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Increased interhemispheric resting-state functional connectivity in healthy participants with insomnia symptoms

A randomized clinical consort study

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Abstract

Background: Abnormalities within the insular cortex of the salience and thalamus of the hyperarousal network have been increasingly reported in healthy participants with insomnia symptoms by recent resting-state functional magnetic resonance imaging (rsfMRI) studies. However, little is known about the changes in functional interaction between the bilateral cerebral hemispheres in healthy participants with insomnia symptoms.

Methods: In a randomized trial, 27 healthy participants with insomnia symptoms and 27 age-, gender-, and educational level-matched healthy participants without insomnia symptoms underwent rsfMRI. Voxel-mirrored homotopic connectivity (VMHC) was used to measure functional connectivity between any pair of symmetrical interhemispheric voxels (i.e., functional homotopy).

Results: The healthy participants with insomnia symptoms displayed significantly increased VMHC compared to healthy participants without insomnia symptoms in the bilateral thalamus/posterior insula (including anterior insula), fusiform, middle cingulate gyrus, inferior parietal lobe, and postcentral gyrus. No regions of decreased VMHC were detected in healthy participants with insomnia symptoms. There were significantly positive correlations between the VMHC values in the anterior cingulate cortex (ACC) and sleep disturbance scores in all healthy participants.

Conclusions: Insomnia is associated with substantial impairment of interhemispheric coordination within the default mode (ACC), salience (insula), hyperarousal (thalamus/posterior insula), and visual (fusiform) networks.

Abbreviations: ACC = anterior cingulate cortex, BOLD = blood oxygen level dependent, DMN = default mode network, DPARSF = Data Processing Assistant for Rest-State fMRI, EEG = electroencephalography, EPI = echo-planar imaging, fALFFs = fractional amplitude of low frequency fluctuations, FD = frame-wise displacement, fMRI = functional magnetic resonance imaging, FOV = field of view, FWHM = full width at half maximum, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, MFG = medial frontal gyrus, MNI = Montreal Neurological Institute, MRI = magnetic resonance imaging, rsfMRI = resting-state functional magnetic resonance imaging, SCID = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), SP6 = Sanyinjiao acupoint, TE = time echo, TR = time repetition, VMHC = voxel-mirrored homotopic connectivity.

Keywords: fMRI, insomnia, resting-state, thalamus, voxel-mirrored homotopic connectivity

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Shandong Provincial Hospital Affiliated to Shandong University committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interest to disclose.

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1. Introduction

Insomnia symptoms can result in diminished cognitive deterioration, for example, deteriorative attention, memory, and decision making, characterized by prolonged sleep latency, difficulty maintaining or staying asleep as long as desired, with a prevalence of about 20% world-wide.[1,2] However, the major contribution of insomnia to societal burden and economic cost is largely due to its effect on next-day functioning, health, safety, and quality of life.[3] Even worse, insomnia is associated with reduced quality of life, deteriorative attention, memory, and decision making, as well as physical complaints.[4–6] Long-term insomnia can lead to exaggerated emotional reactivity, somatic responses, and declined cognitive reactivity.[7] Emerging data show that insomnia can increase vulnerability and comorbidity for psychiatric disorders, for example, anxiety and depression.[8–10] Consequently, development of pharmacological and behavioral therapies requires insight into the neurobiological causes and consequences underlying insomnia.

Most consistent observation across neurophysiological, cognitive, and neuroimaging studies have revealed that insomnia is associated with a hyperarousal state in the development and maintenance of insomnia.[2,11] Liu et al[12] find that healthy participants with insomnia symptoms may have alterations in the fractional amplitude of low frequency fluctuations (fALFFs) of the insular cortex of the salience and thalamus of the hyperarousal network. Apart from the salience and hyperarousal networks, Suh et al[13] report that patients with persistent insomnia symptoms display decreased structural connectivity within regions of the default mode network (DMN), such as the medial frontal gyrus (MFG), anterior cingulate cortex (ACC), and precuneus. A recent review focused on the neural mechanisms of insomnia points out that the alteration of the hyperarousal system (i.e., hypothalamus and brainstem), the reward and salience system (i.e., amygdala, hippocampus, and insula), and the cognitive control system can result in malfunctioning during the wake to sleep transition, sustained sleep difficulties, and cognitive impairment in insomnia.[14] In addition, converging evidence suggests that various core intrinsic connectivity networks are related to insomnia symptoms. Using optimized voxel-based morphometry, Altena et al[15] demonstrate that reduced gray matter volume in the left orbitofrontal cortex is positively associated with insomnia scores in insomnia patients, supporting the reward network as a plausible substrate for the insufficient problem-solving abilities of insomnia. Using combined electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), Chen et al[16] found that the γ ratio power is associated with the blood oxygen level dependent (BOLD) signal in the insula in insomniacs, suggesting that the salience networks may be involved in progressive generation of low-frequency EEG waves as part of the transition to sleep. Further, it has also been found that the gray matter density in the left inferior orbitofrontal cortex bordering the insula is negatively associated with earlier morning awakening in healthy subjects with insomnia symptoms, suggesting that the salience network may be related to the compromised ability to judge thermal comfort.[17] Using tract-based spatial statistics to analyze the integrity of white matter tracts, Li et al[18] observe that the fractional anisotropy in the thalamus and body corpus callosum is associated with the Pittsburgh Sleep Quality Index scores, supporting the notion that white matter tracts related to hyperarousal networks are affected in patients with primary insomnia. The above network abnormalities may in part be due to disruptions in the interhemispheric functional coordination communication between the bilateral cerebral hemispheres.

