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SCIENTIFIC INVESTIGATIONS

Gender Differences in Regional Brain Activity in Patients with Chronic Primary Insomnia: Evidence from a Resting-State fMRI Study

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Study Objectives: To explore the regional brain activities in patients with chronic primary insomnia (PCPIs) and their sex differences.

Methods: Forty-two PCPIs (27 females, 15 males) and 42 good sleepers (GSs; 24 females, 18 males) were recruited. Six PCPIs (3 males, 3 females) were scanned twice by MRI to examine the test-retest reliability. Amplitude of low frequency fluctuation (ALFF) method was used to assess the local brain features. The mean signal values of the different ALFF areas were analyzed with a receiver operating characteristic (ROC) curve. Simple linear regression analysis was performed to investigate the relationships between clinical features and different brain areas.

Results: Both female and male PCPIs showed higher ALFF in the temporal lobe and occipital lobe, especially in female PCPIs. Female PCPIs had lower ALFF in the bilateral cerebellum posterior lobe, left dorsolateral prefrontal cortex, and bilateral limbic lobe; however, male PCPIs showed lower ALFF in the left occipital gyrus. The mean signal value of the cerebellum in female PCPIs showed negative correlations with negative emotions. Compared with male PCPIs, female PCPIs showed higher ALFF in the bilateral middle temporal gyrus and lower ALFF in the left limbic lobe. The different areas showed high test-retest stability (Clusters of contiguous volumes ≥ 1080 mm^3 with an intraclass correlation coefficient ≥ 0.80) and high degree of sensitivity and specificity.

Conclusions: Female PCPIs showed more regional brain differences with higher and lower ALFF responses than male PCPIs. However, they shared analogous excessive hyperarousal mechanism and wide variations in aberrant brain areas.

Keywords: insomnia, amplitude of low frequency fluctuation, functional magnetic resonance imaging, gender difference, blood oxygen level-dependent

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INTRODUCTION

Patients with chronic primary insomnia (PCPIs), who underwent the subjective experience of chronically disturbed sleep, sleep loss, non-refreshing sleep, and heightened arousal in bed with impaired quality of life, showed a decreased ability to disengage from external information processing at sleep onset.[1–3] Occasional episodes of insomnia symptoms are reported in half of all adults, while chronic insomnia is prevalent in 10–15% of the adult population.[4] In spite of a recent increase in neuroimaging research into PCPIs, it has not gleaned a consistent conclusion about its neuropathology after reviewing the neuroimaging studies of primary insomnia, especially with regard to the structural studies of brain alterations.[5] The results of structural studies are either contradictory or required replication. Altena et al. found that PCPIs had a smaller volume of reduced gray matter in the precuneus and left orbitofrontal cortex which strongly correlated with the subjective severity of insomnia, but increased gray matter volume was not found.[6] Joo et al. demonstrated significantly reduced gray matter concentrations in the dorsolateral prefrontal and pericentral cortices, superior temporal gyrus, and cerebellum, and decreased gray matter volumes in the medial frontal lobe and middle temporal lobe in PCPIs compared with good sleepers (GSs),[7] while Riemann et al. only found reduced hippocampal volume between the PCPIs and the GSs.[8] Conversely, Spiegelhalder et al. and Winkelman et al. found no significant between-group differences in the hippocampus.[9,10]

On the functional imaging aspects, the studies are too few and diverse in methodology to yield any general conclusions.

BRIEF SUMMARY

Current Knowledge/Study Rationale: In spite of a recent increase in neuroimaging research into chronic insomnia, it has yet to establish a consistent finding about its neuropathology. The functional studies are too few and diverse in methodology to yield any general conclusions, the results of structural studies are either contradictory or require replication. Previous studies have demonstrated wide sex differences in regional brain activity under different sleep conditions; however, insomnia has not been studied. The current study is to explore the regional brain activity changes in both male and female patients with insomnia.

Study Impact: In the present study we found that male and female patients with primary insomnia showed analogous excessive hyperarousal mechanism, but they exhibited wide sex differences in the aberrant regional brain activity. Therefore, the sex factor should be taken into consideration in future functional MRI studies. These findings may provide novel insights into a deeper understanding of the pathophysiology of chronic primary insomnia.

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Huang et al. found decreased functional connectivity mainly between the amygdala and the insula, striatum, and thalamus, and increased functional connectivity mainly between the amygdala and the premotor cortex and sensorimotor cortex in PCPIs compared with GSs.[4] Killgore et al. found increased functional connectivity between the primary visual cortex and other sensory regions such as the primary auditory cortex, olfactory cortex, and supplementary motor cortex in PCPIs compared with GSs.[11] Our previous study found significant decreased functional connectivity within the default mode network subregions using seed-based region-to-region functional connectivity method.[12] However, the results of abnormal functional connectivity between two remote areas cannot determine which brain area has abnormal spontaneous activity.

The amplitude of low-frequency fluctuations (ALFF), an index in which the square root of the power spectrum is integrated in a low frequency range, can locate which brain region has abnormal regional spontaneous neuronal activity in blood oxygen level-dependent (BOLD) signals.[13,14] Together with the resting-state functional connectivity method, the ALFF method is also an important part of resting-state functional magnetic resonance imaging (rs-fMRI). A previous study has demonstrated that repeated measurements of the ALFF with scan intervals up to a year between chronic, stable schizophrenia patients and healthy subjects have been shown to be highly repeatable.[15] Zuo et al. also represent a systematic and quantitative evaluation of the amplitude, spatial distribution, and test-retest reliability of spontaneous low frequency oscillation within the broad low-frequency range and within four narrowly defined low frequency bands.[16] They found that the ALFF method showed good to moderate test-retest reliability ranging from minimal to robust. Therefore, the simple calculation and reliable characterization of the ALFF measurement make it a potential and useful tool for rs-fMRI data analysis to investigate the functional changes in various brain diseases. Recently, the use of ALFF measurement has been successfully applied into the sleep deprivation,[17,18] wakefulness and light sleep,[19] and obstructive sleep apnea.[20] However, chronic primary insomnia has not been studied.

Previous studies have demonstrated aberrant regional spontaneous brain activities in sleep disorders such as the sleep deprivation and obstructive sleep apnea, and wide gender differences across the brain regions.[21,22] However, whether chronic primary insomnia shows analogous outcomes remains unclear. In this study, we hypothesized that the PCPIs also shows aberrant regional brain activity and gender differences in the regional brain activity. To test the hypothesis, our study is the first to utilize the ALFF method as an index to investigate the potential functional mechanisms of chronic insomnia and its sex trait.

METHODS

Subjects

Forty-two PCPIs (27 females, 15 males; mean age, 49.24 ± 12.26 years) who had sleep onset and/or maintenance insomnia were recruited from the Psychiatry Department of our hospital, and 42 GSs (24 females, 18 males; mean age, 49.14 ± 10.2 years) who were age-, sex-, and education status-matched to the PCPIs were recruited from the community via a newspaper advertisement. Of those patients, 27 PCPIs were females (mean age, 51.52 ± 10.51 years) and 15 PCPIs were males (mean age, 45.07 ± 10.87 years). Twenty-three PCPIs (7 males, 16 females) were not first-time visitors and had taken hypnotic medications or psychoactive medications before; the other 19 PCPIs (8 males, 11 females) were first-time visitors and had never taken medications before. The medication history duration was from 1 month to 5 years. Before the tests, the PCPIs were asked to stop taking any medications for ≥ 2 weeks prior to the data collection and for the duration of this study; however, 3 PCPIs only stopped taking agents for 2–4 days before the test.

