

Abnormal spontaneous regional brain activity in primary insomnia: a resting-state functional magnetic resonance imaging study

Chao Li¹
 Xiaofen Ma²
 Mengshi Dong²
 Yi Yin¹
 Kelei Hua¹
 Meng Li²
 Changhong Li²
 Wenfeng Zhan²
 Cheng Li^{2,3}
 Guihua Jiang²

¹Department of Medical Imaging, The Affiliated Guangdong No 2 Provincial People's Hospital of Southern Medical University, The Third Clinical Medical College of Southern Medical University,

²Department of Medical Imaging,

³Department of Renal Transplantation, The Affiliated Guangdong No 2 Provincial People's Hospital of Southern Medical University, Guangzhou, People's Republic of China

Correspondence: Guihua Jiang
 Department of Medical Imaging,
 The Affiliated Guangdong No 2 Provincial
 People's Hospital of Southern Medical
 University, Guangzhou 510317, People's
 Republic of China
 Tel/fax +86 20 8916 8071
 Email jiangguihua1970@163.com

Cheng Li
 Department of Renal Transplantation,
 The Affiliated Guangdong No 2 Provincial
 People's Hospital of Southern Medical
 University, Guangzhou 510317, People's
 Republic of China
 Tel/fax +86 20 139 2422 8992
 Email 182838li@163.com

Objective: Investigating functional specialization is crucial for a complete understanding of the neural mechanisms of primary insomnia (PI). Resting-state functional magnetic resonance imaging (fMRI) is a useful tool to explore the functional specialization of PI. However, only a few studies have focused on the functional specialization of PI using resting-state fMRI and results of these studies were far from consistent. Thus, the current study aimed to investigate functional specialization of PI using resting-state fMRI with amplitude of low frequency fluctuations (ALFFs) algorithm.

Methods: In this study, 55 PI patients and 44 healthy controls were included. ALFF values were compared between the two groups using two-sample *t*-test. The relationship of abnormal ALFF values with clinical characteristics and duration of insomnia was investigated using Pearson's correlation analysis.

Results: PI patients showed lower ALFF values in the left orbitofrontal cortex/inferior frontal gyrus, right middle frontal gyrus, left inferior parietal lobule, and bilateral cerebellum posterior lobes, while higher ALFF values in the right middle/inferior temporal that extended to the right occipital lobe. In addition, we found that the duration of PI negatively correlated with ALFF values in the left orbitofrontal cortex/inferior frontal gyrus, and the Pittsburgh Sleep Quality Index score negatively correlated with ALFF values in the left inferior parietal lobule.

Conclusion: The present study added information to limited studies on functional specialization and provided evidence for hyperarousal hypothesis in PI.

Keywords: primary insomnia, amplitude of low frequency fluctuations, resting-state fMRI, spontaneous brain activity

Introduction

Primary insomnia (PI) is defined as the presence of insomnia symptoms unrelated to any other medical, physical, or psychiatric disorder.¹ Nearly one-third of adults suffer from insomnia in any given year; if acute insomnia is considered, the diagnostic prevalence rises to almost 50% of the population.^{2,3} Patients with insomnia often suffer from cognitive impairment and even mortality.⁴ Although insomnia seriously affect people's physical and mental health, the neurobiological mechanisms underlying PI are not clear.

Both task-based and resting-state functional magnetic resonance imaging (fMRI) have emerged as a useful tool to explore the neuromechanism of PI⁵⁻¹² or sleep deprivation.¹³ fMRI is a novel noninvasive imaging technique for measuring spontaneous brain activity^{14,15} and more economical to implement than positron emission tomography and single photon emission computed tomography in clinical studies.¹⁶ Using resting-state fMRI with amplitude of low frequency fluctuations (ALFFs) algorithm,