Resting-state functional magnetic resonance imaging (rsfMRI) has attracted much attention to measure spontaneous neuronal activity without any specific tasks.[19] In contrast to more commonly used functional connectivity analysis based on the correlation analysis between a priori seed points and other brain regions, a recently validated approach termed voxel-mirrored homotopic connectivity (VMHC) analysis allow one to perform correlation analysis between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere.[20] VMHC calculates the Pearson correlation between each pair of homotopic voxel low-frequency (0.01–0.08 Hz) spontaneous BOLD fluctuations within whole brain regions.[20] Importantly, homotopic functional connectivity may reflect interhemispheric coordination for integrating the brain functions underlying coherent cognition, emotion, and behavior.[21] This method enables clinicians to gain additional insight into the functional organization of the brain in patients with traumatic axonal injury, depression, heroin-dependence, and sleep deprivation.[11,20,22,23] The purpose of the present study was to analyze the integrity of interhemispheric interactions between healthy participants with insomnia symptoms and healthy participants without insomnia symptoms. We also investigated whether the VMHC measurements are related to clinical scores, for example, sleep disturbance scores, the adjusted Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Rating Scale (HAMA) scores.

2. Materials and methods

2.1. Participants

This prospective study was approved by the ethics committee of the Shandong Provincial Hospital Affiliated to Shandong University. Fifty-four healthy adult participants (29 females, 25 males, mean age ± SD: 38.26 ± 11.66 years; years of education: 14.30 ± 3.20 years) were recruited in this study and screened by the Non-Patient Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (SCID). The criteria for healthy participants were as follows: participants who had a current or history of dependence on alcohol or other substance abuse or other Axis I disorders were excluded; 18 to 60 years of age; right handed assessed by the Edinburgh Inventory (Oldfield, 1971); and medication-naïve. The 17-item HAMD and HAMA were also evaluated. The sleep disturbance scores were determined by the sum of 3 HAMD-17 sleep questions, including items 4 (insomnia-early), 5 (insomnia-middle), and 6 (insomnia-late).[24–26] The healthy participants with insomnia symptoms implies that the number of sleep disturbance scores is greater than 1 and the healthy participants without insomnia symptoms have a score "0" by the number of sleep disturbance scores. To minimize any effect of sleep disturbance on depression severity, adjusted HAMD scores were created by omitting sleep items (questions 4–6) to measure the severity of their depression.[25] We also used HAMA to measure the severity of their anxiety. Though the HAMA also contains insomnia-related items (i.e., items 4), it cannot be considered as the main objective measure of insomnia.

2.2. MRI data acquisition

The images were collected on a 3.0 Tesla MRI system in the Shandong Provincial Hospital Affiliated to Shandong University. Magnetic resonance head coil have 8 channels. A standard bird-

cage head coil was used with the head snugly fixed by a belt and foam pads. The rsfMRI images were obtained by a gradient echo-planar imaging (EPI) sequence with the following scanning parameters: time repetition (TR) = 2000 milliseconds, time echo (TE) = 30 milliseconds, flip angle = 90°, field of view (FOV) = 220 mm × 220 mm, in-plane matrix size = 64 × 64, number of slices = 33, slice thickness = 3.5 mm, gap = 0.7 mm, and total 240 volumes. All participants were instructed to keep their eyes closed, not to think about anything, and not fall asleep. For each subject, the overall resting-state scanning process lasted 8 minutes. After scanning, a simple questionnaire was obtained from all the participants to confirm they complied with the instruction not to fall asleep.

2.3. Data preprocessing

The rsfMRI data preprocessing steps were performed using the Data Processing Assistant for Rest-State fMRI (DPARSF) toolbox based on Statistical Parametric Mapping software (http://www.fi.ion.ucl.ac.uk/spm).[27] The first 10 volumes of each participant were discarded for steady-state longitudinal magnetization, and the remaining 230 volumes were then corrected for the acquisition delay between slices. All functional volumes were realigned to the first volume to correct for head movement. No participants were excluded because they did not exceed ±2 mm translation or ±2° for rotation. Next, the functional images were spatially normalized to the standard Montreal Neurological Institute (MNI) template from statistical parametric mapping and resliced at a resolution of $3 \times 3 \times 3\,mm^3$. Smoothing was performed with a 4-mm full width at half maximum (FWHM) isotropic Gaussian kernel.[20,22] Six movement parameters and the averaged signals from white matter and cerebrospinal fluid were also removed as covariates. We further calculated the mean frame-wise displacement (FD) to measure the microhead motion of each subject. Finally, temporal bandpass filtering (0.01–0.08 Hz) was applied to reduce possible low-frequency drift and high-frequency noise, and the resulting volumes were further detrended to remove the linear trends.