The PCPIs met the following criteria as in our previous study that the regional homogeneity results of a group of 22 PCPIs from the 42 PCPIs were reported.[23] Conformity to the pertinent diagnostic criteria was defined by the International Classification of Sleep Disorders, Second Edition, duration of insomnia > 2 months, Pittsburgh Sleep Quality Index (PSQI) score > 5, sleep diary for > 2 weeks duration, and right-handedness. All GSs met the following criteria: good sleeping habits, good sleep onset and/or maintenance, regular dietary habits, no consumption of any stimulants, medications, caffeine, tea, or coffee during or prior to the study for ≥ 3 months, PSQI score < 5, and Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) < 7.

The exclusion criteria for both groups comprised pathological brain MRI findings, inborn or other acquired diseases, any foreign implants in the body, present or past psychiatric or central nervous system disorders, substance dependency or substance abuse (including heroin, nicotine, or alcohol addiction for GSs), foreign implants in the body, any history of swing shift, shift work, sleep complaints or other sleep disorder, including hypersomnia, parasomnia, sleep related breathing disorder, sleep related movement disorder, or circadian rhythm sleep disorder confirmed by overnight polysomnography (PSG).

Research Design and Procedures

An experienced psychiatrist evaluated the PCPIs with the Diagnostic and Statistical Manual of Mental Disorders, version 4 (DSM-IV) for the life history of psychiatric disorders, as well as an unstructured clinical interview for the history of medicine and sleep disorder. To evaluate the sleep status, PCPIs were asked to wear a Fitbit Flex tracker (http://help.fitbit.com) for 2 consecutive nights and the GSs for one week duration. During the time, the total sleep time, sleep onset latency, sleep efficiency, and number of awakenings were recorded.

All volunteers underwent an rs-fMRI scan, and six PCPIs (3 males, 3 females) were scanned the magnetic resonance imaging (MRI) twice to examine the test-retest reliability. A simple questionnaire was administered immediately after the scans to determine whether the subjects were awake during the scans. The data of the subjects who were asleep during the scans were excluded. This study was approved by the human research ethics committee of our hospital. All volunteers participated voluntarily and were informed of the purposes, methods, and the potential risks; all signed an informed consent form.

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Questionnaires

All volunteers were asked to complete a number of questionnaires, including PSQI, Insomnia Severity Index (ISI), Self-Rating Depression Scale (SDS), Self Rating Anxiety Scale (SAS), Self-Rating Scale of Sleep (SRSS), and Profile of Mood States (POMS). The POMS questionnaire contains of 7 indexes, including 5 negative emotion indexes (nervousness, wrath, fatigue, depression and confusion) and 2 positive emotion indexes (energy and self-esteem).

MRI Parameters

MRI scan was performed on a 3-Tesla MR scanner (Trio, Siemens, Erlangen, Germany). High-resolution T1-weighted images were acquired with a 3-dimensional spoiled gradient-recalled sequence in a sagittal orientation: 176 images (repetition time = 1900 ms, echo time = 2.26 ms, thickness = 1.0 mm, gap = 0.5 mm, acquisition matrix = 256 × 256, field of view = 250 mm × 250 mm, flip angle = 9°) were obtained. Finally, an 8-min rs-fMRI scan was obtained with eyes closed. Total of 240 functional images (repetition time = 2000 ms, echo time = 30 ms, thickness = 4.0 mm, gap = 1.2 mm, acquisition matrix = 64 × 64, flip angle = 90°, field of view = 220 mm × 220 mm, 29 axial slices with Gradient-Recalled Echo-Planar Imaging pulse sequence) covering the whole brain were obtained.

Data Analysis

Functional data were checked by MRIcro software (www.MRIcro.com) to exclude the defective data. The first 10 time points of the functional images were discarded due to the possible instability of the initial MRI signal and the participants' adaptation to the scanning environment. On the basis of MATLAB2010a (Mathworks, Natick, MA, USA), the rest of the data pre-processing was performed by DPARSFA (http://rfmri.org/DPARSF) software, including Digital Imaging and Communications in Medicine (DICOM) standards for form transformation, slice timing, head motion correction, spatial normalization, smooth with a Gaussian kernel of 6×6×6 mm^3 full-width at half-maximum. The participants who had more than 1.5 mm maximum translation in x, y, or z and 1.5° degree of motion rotation were rejected. The Friston six head motion parameters were used to regress out the head motion effects based on recent work showing that the higher-order models were more effective in removing the head motion effects.[24,25] Linear regression was also applied to remove other sources of spurious covariates along with their temporal derivatives, including the signal from a ventricular region of interest (ROI), and the signal from a region centered in white matter.[26] Of note, the global signal was not regressed out in the present data, as described by Guo et al.,[27] for the reason that there is still controversy concerning removing the global signal in the preprocessing of the resting-state data.[26,28] After the head-motion correction, the functional MRI images were spatially normalized to the Montreal Neurological Institute (MNI) space and re-sampled at a resolution of 3 mm × 3 mm × 3 mm. After the pre-processing, the time series for each voxel was temporally bandpass filtered (0.01–0.08 Hz) and linearly detrended to reduce low-frequency drift and physiological high frequency respiratory and cardiac noise. The details of the ALFF calculation have been reported in the previous studies.[18,23,29] To reduce the global effects of variability across the participants, the mean ALFF value of each voxel was divided by the global mean ALFF value for each participant.

Groups

It was shown that many brain areas had obvious gender differences both during rested wakefulness and during sleep deprivation.[21] In this study, there was a lopsided sex ratio in PCPIs, and 23 PCPIs had taken medications before. However, whether the medication or gender had any effects is still unknown. Because of these limitations, we further divided the PCPIs into 4 groups to explore whether there is interaction effect between sex and medicine, including female PCPIs (PCPI-Fs) with medicine, PCPI-Fs without medicine, male PCPIs (PCPI-Ms) with medicine, and PCPI-Ms without medicine.

Receiver Operating Characteristic Curve

It was shown that the ALFF method showed high sensitivity and specificity to distinguish the obstructive sleep apnea patients and long-term sleep deprivation subjects from the GSs.[18,20] In this study, the receiver operating characteristic (ROC) curve was used to investigate whether these specific ALFF differences have the sensitivity and specificity to distinguish the PCPIs from the GSs.

Regression Analysis

Based on the ALFF findings, the different brain regions between-groups were classified as ROIs. For each ROI, the mean ALFF signal value was extracted by averaging the ALFF value over all voxels. Then, simple linear regression analysis was performed to investigate the relationships between the related sleep questionnaires (dependent variable) and the mean ALFF value in each of those different areas (independent variable) in insomnia groups. A p value < 0.05 was considered statistically significant.

