG and posterior PHG/HIP both connected to visual system, we suggested that the alteration of visual system can represent a biomarker of insomnia in patients with MDD.

Accumulating evidence from previous neuroimaging studies have suggested that patients with MDD may have functional abnormalities in many regions and in the connectivity between networks (Drevets et al., 2008; Gong and He, 2015; Sheline, 2011). In the present study, we found that the MDD group showed increased altered neural patterns in the bilateral PHG/HIP, but that these were decreased in the left FFA. These findings are in line with those of previous studies using a global functional connectivity approach. For instance, Zhang et al. found that the weighted global brain connectivity in the PHG and the FC between the PHG and inferior frontal gyrus was increased in patients with MDD (Zhang et al., 2018). Our previous study also found that gFCD in the FFA, which is involved in face-related information processing and the visual network (Kanwisher et al., 1997), was increased in patients with MDD (Gong et al., 2017). The heterogeneity of depression may explain some of the inconsistencies in the functional abnormalities reported.

The PHG/HIP is a core area involved in memory, recognition, and spatial information processing (Eichenbaum et al., 2007; Squire et al., 2004). The cognitive processes associated with these areas do not exhibit a simply dichotomy (Squire et al., 2004). Specifically, while the hippocampus is primarily involved in episodic memory and learning, the PHG is principally involved in contextual associative processing (Aminoff et al., 2013; Horner and Doeller, 2017). Structural and functional abnormalities have been observed in the PHG and HIP in patients with either MDD or primary insomnia (Ambrosi et al., 2018; Drevets et al., 2008; Li et al., 2016b; Lui et al., 2009; Noh et al., 2012;

Winkelman et al., 2010). In our study, the gFCD in the bilateral PHG/HIP was increased in both MDD groups, but the gFCD in the MDD-LI group was higher than that in the MDD-HI group. We propose that there may be a compensatory mechanism in MDD, but when the patients also have severe insomnia, the function of this mechanism would be disrupted and gFCD would decrease compared to that in patients with less severe insomnia. This finding illustrates the complex neuropathological mechanisms underlying the different subtypes of MDD.

According to the hyperarousal hypothesis of insomnia, the level of arousal in patients with insomnia is increased both during the daytime and at night (Riemann et al., 2010). Yu et al. found that gFCD was widely increased in brain networks including the DMN, ECN, SN, and visual network (Yu et al., 2018). In the present study, we found that the patients with MDD-HI showed higher gFCD in the left ITG than the HC and MDD-LI groups, and the increased gFCD in the left ITG was associated with more severe insomnia in patients with MDD. The ITG corresponds to the ventral stream of visual processing (Denys et al., 2004). A previous R-fMRI study also found that local activity in the ITG was increased in patients with insomnia (Li et al., 2016a). These results might indicate that visual processing is in a hyperarousal state during the resting state in patients with MDD with more severe insomnia.

Interestingly, although a similar altered gFCD pattern was found in the left PHG/HIP in the MDD group, such alterations were associated with different clinical manifestations: the gFCD in the anterior PHG/HIP was associated with non-insomnia depression symptoms while the posterior PHG/HIP was associated with insomnia in the MDD group. Recently, neuroimaging studies have reported that both the anterior and posterior hippocampal and parahippocampal gyri have different topographic connections and functions in the human brain (Aminoff et al., 2013; Chase et al., 2015; Christiansen et al., 2017). Henry et al. found that the regions in the anterior hippocampus were primarily connected with the DMN, ventral striatum, midbrain, and amygdala, which are involved in stress and motivation, while the posterior regions of the hippocampus were more strongly connected to "task positive" regions that contribute to spatial and mnemonic processing (Chase et al., 2015). The posterior PHG is optimized to process spatial contextual associations, while the anterior PHG is implicated in the processing of contextual associations in the non-spatial domains (Aminoff et al., 2013). Functional connectivity analysis revealed that the anterior PHG is more strongly connected to the DMN, and the posterior PHG is more strongly connected to the occipital visual regions (Baldassano et al., 2013). Taken together, these findings suggest that different neural mechanisms underlie insomnia and non-insomnia symptoms in patients with MDD. These results may aid in developing more targeted treatment strategies for patients with different subtypes of MDD. As the ITG and posterior PHG/HIP both connected to visual system, we also suggested that the alteration of visual system would serve as a useful biomarker for transferring of insomnia in MDD patients.