2.4. VMHC analysis

Next, homotopic functional connectivity was applied using the Pearson correlation coefficient between each voxel's residual time series and its mirrored symmetrical counterpart in the opposite hemisphere based on a symmetric gray brain mask. Then, VMHC maps were Fisher *z*-transformed to improve their normality.

2.5. Statistical analysis

For clinical variables, the group differences were examined independently by the 2-sample *t* test or the Chi-squared test ($P < .05$). Group comparisons of global VMHC were performed using 2-sample *t* tests between the healthy participants with insomnia symptoms and healthy participants without insomnia symptoms without HAMA and adjusted HAMD as covariates. The significance levels were set at $P < .05$ (combined height threshold $P < .05$ and a minimum cluster size 85). A statistical corrected threshold of $P < .05$ within the whole-brain mask (size: 276,133 mm^3) was used in Monte Carlo simulations (parameters: single voxel $P = .05$, FWHMx = 6.684 mm, FWHMy = 7.558 mm, FWHMz = 7.793 mm, cluster size = 8991 mm^3 (333 voxels), and 1000 iterations). Further, group differences with HAMA and adjusted HAMD as covariates were also performed using 2-sample *t* tests. A statistical corrected threshold of $P < .05$ within the whole-brain mask (size: 276,133 mm^3) was also used in Monte Carlo simulations (parameters: single voxel $P = .05$, FWHMx = 6.499 mm, FWHMy = 7.097 mm, FWHMz = 7.433 mm, cluster size = 7587 mm^3 (281 voxels), and 1000 iterations). Whole-brain voxel-based Pearson correlation analyses were used to investigate the correlation between the VMHC values and the various clinical measures in all healthy participants. The significance levels were set at $P < .05$ (combined height threshold $P < .05$ and a minimum cluster size 85). "REST Slice Viewer" reports cluster information, including the number of voxels, peak coordinates (in MNI system), anatomical term of location, and Brodmann areas based on "xjview" (by Xu Cui, http://www.alivelearn.net/xjview/).

3. Results

3.1. Demographic and clinical data

As shown in Table 1, there were no significant differences in the participants' ages, sex, and educational level (all $P > .05$) between the 2 groups. However, there were significant differences in sleep disturbance scores, adjusted HAMD, and HAMA scores between the 2 groups ($P < .05$).

3.2. Group differences in VMHC

The healthy participants with insomnia symptoms revealed 10 clusters with significantly increased VMHC in the bilateral thalamus/posterior insula (including anterior insula), fusiform, middle cingulate gyrus, inferior parietal lobe, and postcentral gyrus relative to healthy participants without insomnia symptoms (Table 2). The thalamus/posterior insula (including anterior insula) and fusiform, which are the main findings of the present work, can also survive using voxels with $P < .05$ and cluster size $>8181\,mm^3$ (303 voxels) (corrected) (Fig. 1A). After regressing out the HAMA and adjusted HAMD, the healthy participants with insomnia symptoms revealed increased VMHC in the

Table 1

Group demographics and clinical measures.

Measure (mean ± SD)	HC-insomnia (N = 27)	HC-non (N = 27)	Statistical value	*P*
Sex, male/female	12/15	17/10	1.86	.17
Age, y	38.37 ± 11.87	38.15 ± 11.68	0.07	.95
Education level, y	14.04 ± 3.48	14.56 ± 2.93	−0.59	.56
Adjusted HAMD	1.06 ± 1.56	0.98 ± 1.59	3.4	.01
HAMA	3.41 ± 2.14	0.70 ± 1.03	5.93	.00
Sleep disturbance	1.67 ± 0.92	0.00 ± 0.00	9.24	.00

HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, HC-insomnia = healthy participants with insomnia symptoms, HC-non = healthy participants without insomnia symptoms, SD = standard deviation.

Table 2

VMHC comparisons between healthy participants with insomnia symptoms (HC-insomnia) and healthy participants without insomnia symptoms (HC-non).

Brain regions	Side	Brodmann areas (BA)	MNI coordinates			K	t
			x	y	z		
HC-insomnia > HC-non							
Fusiform	Right	18	24	−78	−9	943	5.52
Fusiform	Left	18	−24	−78	−9	955	5.52
Thalamus/posterior insula	Right		54	−21	12	583	4.55
Thalamus/posterior insula	Left		−54	−21	12	562	4.55
Middle cingulate cortex	Right		3	−9	48	203	3.99
Middle cingulate cortex	Left	24	−3	−9	48	202	3.99
Inferior parietal lobe	Right		−54	−24	45	106	3.84
Inferior parietal lobe	Left	2	54	−24	45	125	3.84
Postcentral gyrus	Right	7	30	−57	54	124	4.36
Postcentral gyrus	Left	7	−30	−57	54	124	4.37

K = cluster number, MNI = Montreal Neurological Institute, VMHC = voxel-mirrored homotopic connectivity.

bilateral fusiform, thalamus/posterior insula (without anterior insula), and middle cingulate gyrus relative to healthy participants without insomnia symptoms using voxels with $P < .05$ and cluster size $>7587\,mm^3$ (281 voxels) (corrected) (Fig. 1B).