Statistical Analysis

Two-way ANOVA analysis was used to assess the differences among the insomnia groups in age, years of education, duration of insomnia, and other sleep characteristics, and a least significant difference (LSD) procedure test was used to assess the differences between 2 groups. A χ^2 test was used for categorical data. All the results were quoted as two-tailed p values, and $p < 0.05$ was considered statistically significant. The statistical analysis was performed using IBM SPSS 21.0.

The interaction effect of the gender and the medicine among the insomnia groups based on the ALFF method was investigated using a two-way ANOVA analysis (full factorial model), and a 2-sample *t*-test was used to assess the differences in brain activity between 2 groups with age, sex, and years of education as nuisance covariates of no interest. A corrected significance level of individual voxel $p < 0.01$ and the contiguous cluster volume ≥ 1080 mm^3, using an AlphaSim corrected threshold of cluster $p < 0.05$, were used to determine the statistical significance.

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Table 1—Demographics and sleep characteristics of chronic insomnia groups and GSs.

	PCPIs	PCPI-Fs	PCPI-Ms	GSs	GSs-Fs	GSs-Ms
Demographics (n = 42)						
Mean age, year	49.21 ± 10.96	51.52 ± 10.51	45.07 ± 10.87	49.14 ± 10.2	49.58 ± 7.12	53.83 ± 6.11
Sex (Male, Female)	42 (15, 27)	27 (0, 27)	15 (15, 0)	42 (18, 24)	24 (0, 24)	18 (18, 0)
Education, year	6.16 ± 5.33	6.96 ± 4.06	8.73 ± 3.63	7.83 ± 3.34	6.88 ± 3.04	9.11 ± 3.38
Sleep questionnaires (n = 42)						
Duration of insomnia, year	5.44 ± 5.23	6.40 ± 5.56	3.71 ± 4.24	N/A	N/A	N/A
PSQI score	15.17 ± 2.16	15.19 ± 2.20	15.13 ± 2.17	2.50 ± 0.89	2.25 ± 0.90	2.83 ± 0.79
PSQI total sleep time, hour	3.78 ± 1.13	3.34 ± 1.02#	4.57 ± 0.88#	7.51 ± 0.57	7.53 ± 0.54	7.47 ± 0.62
PSQI sleep efficiency, %	46.55 ± 14.34	40.89 ± 12.41#	56.76 ± 11.94#	87.8 ± 5.7	88.28 ± 5.3	87.19 ± 6.27
SRSS score	34.90 ± 4.59	35.93 ± 4.34	33.07 ± 4.59	15.29 ± 1.66	14.92 ± 1.44	15.78 ± 1.83
ISI score	18.43 ± 2.96	18.74 ± 2.85	17.87 ± 3.16	N/A	N/A	N/A
SAS standard score	41.27 ± 8.43	42.28 ± 8.91	39.47 ± 7.43	26.36 ± 3.16	25.83 ± 3.09	27.06 ± 3.21
SDS standard score	48.26 ± 9.55	48.99 ± 10.89	46.93 ± 6.63	30.12 ± 3.44	25.96 ± 3.50	30.33 ± 3.45
POMS negative index	31.69 ± 18.86	29.96 ± 18.58	34.80 ± 19.61	8.55 ± 3.32	8.04 ± 3.28	9.22 ± 3.37
POMS positive index	13.95 ± 8.04	13.41 ± 9.16	14.93 ± 5.66	25.76 ± 3.76	27.42 ± 3.86	23.56 ± 2.23
POMS total score	117.93 ± 23.92	116.85 ± 24.17	119.87 ± 24.18	82.79 ± 5.85	80.63 ± 5.84	85.67 ± 4.59
Fitbit Flex tracker (38 PCPIs and 35 GSs)						
Total sleep time, hour	4.99 ± 0.7	4.81 ± 0.61	5.31 ± 0.75	6.79 ± 0.49	6.89 ± 0.51	6.65 ± 0.44
Sleep efficiency, %	64.56 ± 8.48	62.62 ± 5.97#	67.87 ± 8.86#	85.18 ± 4.81	86.17 ± 4.58	83.86 ± 4.95
Sleep onset latency, min	67.26 ± 43.53	76.58 ± 48.45	51.29 ± 28.38	8.89 ± 2.01	8.75 ± 1.86	9.07 ± 2.25
Number of awakenings	8.8 ± 4.2	11.96 ± 4.38#	9.07 ± 2.37#	4.31 ± 1.25	4.1 ± 1.33	4.6 ± 1.12

#Significant differences between PCPI-Fs and PCPI-Ms ($p < 0.05$). POMS negative index contains of nervousness, wrath, fatigue, depression and confusion, and POMS positive index contains of energy and self-esteem. PCPIs, patients with chronic primary insomnia; PCPI-Fs, female PCPIs; PCPI-Ms, male PCPIs; GSs, good sleepers; GS-Fs, good female sleepers; GS-Ms, good male sleepers; N/A, not applicable; PSQI, Pittsburgh Sleep Quality Index; SRSS, Self-Rating Scale of Sleep; ISI, Insomnia Severity Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; POMS, Profile of Mood States; min, minute.

RESULTS

Sleep Characteristics

No significant differences were found in age, sex, and education among the PCPIs, PCPI-Ms, PCPI-Fs, or GSs ($p > 0.05$). Compared with the GSs groups, the corresponding insomnia groups showed significant differences in the sleep characteristics and Fitbit Flex tracker data (PCPI-Ms vs male GSs (GS-Ms), PCPI-Fs vs female GSs (GS-Fs), all PCPIs vs all GSs; $p < 0.001$). PCPI-Ms showed longer PSQI total sleep time and higher PSQI sleep efficiency than PCPI-Fs ($p < 0.05$). No significant differences were found in the duration of insomnia, PSQI score, SRSS score, ISI score, SAS score, SDS score, POMS negative index, POMS positive index and POMS total score between the PCPI-Ms and the PCPI-Fs ($p > 0.05$). Fitbit Flex tracker found that the PCPI-Fs had lower sleep efficiency ($p = 0.004$) and more number of awakenings ($p = 0.012$) than the PCPI-Ms, while no significant differences were found in the sleep onset latency ($p = 0.084$) and total sleep time ($p = 0.498$). The characteristics are presented in **Table 1**.

High Test-Retest Reliability between Two MRI Scans

To investigate the test-retest stability of the ALFF measurements, voxel-wise intraclass correlation coefficients (ICC), a common index of test-retest reliability which ranges from 0 (no reliability) to 1 (perfect reliability), was used as in Zuo et al.[30] A view of the ICC results are shown in **Figure 1**, overlaid on a structural template. Most of the brain voxels showed an ICC of 0.5 or greater. The clusters of at least 1080 mm^3 contiguous volumes with an ICC ≥ 0.80 were found throughout the cortex.

The largest cluster, 12880 voxels with a maximum ICC of 0.985 ($p < 0.001$), was across the bilateral hemisphere in the frontal lobe, fusiform gyrus, superior temporal gyrus, middle temporal gyrus, cerebellum posterior lobe, precuneus, parietal lobe, limbic lobe, cuneus, lingual gyrus, middle occipital gyrus, and inferior occipital gyrus. The remaining clusters were as follows:

A cluster of 53 voxels with a maximum ICC of 0.917 ($p = 0.008$) was in the left superior frontal gyrus and middle frontal gyrus; a cluster of 51 voxels with a maximum ICC of 0.998 ($p < 0.001$) was in the right limbic lobe and temporal lobe; a cluster of 49 voxels with a maximum ICC of 0.952 ($p = 0.002$) was in the right middle occipital gyrus and inferior occipital gyrus, and a cluster of 43 voxels with a maximum ICC of 0.945 ($p = 0.003$) was in the left cerebellum anterior lobe.