This preliminary study had several limitations. First, we used a subscale of the HAMD to evaluate insomnia, which only contains three insomnia-related items, which may have limited our ability to assess insomnia severity. Further studies could combine objective and subjective rating scales to measure insomnia in MDD. Second, patients with MDD have both insomnia and hypersomnia symptoms (Geoffroy et al., 2018). A future study could explore the neural mechanism of hypersomnia in patients with MDD. Third, this study had a cross-sectional design, and these findings should be further verified by a longitudinal study. Finally, patients with chronic insomnia disorder usually also have comorbid depression, and how depression influences brain function in these patients should also be investigated.

In summary, the present study provides evidence that patients with MDD exhibit differences in functional brain alterations based on the severity of comorbid insomnia. Importantly, we demonstrated that the anterior and posterior PHG/HIPs might play different roles in the presence and absence of insomnia in patients with MDD. Our findings suggested that alterations in gFCD in the visual system can serve as a biomarker can serve as a biomarker of insomnia in patients with MDD.

Author disclosure contributors

LG and CHX design the study and write the manuscript. RHX, DL and BZ contributed to the image data analysis and designed the figures. CTZ and QH contributed to the modification of results and elucidated the results. All authors approved the final manuscript.

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CRediT authorship contribution statement

Liang Gong: Funding acquisition, Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Ronghua Xu:** Project administration, Writing - review & editing. **Duan Liu:** Validation, Methodology, Writing - review & editing. **Chuantao Zhang:** Data curation, Writing - review & editing. **Qun Huang:** Writing - original draft, Writing - review & editing. **Bei Zhang:** Writing - original draft, Writing - review & editing. **Chunhua Xi:** Funding acquisition, Conceptualization, Resources, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors of this manuscript declare no relationships with any companies.

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Supplementary materials

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References

Ambrosi, E., Arciniegas, D.B., Curtis, K.N., Patriquin, M.A., Spalletta, G., Sani, G., Frueh, B.C., Fowler, J.C., Madan, A., Salas, R., 2018. Resting-State functional connectivity of the habenula in mood disorder patients with and without suicide-related behaviors. J. Neuropsychiatry Clin. Neurosci appineuropsych17120351.

Aminoff, E.M., Kveraga, K., Bar, M., 2013. The role of the parahippocampal cortex in cognition. Trends Cogn. Sci. 17, 379–390.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113.

Association, A.P., 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). American Psychiatric Association.

Baldassano, C., Beck, D.M., Fei-Fei, L., 2013. Differential connectivity within the parahippocampal place area. Neuroimage 75, 228–237.

Chai, X.J., Castañón, A.N., Öngür, D., Whitfield-Gabrieli, S., 2012. Anticorrelations in resting state networks without global signal regression. Neuroimage 59, 1420–1428.

Chase, H.W., Clos, M., Dibble, S., Fox, P., Grace, A.A., Phillips, M.L., Eickhoff, S.B., 2015. Evidence for an anterior-posterior differentiation in the human hippocampal formation revealed by meta-analytic parcellation of fMRI coordinate maps: focus on the subiculum. Neuroimage 113, 44–60.

Christiansen, K., Metzler-Baddeley, C., Parker, G.D., Muhlert, N., Jones, D.K., Aggleton, J.P., Vann, S.D., 2017. Topographic separation of fornical fibers associated with the anterior and posterior hippocampus in the human brain: an MRI-diffusion study. Brain Behav. 7, e00604.