3.3. Correlations between VMHC and clinical data in all healthy participants

We found significant positive correlations between regional VMHC values in the bilateral ACC (containing the superior frontal gyrus) and sleep disturbance scores ($r = 0.57$, $P = .00$) in all healthy participant groups (Fig. 2). The positive correlations were also confirmed in the healthy participants with insomnia symptoms group ($r = 0.42$, $P = .03$) (Fig. 2). We found no correlation between VMHC values and adjusted HAMD scores or HAMA scores.

4. Discussion

Here, VMHC was applied for the first time to investigate interhemispheric coordination of healthy participants with insomnia symptoms. Significant increases in VMHC were found in the bilateral thalamus/posterior insula (including anterior insula), fusiform, middle cingulate gyrus, inferior parietal lobe, and postcentral gyrus in healthy participants with insomnia symptoms. Further analysis revealed significant positive correlations between VMHC in the ACC and sleep disturbance score in all healthy participants. These VMHC variations may provide empirical evidence for interhemispheric coordination dysfunctions within the salience network, the hyperarousal network, and the DMN in healthy participants with insomnia symptoms.

Consistent with our expectations, the thalamus/posterior insula, as well as the junction between the pons and the prefrontal cortex, is recognized as the core region of the hyperarousal network, which are key structures for the regulation of sleep and wakefulness.[28] Importantly, the thalamus mediates bottom-up arousal by means of inputting from the brainstem or middle brain and projecting to cortical areas.[29] Insomnia mechanisms modulating the arousal network has been suggested from the thalamus.[30–32] Zhu et al[21] reveal a significant increase in VMHC in the thalamus in 28 healthy participants after a total night of sleep deprivation. Li et al.[18] find reduced fractional anisotropy in the thalamus, as well as negative correlation between fractional anisotropy in the thalamus and disease duration, in primary insomnia. Allen et al[33] find increased thalamic Gln plus Glu (Glx)/creatine/phosphocreatine (Cr) in patients with restless legs, which is correlated with the wake time during the sleep period. Under the sleep deprivation condition, Gao et al[34] find significant activations in the thalamus in both the Sham group with acupuncture and sleep deprivation group with acupuncture on Sanyinjiao acupoint (SP6), suggesting compensation of maintaining awareness and alertness (thalamus and pons) under extreme sleepy conditions. Huang et al[35] also report decreased functional connectivity between the amygdala and thalamus in patients with primary insomnia during resting state. Liu et al[12] report that healthy adults with insomnia symptoms have decreased fALFF in the left thalamus and pons relative to healthy adults without insomnia symptoms in the resting state. The decreased regional fluctuations in the thalamus and increased intra-thalamic connectivity found in our study may reflect the compensatory involvement of the bilateral thalamus to maintain cognitive performance when arousal is low in insomnia.[20] Converging evidence from task fMRI,[36] resting-state fMRI,[12,37] spectroscopy MRI,[33] and structural MRI[20] as listed above suggest that dysfunction in the bilateral thalamus may be involved in the biological basis of insomnia, which is particularly critical because important constituents of the biologic clock are located in the thalamus.[38] Importantly, the increased VMHC in the right posterior insula closer to the thalamus was correlated with adjusted HAMD scores. This is reasonable because the thalamus is a vulnerable brain area that is affected in various fMRI studies of depression.[38,39]

We also found increased VMHC in the bilateral anterior insula, which are key nodes within the salience network.[40] The salience network is thought to be involved in multiple functions, ranging from processing of sensory information and integrating external sensory stimuli with internal states to guide behavior.[15,40] Using source modeling of high-density EEG, Murphy et al[39] reveal that sleep slow waves preferentially originate in the anterior insula, travel along the anterior–posterior axis, and propagate along the cingulate. Aberrant insula within salience networks has been reported in normal subjects after sleep deprivation and patients with primary insomnia, suggesting that these networks contribute to the neural circuitry underlying insomnia. For example, Gao et al[34] show significantly increased regional brain activity in the bilateral insula in 16 healthy volunteers after sleep deprivation with acupuncture on SP6. Using a dual regression approach with simultaneous fMRI and EEG, Chen et al[16] demonstrate increased bilateral anterior