ALFF Differences

PCPIs vs GSs

Compared with the GS-Fs, the PCPI-Fs showed significant lower ALFF in the bilateral cerebellum posterior lobe, and the

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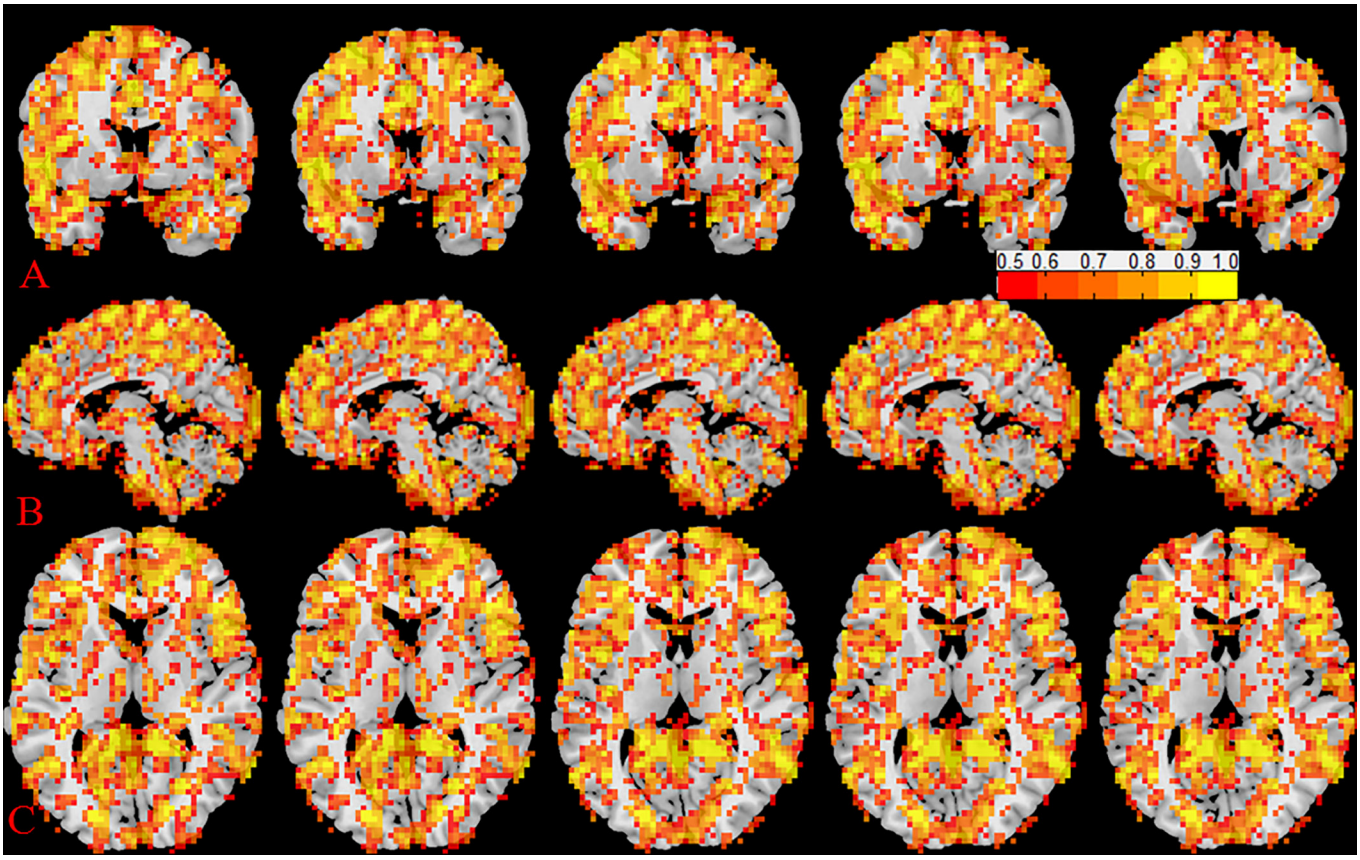
Figure 1—The test-retest stability of the ALFF measure.



The ICC image thresholded at 0.5 or greater overlaid on the MNI template brain, in coronal **(A)**, sagittal **(B)** and axial **(C)** views. The color bar covers from red (ICC = 0.5) to yellow (ICC = 1). ALFF, amplitude of low-frequency fluctuations; ICC, intraclass correlation coefficients; MNI, Montreal Neurological Institute.

left cluster of the premotor cortex (BA 6, BA 8) and dorsolateral prefrontal cortex (BA 9), and significant higher ALFF in the left fusiform gyrus (BA 37) and bilateral occipital lobe (cuneus, lingual gyrus and middle occipital gyrus; BA 17, BA 18, BA 19). Furthermore, they also showed different ALFF values in the limbic system, including lower ALFF in the bilateral ventral medial prefrontal cortex (VMPFC) (rectal gyrus, orbital gyrus, subcallosal gyrus, olfactory bulb and medial frontal gyrus; BA 10, BA 11) and right medial temporal lobe (MTL) (anterior cingulate gyrus; BA 32), and higher ALFF in the bilateral MTL (parahippocampal gyrus, posterior cingulate gyrus; BA 27, BA 30). The details are presented in **Figure 2** and **Table 2**.

Compared with the GS-Ms, the PCPI-Ms showed significant higher ALFF in the right cluster of the temporal gyrus (BA 21), angular gyrus (BA39) and occipital gyrus (BA19), and significant lower ALFF in the left occipital gyrus (BA17, BA18). The details are presented in **Figure 3** and **Table 2**.

Compared with the total GSs with males and females combined, the total PCPIs had different areas in the bilateral MTL, bilateral visual cortex, and right VMPFC. They showed significant higher ALFF in the right cluster of the PCC, corpus callosum and lingual gurus, and the left cluster of the PCC, precuneus and cuneus, and showed lower ALFF in the right cerebellum posterior lobe and the right cluster of the rectal gyrus and orbital gyrus. The details are presented in **Table 2**.

PCPI-Fs vs PCPI-Ms

Full factorial ANOVA analysis showed significant difference in the main effect of gender, while no significant differences were found in the main effect of medicine and the interaction between gender and medicine ($p > 0.05$). Therefore, in this study we only explored the sex difference between the PCPI-Fs and the PCPI-Ms, and did not take the effect of medicine and the effect of gender by medicine interaction into consideration.

Compared with the PCPI-Ms, the PCPI-Fs showed significant higher ALFF values in the bilateral temporal gyrus (BA 21, BA 37), and significant lower ALFF values in the left VMPFC (BA 10, BA 11) and left ventral lateral prefrontal cortex (VLPFC, BA 47). The details are presented in **Figure 4** and **Table 2**.