Cleary, P., Guy, W., 1977. Factor analysis of the Hamilton Depression Scale. Drugs Exp. Clin. Res. 1, 115–120.
Denys, K., Vanduffel, W., Fize, D., Nelissen, K., Peuskens, H., Van Essen, D., Orban, G.A., 2004. The processing of visual shape in the cerebral cortex of human and nonhuman primates: a functional magnetic resonance imaging study. J. Neurosci. 24, 2551–2565.
Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.
Eichenbaum, H., Yonelinas, A.P., Ranganath, C., 2007. The medial temporal lobe and recognition memory. Annu. Rev. Neurosci. 30, 123–152.
Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8, 700–711.
Geoffroy, P.A., Hoertel, N., Etain, B., Bellivier, F., Delorme, R., Limosin, F., Peyre, H., 2018. Insomnia and hypersomnia in major depressive episode: prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. J. Affect. Disord. 226, 132–141.
Gong, L., He, C., Yin, Y., Ye, Q., Bai, F., Yuan, Y., Zhang, H., Lv, L., Zhang, H., Zhang, Z., Xie, C., 2017. Nonlinear modulation of interacting between COMT and depression on brain function. Eur. Psychiatry 45, 6–13.
Gong, Q., He, Y., 2015. Depression, neuroimaging and connectomics: a selective overview. Biol. Psychiatry 77, 223–235.
Horner, A.J., Doeller, C.F., 2017. Plasticity of hippocampal memories in humans. Curr. Opin. Neurobiol. 43, 102–109.
Horovitz, S.G., Braun, A.R., Carr, W.S., Picchioni, D., Balkin, T.J., Fukunaga, M., Duyn, J.H., 2009. Decoupling of the brain's default mode network during deep sleep. In: Proceedings of the National Academy of Sciences of the United States of America. 106. pp. 11376–11381.
Kaiser, R.H., Whitfield-Gabrieli, S., Dillon, D.G., Goer, F., Beltzer, M., Minkel, J., Smoski, M., Dichter, G., Pizzagalli, D.A., 2016. Dynamic resting-state functional connectivity in major depression. Neuropsychopharmacol 41, 1822–1830.
Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J. Neurosci. 17, 4302–4311.
Li, C., Ma, X., Dong, M., Yin, Y., Hua, K., Li, M., Li, C., Zhan, W., Li, C., Jiang, G., 2016a. Abnormal spontaneous regional brain activity in primary insomnia: a resting-state functional magnetic resonance imaging study. Neuropsychiatr. Dis. Treat. 12, 1371–1378.
Li, S.X., Lam, S.P., Chan, J.W., Yu, M.W., Wing, Y.K., 2012. Residual sleep disturbances in patients remitted from major depressive disorder: a 4-year naturalistic follow-up study. Sleep 35, 1153–1161.
Li, Y., Liu, L., Wang, E., Zhang, H., Dou, S., Tong, L., Cheng, J., Chen, C., Shi, D., 2016b. Abnormal neural network of primary insomnia: evidence from spatial working memory task fMRI. Eur. Neurol. 75, 48–57.
Liu, C.-H., Guo, J., Lu, S.-L., Tang, L.-R., Fan, J., Wang, C.-Y., Wang, L., Liu, Q.-Q., Liu, C.-Z., 2018. Increased salience network activity in patients with insomnia complaints in major depressive disorder. Front. Psychiatry 9, 93.
Lui, S., Parkes, L.M., Huang, X., Zou, K., Chan, R.C., Yang, H., Zou, L., Li, D., Tang, H., Zhang, T., Li, X., Wei, Y., Chen, L., Sun, X., Kemp, G.J., Gong, Q.Y., 2009. Depressive disorders: focally altered cerebral perfusion measured with arterial spin-labeling MR imaging. Radiology 251, 476–484.
Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44, 893–905.
Noh, H.J., Joo, E.Y., Kim, S.T., Yoon, S.M., Koo, D.L., Kim, D., Lee, G.H., Hong, S.B., 2012. The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. J. Clin. Neurol. 8, 130.