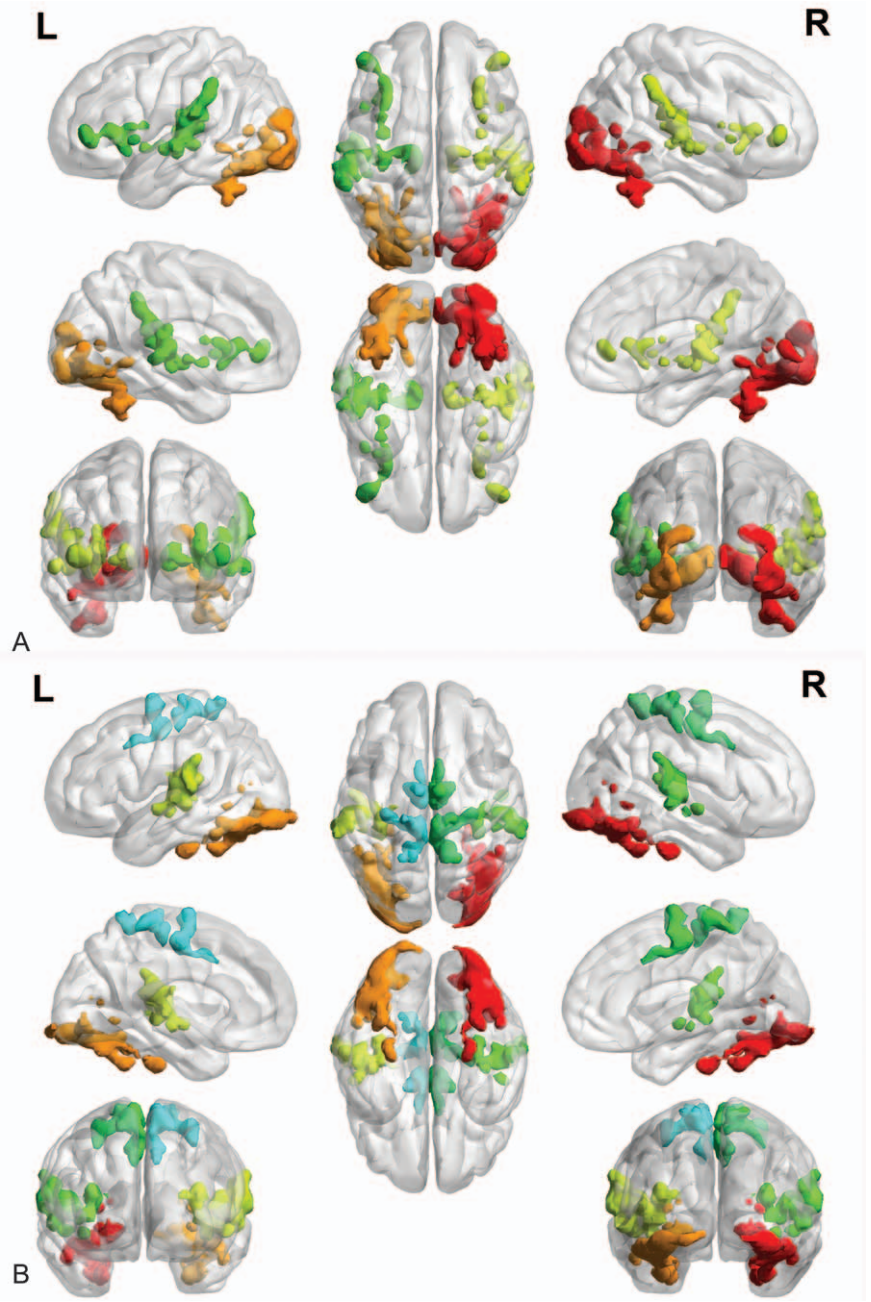

Figure 1. (A) Group comparisons of global VMHC between the healthy participants with insomnia symptoms and healthy participants without insomnia symptoms without HAMA and adjusted HAMD as covariates. (B) Group comparisons of global VMHC between the healthy participants with insomnia symptoms and healthy participants without insomnia symptoms with HAMA and adjusted HAMD as covariates. HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, VMHC = voxel-mirrored homotopic connectivity.

insula regional activity, as well as insula-associated high-frequency γ frequency, in insomniacs. Using making immediate and smaller (impulsive) monetary choices during a delay discounting task, Martin et al[40] demonstrate significantly lower brain activation in the right inferior frontal gyrus and bilateral insula in poor quality sleepers compared to the baseline condition. Using regional homogeneity analysis, Wang et al[41] present increased regional spontaneous activities in the left insula in primary insomnia patients, which are positively correlated with HAMA scores. After regressing out the HAMA and adjusted HAMD, the increased VMHC in the anterior insula will disappear in healthy participants with insomnia symptoms. The results from both Wang et al[41] and Liu et al[12] suggest that the increased VMHC in the bilateral anterior insula may be part of the underlying neurobiological mechanisms for anxiety in sleep initiation.