ALFF Analysis Shows High Sensitivity and Specificity

Since the different ALFF areas might be utilized as markers to separate the PCPIs from the GSs, the mean signal values of the different areas were extracted and used for ROC curve analysis.

The discrimination results are considered excellent for the area under curve (AUC) values between 0.9 and 1, good between 0.8 and 0.9, fair between 0.7 and 0.8, poor between 0.6 and 0.7, and failed between 0.5 and 0.6.[31] In the present

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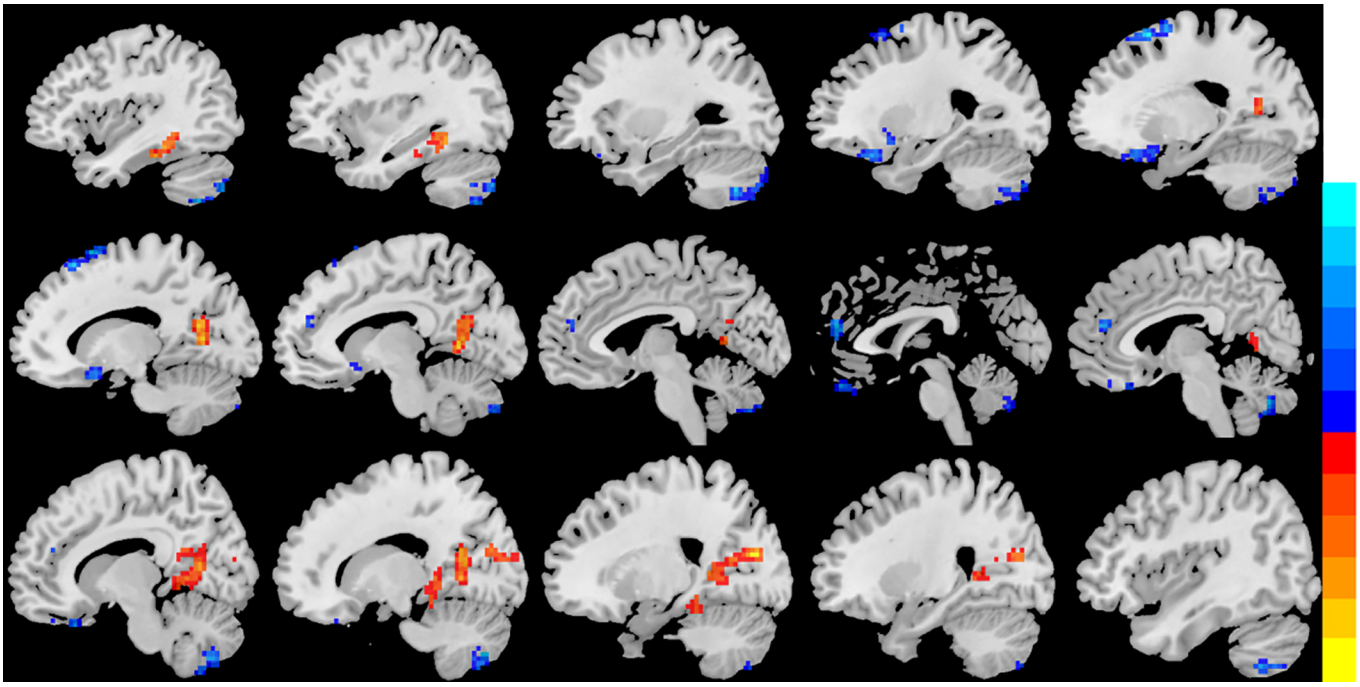
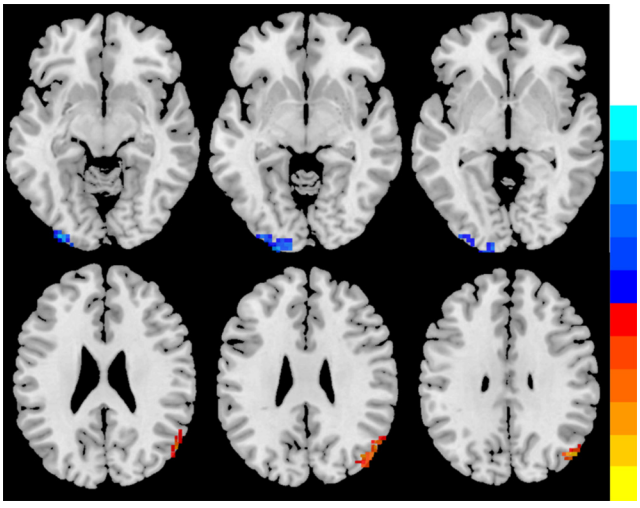
Figure 2—Altered ALFF areas between the PCPI-Fs and GS-Fs.



Brain regions showing ALFF differences in the cingulate gyrus, parahippocampa gyrus, occipital gyrus, fusiform gyrus, precuneus, cerebellum posterior lobe and frontal gyrus. Red areas denote higher ALFF brain regions, and blue areas denote lower ALFF brain regions. ALFF, amplitude of low-frequency fluctuations; PCPI-Fs, female PCPIs; GS-Fs, good female sleepers.

Figure 3—Altered ALFF areas between the PCPI-Ms and GS-Ms.



Brain regions showing ALFF differences in the temporal gyrus, angular gyrus and occipital gyrus. Red areas denote higher ALFF brain regions, blue areas denote lower ALFF brain regions. The right side of the picture indicates the right side of the brain, and the corresponding left side indicates the left side of the brain. ALFF, amplitude of low-frequency fluctuations; PCPI-Ms, male PCPIs; GS-Ms, good male sleepers.

study, the ROC analysis revealed that the different ALFF areas of both the PCPI-Fs and the PCPI-Ms showed high AUC values and high degree of sensitivities and specificities. However, the different ALFF areas of total PCPIs showed one poor, two fair, and one good AUC value, with neither high degree of sensitivity nor specificity. This indicates that the different ALFF areas could serve as excellent or good markers to distinguish the PCPI-Fs from the GS-Fs or distinguish the PCPI-Ms from the GS-Ms. The details are presented in **Table 3**.

Correlation between Different Areas and Sleep Characteristics

In the PCPI-Fs, there was an approximate weak linear positive correlation between the PSQI time in bed (dependent variable) and the Cluster 3 ($R^2 = 0.131$, $p = 0.064$). The Cluster 4 (independent variable) showed weak linear negative correlations with three other measurements including the SDS score ($R^2 = 0.22$, $p = 0.014$), POMS negative score ($R^2 = 0.233$, $p = 0.011$) and POMS total score ($R^2 = 0.256$, $p = 0.007$). Age revealed a weak linear negative correlation with the Cluster 3 ($R^2 = 0.19$, $p = 0.023$), an approximate weak linear negative correlation with the Cluster 8 ($R^2 = 0.144$, $p = 0.051$), and showed a weak linear positive correlation with the Cluster 4 ($R^2 = 0.162$, $p = 0.037$) and an approximate weak linear positive correlation with the Cluster 5 ($R^2 = 0.135$, $p = 0.06$). In the PCPI-Ms, the Cluster 10 (independent variable) showed approximate weak linear positive correlations with the PSQI total score ($R^2 = 0.260$, $p = 0.052$) and ISI score ($R^2 = 0.230$, $p = 0.07$). The details are presented in **Table 4**.