O'Byrne, J.N., Berman Rosa, M., Gouin, J.P., Dang-Vu, T.T., 2014. Neuroimaging findings in primary insomnia. Pathol. Biol. 62, 262–269.
Park, S.C., Kim, J.M., Jun, T.Y., Lee, M.S., Kim, J.B., Jeong, S.H., Park, Y.C., 2013. Prevalence and clinical correlates of insomnia in depressive disorders: the crescend study. Psychiatry Investig. 10, 373–381.
Perlis, M.L., Giles, D.E., Buysse, D.J., Tu, X., Kupfer, D.J., 1997. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. J. Affect. Disord. 42, 209–212.
Phelps, E.A., 2004. Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr. Opin. Neurobiol. 14, 198–202.
Pigeon, W.R., Hegel, M., Unutzer, J., Fan, M.Y., Sateia, M.J., Lyness, J.M., Phillips, C., Perlis, M.L., 2008. Is insomnia a perpetuating factor for late-life depression in the impact cohort? Sleep 31, 481–488.
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.
Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., Nissen, C., 2010. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med. Rev. 14, 19–31.
Sharpley, C.F., Bitsika, V., 2013. Differences in neurobiological pathways of four "clinical content" subtypes of depression. Behav. Brain Res. 256, 368–376.
Sharpley, C.F., Bitsika, V., 2014. Validity, reliability and prevalence of four 'clinical content' subtypes of depression. Behav. Brain Res. 259, 9–15.
Sheline, Y.I., 2011. Depression and the hippocampus: cause or effect? Biol. Psychiatry 70, 308–309.
Smith, K., 2014. Mental health: a world of depression. Cah. Rev. The. 515, 181.
Smith, T., Gildeh, N., Holmes, C., 2007. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. Can. J. Psychiatry 52, 329–332.
Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu. Rev. Neurosci. 27, 279–306.
Sui, X., Zhu, M., Cui, Y., Yu, C., Sui, J., Zhang, X., Liu, J., Duan, Y., Zhang, Z., Wang, L., Zhang, X., Jiang, T., 2015. Functional connectivity hubs could serve as a potential biomarker in alzheimer's disease: a reproducible study. Curr. Alzheimer. Res. 12, 974–983.
Tomasi, D., Shokri-Kojori, E., Volkow, N.D., 2016. High-Resolution functional connectivity density: hub locations, sensitivity, specificity, reproducibility, and reliability. Cereb. Cortex 26, 3249–3259.
Tomasi, D., Volkow, N.D., 2010. Functional connectivity density mapping. Proc. Natl. Acad. Sci. U. S. A. 107, 9885–9890.
Tomasi, D., Volkow, N.D., 2011. Functional connectivity hubs in the human brain. Neuroimage 57, 908–917.
Tomasi, D., Volkow, N.D., 2012. Aging and functional brain networks. Mol. Psychiatry 17 (471) 549-458.
Winkelman, J.W., Benson, K.L., Buxton, O.M., Lyoo, I.K., Yoon, S., O'Connor, S., Renshaw, P.F., 2010. Lack of hippocampal volume differences in primary insomnia and good sleeper controls: an MRI volumetric study at 3 Tesla. Sleep Med. 11, 576–582.
Yu, S., Guo, B., Shen, Z., Wang, Z., Kui, Y., Hu, Y., Feng, F., 2018. The imbalanced anterior and posterior default mode network in the primary insomnia. J. Psychiatr. Res. 103, 97–103.
Zhang, L., Wu, H., Xu, J., Shang, J., 2018. Abnormal global functional connectivity patterns in medication-free major depressive disorder. Front. Neurosci. 12, 692.
Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., Yao, S., 2012. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol. Psychiatry 71, 611–617.
Zuo, X.N., Di Martino, A., Kelly, C., Shehzad, Z.E., Gee, D.G., Klein, D.F., Castellanos, F.X., Biswal, B.B., Milham, M.P., 2010. The oscillating brain: complex and reliable. Neuroimage 49, 1432–1445.