The ACC is the core brain region of the DMN, which is involved in affective control, decision making, and evaluation of the self-relevance of rewards.[42–44] It has been frequently reported that primary insomnia includes impaired neuropsychological performance in tests involving the prefrontal cortex.[4] In our study, positive association between the VMHC of the bilateral ACC and sleep disturbance scores are somewhat consistent with research by Suh et al. (2016),[13] which

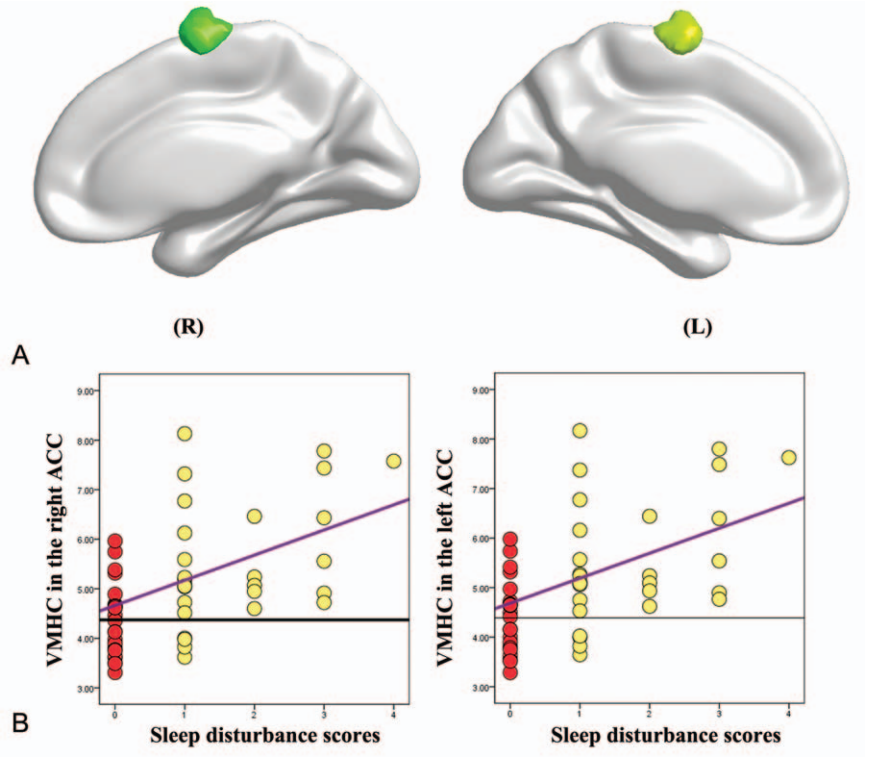

Figure 2. (A) Voxel-wise correlation between the VMHC values in bilateral anterior cingulate cortex (ACC) and sleep disturbance scores in all healthy participants. (B) The scatterplots of the VMHC values in left ACC (peak coordinate: −6, −6, 69; cluster size: 93) or right ACC (peak coordinate: 6, −6, 69; cluster size: 94) and sleep disturbance scores in all healthy participants. The mean VMHC values were extracted from the whole-brain voxel-wise correlation analysis of the bilateral ACC. L = left, R = right, red = no insomnia, VMHC = voxel-mirrored homotopic connectivity, yellow = insomnia.

demonstrates that decreased structural covariance with the DMN is associated with low sleep quality index in patients with persistent insomnia. This may reflect adaptive cognitive functioning in sleep disruption, in which the MFG may become increased in an effort to compensate for the malfunction or structural damage within the DMN.

We also found increased VMHC in the bilateral fusiform in healthy participants with insomnia symptoms. Increased regional homogeneity in brain activity in these regions in chronic primary insomnia during the resting state has also been reported in the literature.[45] Regional alterations in relative glucose metabolism in the left fusiform in primary insomnia during waking and nonrapid eye movement sleep states have also been reported by Kay et al.[46] The fusiform gyrus belongs to the visual network, which is responsible for processing words and colors, as well as face identification, and may play a regulative role in mood disorder.[47] Our findings suggest that the fusiform gyrus could be useful for indexing the extent of insomnia traits and anxiety state, and the hyperarousal reactivity of insomnia symptoms may contribute to changes in increased activity in the fusiform gyrus.

The increased interhemispheric synchrony or homotopy in specific brain regions, such as the thalamus and postcentral gyrus, has been associated with sleep deprivation[21] and studies have shown increased connectivity between insula and emotion-related regions and decreased connectivity between insula and cognitive-related regions in primary insomnia patients.[48] Since VMHC can reflect interhemispheric disturbance of functional coordination for high-level functions, such as cognitive control, interoception, and emotion regulation,[49,50] it may provide more complete evidence for interhemispheric disconnection associated with insomnia.[20,51] A recent meta-analysis study has showed increased bilateral thalamic activation and reduced frontal-parietal activation following sleep deprivation.[6] In the present study, we revealed increased VMHC in the bilateral thalamus/posterior insula (including anterior insula), fusiform, middle cingulate gyrus, inferior parietal lobe, and postcentral gyrus in healthy participants with sleep disturbance. According to increased VMHC induced by sleep deprivation[21] and reduced frontal–parietal activation after sleep deprivation,[6] our results might reflect compensatory adaptation for dysfunction of the cognitive network after sleep disturbance. Obviously, a more comprehensive task design is needed to test this hypothesis.