DISCUSSION

To the best of our knowledge, this study was the first to use the resting-state ALFF method to investigate the regional brain

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Table 2—The ALFF differences between insomnia groups and GSs group.

Conditions	Cluster Number	Brain Regions of Peak Coordinates	R/L	BA	Volume (mm^3)	t-score of Peak Voxel	MNI Coordinates of Peak Voxel
PCPI-Fs compared with GS-Fs							
PCPI-Fs > GS-Fs	Cluster 1	Cuneus, Lingual Gyrus, Middle Occipital Gyrus, Parahippocampal Gyrus, Posterior Cingulate Gyrus	R	17, 18, 19, 27, 30	334	5.0531	21 −78 18
PCPI-Fs > GS-Fs	Cluster 2	Fusiform Gyrus, Parahippocampal Gyrus	L	37	53	4.1896	−39 −36 −15
PCPI-Fs > GS-Fs	Cluster 3	Posterior Cingulate, Precuneus, Occipital Lobe	L	17, 18, 23	109	4.6389	−15 −63 9
PCPI-Fs < GS-Fs	Cluster 4	Cerebellum Posterior Lobe, Cerebellar Tonsil	R	N/A	151	−4.3523	15 −75 −54
PCPI-Fs < GS-Fs	Cluster 5	Cerebellum Posterior Lobe	L	N/A	184	−4.1562	−39 −69 −54
PCPI-Fs < GS-Fs	Cluster 6	Rectal Gyrus, Orbital Gyrus	R	11	46	−3.8140	0 45 −24
PCPI-Fs < GS-Fs	Cluster 7	Inferior Frontal Gyrus, Subcallosal Gyrus, olfactory bulb	L	11	88	−3.8360	−24 24 −21
PCPI-Fs < GS-Fs	Cluster 8	Medial Frontal Gyrus, Anterior Cingulate Gyrus	R	10, 32	54	−4.7611	3 48 18
PCPI-Fs < GS-Fs	Cluster 9	Superior Frontal Gyrus, Middle Frontal Gyrus	L	6, 8, 9	103	−4.4349	−21 15 63
PCPI-Ms compared with GS-Ms							
PCPI-Ms > GS-Ms	Cluster 10	Superior Temporal Gyrus, Middle Temporal Gyrus, Angular Gyrus, Occipital Gyrus	R	19, 21, 39	47	4.1557	51 −72 33
PCPI-Ms < GS-Ms	Cluster 11	Cuneus, Middle Occipital Gyrus, Inferior Occipital Gyrus	L	17, 18	47	−3.6400	−33 −93 −9
PCPI-Fs compared with PCPI-Ms							
PCPI-Fs > PCPI-Ms	Cluster 12	Superior Temporal Gyrus, Middle Temporal Gyrus	L	37	56	5.3353	−48 −60 9
PCPI-Fs > PCPI-Ms	Cluster 13	Middle Temporal Gyrus	R	21	56	3.5075	66 −39 0
PCPI-Fs < PCPI-Ms	Cluster 14	Medial Frontal Gyrus, Inferior Frontal Gyrus, Subcallosal Gyrus, Rectal Gyrus	L	11	166	−4.7890	−24 21 −21
PCPI-Fs < PCPI-Ms	Cluster 15	Superior Frontal Gyrus, Middle Frontal Gyrus	L	11, 47	41	−4.8195	−27 57 −3
PCPI-Fs < PCPI-Ms	Cluster 16	Middle Frontal Gyrus	L	10	43	−4.1951	−3 57 −3
All PCPIs compared with all GSs							
PCPIs > GSs	Cluster 17	Posterior Cingulate, Corpus Callosum, Lingual gurus	R	17, 23, 29, 30	109	3.7652	9 −57 15
PCPIs > GSs	Cluster 18	Posterior Cingulate, Precuneus, Cuneus	L	17,18,23	71	4.0359	−12 −63 21
PCPIs < GSs	Cluster 19	Cerebellum Posterior Lobe	R	N/A	40	−3.6554	6 −69 −45
PCPIs < GSs	Cluster 20	Rectal Gyrus, Orbital Gyrus	R	11	50	−3.8564	0 30 −24

The statistical threshold was set at voxel with $p < 0.01$, cluster size with $p < 0.05$ and cluster volume ≥ $1080mm^3$ between PCPIs and GSs, corrected by AlphaSim. ALFF, amplitude of low-frequency fluctuations; GSs, good sleepers; PCPIs, patients with chronic primary insomnia; PCPI-Fs, female PCPIs; GS-Fs, good female sleepers; N/A, not applicable; PCPI-Ms, male PCPIs; GS-Ms, good male sleepers; R, right; L, left; BA, Brodmann area; MNI, Montreal Neurological Institute.

differences between the PCPIs and the GSs, and their sex differences. In our study, the ALFF differences in regional brain areas of the PCPIs showed a high test-retest stability between the two MRI scans. Furthermore, we investigated the correlations between the sleep characteristics and the mean ALFF value in each of those different areas in PCPI-Fs and PCPI-Ms. Further ROC analysis revealed that the altered ALFF areas of the PCPI-Fs or PCPI-Ms could serve as markers to distinguish the insomnia patients from the GSs. However, the different ALFF areas of the total PCPIs showed defective AUC values, and neither high degree of sensitivity nor specificity, indicating that they cannot distinguish the PCPIs from the GSs. The reliability of the ALFF differences of the PCPI-Fs and PCPI-Ms allowed us to explore the ALFF differences within each sex group, respectively. In our study, we found that patients with insomnia showed wide sex differences in the bilateral cerebellum, bilateral limbic lobe (VMPFC and MTL), left premotor cortex, and left dorsolateral prefrontal cortex. Compared with the GS-Fs, the PCPI-Fs showed lower ALFF in the cerebellum posterior lobe and frontal lobe, while PCPI-Ms showed lower ALFF in the occipital lobe compared with the GS-Ms. However, both PCPI-Fs and PCPI-Ms showed analogous higher

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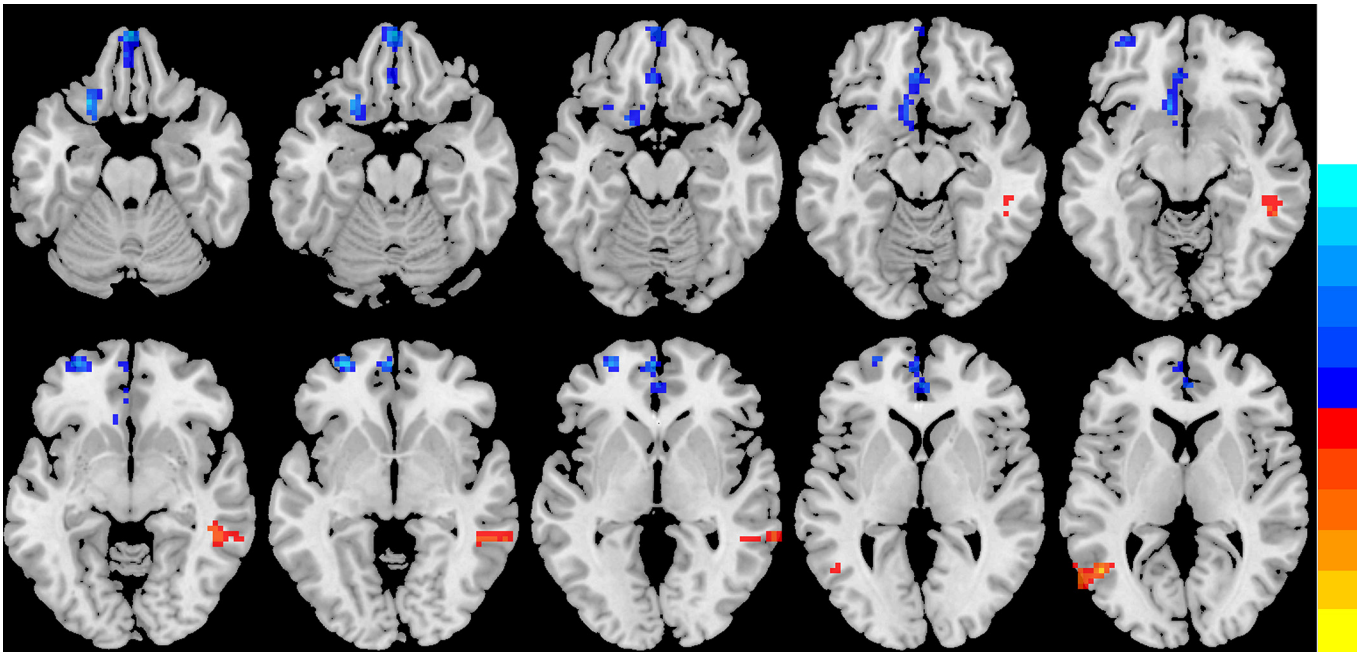
Figure 4—Altered ALFF areas between between PCPI-Fs and PCPI-Ms.



Brain regions showing ALFF differences in the temporal gyrus and frontal gyrus. Red areas denote higher ALFF brain regions, and blue areas denote lower ALFF brain regions. The right side of the pictures indicate the right side of the brain, and the corresponding left side indicates the left side of the brain. ALFF, amplitude of low-frequency fluctuations; PCPI-Fs, female PCPIs; PCPI-Ms, male PCPIs.

ALFF in the temporal lobe and occipital lobe. Our findings may suggest that the insomnia is associated with the model of excitation-inhibition imbalance in the central nervous system.

Previous physiological, neuroimaging, and neurocognitive studies have demonstrated the ruminative, hypervigilant and/or excessive hyperarousal and increase of global cerebral metabolic rate for glucose utilization in chronic insomnia.[32–34] The excess arousal refers to the exaggerated cortical, somatic, and cognitive activation, which leads to increased sensory information processing and inability to initiate or maintain sleep.[5,35] These studies provided supported evidence that the hyperarousal model is a core predisposing or perpetuating factor of chronic insomnia.[36] Our previous sleep deprivation study found that the female sleep deprivation subjects showed hyperarousal re-activation in the bilateral occipital gyrus compared with the GS-Fs,[21] and our previous regional homogeneity study demonstrated the excessive hyperarousal reactivities in the temporal lobe in the PCPIs, PCPI-Ms and PCPI-Fs, and the excessive hyperarousal reactivation in the occipital cortex in the PCPI-Fs.[23] The vision-related regions were not only activated by real vision, but also by visual mental imagery,[37,38] since the visual cortex was relevant to emotional activities, as emotional changes could lead to higher BOLD signal regions in the visual cortex.[39,40] These findings supported our results that both PCPI-Fs and PCPI-Ms had higher ALFF in the occipital gyrus and temporal lobe. Therefore, the excessive hyperarousal reactivities in the visual cortex and temporal lobe may be a core predisposing or perpetuating factor of ultimately hampering the ability to initiate or maintain sleep. Our previous sleep deprivation study found that the occipital gyrus was strengthened in the females and weakened in the males from a rested wakeful status to a sleep deprivation status,[21] which may explain why the PCPI-Ms had few lower ALFF response in the occipital gyrus.

Interestingly, compared with their corresponding control groups, we found that the PCPI-Fs had more brain areas with both higher and lower ALFF values than PCPI-Ms, but both groups had similar brain areas with the higher ALFF values. This implies that the numbers of the brain areas with higher ALFF values may be positive correlations with the numbers of the brain areas with lower ALFF values. Furthermore, we found that the higher ALFF in the temporal gyrus of PCPI-Ms had approximate weak linear positive correlations with the severity indicators. These findings suggest that the strong hyperarousal may exacerbate the insomnia and lead to more brain dysfunction areas.

The MTL, which consists of several critical memory-related structures, including the hippocampus, amygdala, cingulate gyrus, and the surrounding hippocampal areas (such as the entorhinal, perirhinal, and parahippocampal cortices)[41] was associated with a variety of sensory information integration. The limbic system, which consists of subcortical structures associated with the limbic lobe[42] such as the MTL, medial thalamic nucleus, and VMPFC, is related to the emotions and cognitive functions, such as memory, learning, and visuospatial tasks,[43] and plays an active role in the generation of arousal and insomnia.[44] Joo et al. found decreased volume of gray matter in the MPFC in the PCPIs compared with the GSs.[7] Altena et al. found a smaller gray matter volume in the left orbitofrontal cortex in the PCPIs compared with the GSs.[45] Our previous regional homogeneity study found that both the PCPI-Fs and the PCPI-Ms showed lower regional

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homogeneity in the VMPFC,[23] and our previous functional connectivity study found that the PCPIs showed significant decreased functional connectivity between the MPFC and the right MTL, and between the left MTL and the left inferior parietal cortices using the seed-based region-to-region functional connectivity method.[12] In support of these findings, in the present study we found that the PCPI-Fs showed higher ALFF in the bilateral MTL and lower ALFF in the bilateral VMPFC and right MTL compared with the GS-Fs. These findings indicated that the limbic system had structural and functional impairments in the PCPIs, which may be a non-ignorable factor of the insomnia yet need more evidences to prove. As we know, the sleep time and sleep efficiency are decreased with the age. In the present study we found that age showed negative correlations with the different ALFF brain areas in the limbic system, which indicates that the limbic system may be closely associated with the senile insomnia.

It is well known that the sleep plays an important role in the formation and consolidation of memories,[46] which is impaired in the PCPIs.[47] Noh et al. found that the significant lower scores on the tests of attention and cognition function, especially for the frontal lobe function, were significantly worse in the PCPIs than in the GSs, which suggest that the memory deficit in the PCPIs might be directly influenced by impaired attention and frontal lobe function.[48] Joo et al. found that the PCPIs showed significant reduction of gray matter concentrations in the dorsolateral prefrontal cortices compared with the GSs.[7] Our

Table 3—ROC curve analysis for the different ALFF areas between insomnia groups and GSs.