Nardo et al[52] investigated both structural and functional alterations and demonstrated reduced gray matter volume in anterior and posterior insula and increased regional cerebral blood flow in posterior insula in posttraumatic stress disorder (PTSD) with higher insomnia/nightmares symptoms. Importantly, our VMHC results largely overlap with regions reported in Nardo et al.[52] This indicates that PTSD and insomnia share a substantial neurobiological substrate.[53] A noticeable difference between our current findings and those reported by Nardo et al[52] concerns the insular subregion. The dorsal anterior insula is believed to be involved in appraisal and expression of negative emotion[54] and the posterior insula is more related to interoception and emotion-related bodily sensation.[55] Hence, our finding of increased VMHC in the bilateral thalamus/posterior insula (without anterior insula) with the HAMA and adjusted HAMD as covariate might be associated with negative bodily sensations, which in turn might contribute to sleep symptoms and the bilateral thalamus/posterior insula (including

anterior insula) without the HAMA and adjusted HAMD might reflect compensatory mechanism for emotional processing. Therefore, our findings do not conflict with or replicate Nardo et al[52] studies.

We acknowledge that there are several limitations associated with our study. First, the group's size was relatively small. Second, additional neuropsychological tests (e.g., the Pittsburgh sleep quality test or Duke structured interview for sleep disorders) are also needed. Third, heartbeat and breathing physiological noise should be recorded in the future studies. Fourth, no voxel-based morphometry or white matter diffusivity was analyzed. Despite these limitations, the current findings suggest that healthy participants with insomnia symptoms can impact the interhemispheric information interactions at resting state, and the VMHC deficits may play an important role in function impairments of insomnia.

5. Conclusions

Insomnia symptoms were characterized by increased functional synchronization in multiple brain regions. Significantly increased VMHC values in the bilateral thalamus/posterior insula (including anterior insula), fusiform, middle cingulate gyrus, inferior parietal lobe, and postcentral gyrus suggest that insomnia is associated with interhemispheric information interaction deficits of brain regions involved in hyperarousal (thalamus/posterior insula), salience (anterior insula), self-referential processes (ACC), and the visual (fusiform) network at resting state. Although replication is warranted, the VMHC deficits in these networks, especially the hyperarousal network, should be the to-be-tested psychosocial function impairments under insomnia models in the future.

References

[1] Buysse DJ. Insomnia. JAMA 2013;309:706–16.
[2] Punnoose AR, Golub RM, Burke AE. JAMA patient page. Insomnia. JAMA 2012;2653.
[3] Rosekind MR, Gregory KB. Insomnia risks and costs: health, safety, and quality of life. Am J Manag Care 2010;16:617–26.
[4] Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, et al. Insomnia and daytime cognitive performance: a meta-analysis. Sleep Med Rev 2012; 16:83–94.
[5] Kyle SD, Morgan K, Espie CA. Insomnia and health-related quality of life. Sleep Med Rev 2010;14:69–82.
[6] Ma N, Dinges DF, Basner M, et al. How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. Sleep 2015; 38:233–40.
[7] Wulff K, Gatti S, Wettstein JG, et al. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci 2010;11:589–99.
[8] Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 2011;135:10–9.
[9] Baglioni C, Spiegelhalder K, Regen W, et al. Insomnia disorder is associated with increased amygdala reactivity to insomnia-related stimuli. Sleep 2014;37:1907–17.
[10] Sunderajan P, Gaynes BN, Wisniewski SR, et al. Insomnia in patients with depression: a STAR*D report. CNS Spectr 2010;16:394–404.
[11] Joo EY, Noh HJ, Kim JS, et al. Brain gray matter deficits in patients with chronic primary insomnia. Sleep 2013;36:999–1007.
[12] Liu CH, Liu CZ, Zhang J, et al. Reduced spontaneous neuronal activity in the insular cortex and thalamus in healthy adults with insomnia symptoms. Brain Res 2016;1648:317–24.
[13] Suh S, Kim H, Dang-Vu TT, et al. Cortical thinning and altered cortico-cortical structural covariance of the default mode network in patients with persistent insomnia symptoms. Sleep 2016;39:161–71.
[14] Spiegelhalder K, Regen W, Baglioni C, et al. Neuroimaging insights into insomnia. Curr Neurol Neurosci Rep 2015;15:9.
[15] Altena E, Vrenken H, Van Der Werf YD, et al. Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. Biol Psychiatry 2010;67:182–5.
[16] Chen MC, Chang C, Glover GH, et al. Increased insula coactivation with salience networks in insomnia. Biol Psychol 2014;97:1–8.
[17] Stoffers D, Moens S, Benjamins J, et al. Orbitofrontal gray matter relates to early morning awakening: a neural correlate of insomnia complaints? Front Neurol 2012;3:105.
[18] Li S, Tian J, Bauer A, et al. Reduced integrity of right lateralized white matter in patients with primary insomnia: a diffusion-tensor imaging study. Radiology 2016;280:520–8.
[19] Biswal B, Yetkin FZ, Haughton VM, et al. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995;34:537–41.
[20] Zuo XN, Kelly C, Di Martino A, et al. Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. J Neurosci 2010;30:15034–43.
[21] Zhu Y, Feng Z, Xu J, et al. Increased interhemispheric resting-state functional connectivity after sleep deprivation: a resting-state fMRI study. Brain Imaging Behav 2016;10:911–9.
[22] Kelly C, Zuo XN, Gotimer K, et al. Reduced interhemispheric resting state functional connectivity in cocaine addiction. Biol Psychiatry 2011;69:684–92.
[23] Lai CH, Wu YT. Decreased inter-hemispheric connectivity in anterior sub-network of default mode network and cerebellum: significant findings in major depressive disorder. Int J Neuropsychopharmacol 2014;17:1935–42.
[24] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
[25] Lowe A, Rajaratnam SM, Hoy K, et al. Can sleep disturbance in depression predict repetitive transcranial magnetic stimulation (rTMS) treatment response? Psychiatry Res 2013;210:121–6.
[26] Trivedi MH, Bandelow B, Demyttenaere K, et al. Evaluation of the effects of extended release quetiapine fumarate monotherapy on sleep disturbance in patients with major depressive disorder: a pooled analysis of four randomized acute studies. Int J Neuropsychopharmacol 2013; 16:1733–44.
[27] Chao-Gan Y, Yu-Feng Z. DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. Front Syst Neurosci 2010;14:13.
[28] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257–63.
[29] Steriade M, Llinás RR. The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 1988;68:649–742.
[30] Chee MW, Chuah LY. Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. Curr Opin Neurol 2008;21:417–23.
[31] Spiegelhalder K, Regen W, Prem M, et al. Reduced anterior internal capsule white matter integrity in primary insomnia. Hum Brain Mapp 2014;35:3431–8.
[32] Steriade M. Grouping of brain rhythms in corticothalamic systems. Neuroscience 2006;137:1087–106.
[33] Allen RP, Barker PB, Horská A, et al. Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. Neurology 2013;80:2028–34.
[34] Gao L, Zhang M, Gong H, et al. Differential activation patterns of FMRI in sleep-deprived brain: restoring effects of acupuncture. Evid Based Complement Altern Med 2014;2014:465760.
[35] Huang Z, Liang P, Jia X, et al. Abnormal amygdala connectivity in patients with primary insomnia: evidence from resting state fMRI. Eur J Radiol 2012;81:1288–95.
[36] Dichter GS, Kozink RV, McClernon FJ, et al. Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. J Affect Disord 2012;136:1126–34.
[37] Coulon P, Budde T, Pape HC. The sleep relay—the role of the thalamus in central and decentral sleep regulation. Pflugers Arch 2012;463: 53–71.
[38] Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349–56.
[39] Murphy M, Riedner BA, Huber R, et al. Source modeling sleep slow waves. Proc Natl Acad Sci U S A 2009;106:1608–13.
[40] Martin LE, Pollack L, McCune A, et al. Comparison of obese adults with poor versus good sleep quality during a functional neuroimaging delay discounting task: a pilot study. Psychiatry Res 2015;234:90–5.
[41] Wang T, Li S, Jiang G, et al. Regional homogeneity changes in patients with primary insomnia. Eur Radiol 2016;26:1292–300.