	ROC Curve			
ALFF Index	AUC	Sensitivity	Specificity	Cutoff Point*
Cluster 1	0.921	77.8%	91.7%	0.325
Cluster 2	0.866	85.2%	79.2%	−0.735
Cluster 3	0.817	55.6%	95.8%	0.935
Cluster 4	0.799	92.6%	75.0%	−0.260
Cluster 5	0.837	88.9%	75.0%	−0.135
Cluster 6	0.754	81.5%	62.5%	−0.065
Cluster 7	0.795	74.1%	87.5%	−0.250
Cluster 8	0.891	66.7%	95.8%	0.335
Cluster 9	0.917	81.5%	91.7%	0.135
Cluster 10	0.852	93.3%	72.2%	0.220
Cluster 11	0.867	92.3%	75.0%	0.460
Cluster 17	0.818	80.0%	77.8%	0.495
Cluster 18	0.763	64.3%	81.0%	0.720
Cluster 19	0.658	81.0%	54.8%	−0.200
Cluster 20	0.765	64.3%	73.8%	0.050

*Cutoff point of mean ALFF signal value. Both PCPI-Fs (Cluster 1 to Cluster 9) and PCPI-Ms (Cluster 10 to Cluster 11) had higher area under curve values, and higher degree of sensitivity and specificity than that of PCPIs (Cluster 17 to Cluster 20). ROC, receiver operating characteristic; ALFF, amplitude of low-frequency fluctuations; GSs, good sleepers; AUC, area under curve; PCPIs, patients with chronic primary insomnia; PCPI-Fs, female PCPIs; PCPI-Ms, male PCPIs.

Table 4—The regression analysis between the different ALFF areas and sleep characteristics.

Dependent Variable	Independent Variables	Coefficient (R^2)	β	Standard Error	p value
PSQI total score	Cluster 10	0.260	1.835	0.859	0.052
PSQI time in bed	Cluster 3	0.131	1.401	0.723	0.064
	Cluster 19	0.084	−2.495	1.305	0.063
Duration of insomnia	Cluster 20	0.083	−3.982	2.097	0.065
ISI score	Cluster 10	0.230	2.518	1.277	0.070
SAS score	Cluster 19	0.087	−11.482	5.885	0.058
SDS score	Cluster 4	0.220	−34.592	13.015	0.014
	Cluster 19	0.100	−13.950	6.620	0.041
POMS negative index score	Cluster 4	0.233	−60.678	22.029	0.011
	Cluster 19	0.130	−31.441	12.855	0.019
POMS positive index score	Cluster 20	0.079	5.994	3.227	0.071
POMS total score	Cluster 4	0.256	−82.703	28.219	0.007
	Cluster 19	0.128	−39.592	16.319	0.020
Age	Cluster 3	0.190	−8.301	3.179	0.023
	Cluster 4	0.162	27.872	12.681	0.037
	Cluster 5	0.135	20.129	10.197	0.060
	Cluster 8	0.144	−12.173	5.948	0.051
	Cluster 19	0.095	17.427	8.522	0.047

The behavioral performances showed weak and approximate weak linear correlations with the mean ALFF signals of the different areas. ALFF, amplitude of low-frequency fluctuations; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; POMS, Profile of Mood States.

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previous study also found the PCPI-Ms showed lower regional homogeneity in the dorsolateral prefrontal cortex compared with the GS-Ms.[23] In support of these findings, in the present study we found that the PCPI-Fs showed lower ALFF in the left dorsolateral prefrontal cortex compared with the GS-Fs. These findings suggest that the attentional and cognitive dysfunction may contribute to the impaired dorsolateral prefrontal cortex.

The cerebellum that interconnects a network with the extensive cortical and subcortical areas automatically adjust the execution of laughter or crying for cognitive and emotional regulation.[23,49,50] The cerebellum posterior lobe(s) has been widely used for the adjusting nerve function, and adjusting the start and planning and the coordinating movement.[21] It also works together with the cerebrum to complete the functions such as the cognition, language, and emotion. Mounting evidence for cerebellar involvement in various neurologic and psychiatric conditions, including obstructive sleep apnea,[51] depression,[52] and mood disorders.[53] Insomnia is usually associated with the emotional disorders; the excitable increase in emotion is considered to be an important factor in the etiology of insomnia.[54] In supporting of these findings, in the present study the PCPI-Fs showed lower ALFF in the bilateral cerebellum posterior lobe which was involved in the post-insomnia negative mood. This finding provided an evidence that post-insomnia negative emotion may be a key factor in the etiology of insomnia.

The cerebellum influences the cardiovascular system by sending out a mesh structure of fibers that further branch out separately to the vagus nerves and sympathetic nerves, and can change the blood pressure and heart rate. The reduced duration of sleep is associated with a higher risk of hypertension among females only.[55] In supporting of this finding, our previous study found that the PCPI-Fs showed lower regional homogeneity in the cerebellum while the PCPI-Ms did not,[23] and wide gender differences were found in the left cerebellar posterior lobe in healthy subjects during sleep deprivation.[21] These findings explained why the decreased ALFF in the bilateral cerebellum posterior lobe was found in PCPI-Fs only. However, further studies should be carried out to exclude the factor of the differences in the PSQI sleep efficiency and numbers of awakenings between the PCPI-Ms and the PCPI-Fs. Furthermore, in the present study we found that the bilateral cerebellum posterior lobe showed a positive correlation with age, which may reflect a reduced influence from the cerebellum on the cardiovascular system and/or post-insomnia negative emotion with increasing age.

CONCLUSIONS

Our study provided an objective evidence that the PCPI-Ms and the PCPI-Fs had a homologous excessive hyperarousal mechanism, but showed sex differences in a variety of aberrant brain regions. The brain regions of the limbic system, cerebellum, dorsolateral prefrontal cortex, and occipital gyrus should be paid special attention to. These findings will help us insight into a deeper understanding of the pathophysiological mechanism of the chronic primary insomnia. Furthermore, the sex factor should be taken into consideration in future functional MRI studies. However, there are several limitations that should be noted. First, a larger sample size should be studied in the future. Second, we used the Fitbit Flex tracker to monitor the sleep quality in our experience. Although we cannot provide direct evidence to prove whether the FITBIT tracker provides a valid and reliable measure of objective sleep, we compared some patients' data between the FITBIT and the PSG, and found the results were similar.

ABBREVIATIONS

ALFF, amplitude of low frequency fluctuation
AUC, area under curve
DICOM, Digital Imaging and Communications in Medicine
DSM, Diagnostic and Statistical Manual of Mental Disorders
GSs, good sleepers
GS-Fs, female GSs
GS-Ms, male GSs
HAMA, Hamilton Anxiety Rating Scale
HAMD, Hamilton Depression Rating Scale
ICC, intraclass correlation coefficients
ISI, Insomnia Severity Index
LSD, least significant difference
MNI, Montreal Neurological Institute
MRI, magnetic resonance imaging
MTL, medial temporal lobe
PCPIs, patients with chronic primary insomnia
PCPI-Fs, female PCPIs
PCPI-Ms, male PCPIs
POMS, Profile of Mood States
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
ROC, receiver operating characteristic
ROI, region of interest
rs-fMRI, resting-state functional magnetic resonance imaging
SAS, Self Rating Anxiety Scale
SDS, Self-Rating Depression Scale
SRSS, Self-Rating Scale of Sleep
VLPFC, ventral lateral prefrontal cortex
VMPFC, ventral medial prefrontal cortex

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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