[42] Casement MD, Keenan KE, Hipwell AE, et al. Neural reward processing mediates the relationship between insomnia symptoms and depression in adolescence. Sleep 2016;39:439–47.
[43] Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci 2011;15:85–93.
[44] Lemogne C, Delaveau P, Freton M, et al. Medial prefrontal cortex and the self in major depression. J Affect Disord 2012;136:e1–1.
[45] Dai XJ, Peng DC, Gong HH, et al. Altered intrinsic regional brain spontaneous activity and subjective sleep quality in patients with chronic primary insomnia: a resting-state fMRI study. Neuropsychiatr Dis Treat 2014;10:2163–75.
[46] Kay DB, Karim HT, Soehner AM, et al. Sleep-wake differences in relative regional cerebral metabolic rate for glucose among patients with insomnia compared with good sleepers. Sleep 2016;39:1779–94.
[47] Groenewold NA, Opmeer EM, de Jonge P, et al. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci Biobehav Rev 2013;37:152–63.
[48] Wang T, Yan J, Li S, et al. Increased insular connectivity with emotional regions in primary insomnia patients: a resting-state fMRI study. Eur Radiol 2017.
[49] Davis SW, Cabeza R. Cross-hemispheric collaboration and segregation associated with task difficulty as revealed by structural and functional connectivity. J Neurosci 2015;35:8191–200.
[50] Qiu YW, Jiang GH, Ma XF, et al. Aberrant interhemispheric functional and structural connectivity in heroin-dependent individual. Addict Biol 2016.
[51] Stark DE, Margulies DS, Shehzad ZE, et al. Regional variation in interhemispheric coordination of intrinsic hemodynamic fluctuations. J Neurosci 2008;28:13754–64.
[52] Nardo D, Högberg G, Jonsson C, et al. Neurobiology of sleep disturbances in PTSD patients and traumatized controls: MRI and SPECT findings. Front Psychiatry 2015;28:134.
[53] Craig AD. Significance of the insula for the evolution of human awareness of feelings from the body. Ann N Y Acad Sci 2011;1225: 72–82.
[54] Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry 2013;170:372–82.
[55] Miller EK. The prefrontal cortex and cognitive control. Nat Rev Neurosci 2000;1:59–65.