Gao et al¹³ found that 24 hours sleep deprivation led prominently decreased ALFF values in the right inferior parietal lobule, bilateral orbitofrontal cortex, and dorsolateral prefrontal cortex, while increased ALFF values in the visual cortex, left sensorimotor cortex, and fusiform gyrus. Using resting-state fMRI with functional connectivity method, Huang et al⁵ explored decreased temporal connectivity between the amygdala and striatum, insula, and thalamus, which is mainly an emotion circuit, which provided further evidence for hyperreactivity to perceived threat¹⁷ in PI patients. Li et al⁶ examined the temporal correlation between the superior parietal lobe and whole-brain regions in PI patients. They found that PI patients showed abnormal functional connectivity between the parietal and prefrontal cortices and the anterior cingulate gyrus, which they thought may be due to the impairment of spatial and verbal working memory.

However, to our best knowledge, only a few studies^{7,8,18} have explored the spontaneous regional brain activity or functional specialization in PI using resting-state fMRI. Paying attention to functional specialization is crucial for detecting precisely which region of the brain was abnormal and completely understanding of the neuromechanisms in PI. Unfortunately, results of these studies focusing on function specialization were far from consistent. For example, Dai et al¹⁸ found that compared with good sleepers, PI patients showed higher regional homogeneity (ReHo) in the left fusiform gyrus and lower ReHo in the bilateral cingulate gyrus and right cerebellum anterior lobe. In contrast to the study of Dai et al, Wang et al¹⁸ reported increased ReHo in the left insula, right anterior cingulate gyrus, bilateral precentral gyrus, and left cuneus, as well as decreased ReHo in the right middle cingulate cortex and left fusiform. Recently, Dai et al⁷ found that both PI female and male patients showed higher ALFF in the temporal lobe and occipital lobe. They also found female PI patients had lower ALFF in the bilateral cerebellum posterior lobe, left dorsolateral prefrontal cortex, and bilateral limbic lobe; however, male PI patients showed lower ALFF in the left occipital gyrus. The question remains as whether and how can the PI affect the regional spontaneous activity pattern of human brain.

Thus, the objective of this study was to explore the spontaneous regional brain activity of PI. We selected resting-state fMRI with an ALFF algorithm as an index to measure spontaneous regional brain activity. Compared with other algorithms, such as a ReHo and functional connectivity, ALFF can directly reflect the intensity or amplitude of spontaneous regional brain activity.¹⁹ Besides, ALFF method has favorable test–retest reliability.²⁰ ALFF has been successfully applied in many psychiatric and neurological diseases, such

as major depressive disorder,²¹ schizophrenia,²² and attention deficit hyperactivity disorder.¹⁹ We hypothesized that PI patients may have different ALFF values in some brain regions, such as lower ALFF values in the prefrontal cortex based on previous consistent findings^{11,23–26} and higher ALFF values in auditory and visual cortices based on hyperarousal hypothesis^{27,28} and previous findings.⁷ We also hypothesized that ALFF values in abnormal regions may be correlated with some clinical characteristics and duration of insomnia.

Methods

Subjects

The study was approved by the local ethics committee of the Institute of Mental Health at the Guangdong No 2 Provincial People's Hospital. All subjects signed written informed consent prior to inclusion. From April 2010 to April 2016, 55 patients with PI ([mean age: 39±10 years], including 24 men [mean age: 39±10 years] and 31 women [mean age: 39±10 years]) were included. Patients who met the following criteria were included in the study: 1) conformity to the definition of PI by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; 2) insomnia lasting ≥1 months, with a complaint of difficulty falling asleep, maintaining sleep, or early awakening; 3) no other sleep disorders (such as hypersomnia, parasomnia, or sleep-related movement disorder) or other psychiatric disorders determined by a semistandardized psychiatric and sleep-related interview conducted by an experienced psychiatrist; 4) insomnia dose not due to the effects of medications/substance abuse, such as caffeine or nicotine or alcohol; 5) right-hand dominance; 6) no serious organic disease; 7) no foreign implants in the body; 8) age 25–60 years; 9) no abnormal signal as verified by conventional T1- or T2-fluid-attenuated inversion recovery (FLAIR) MRI; and 10) head motion <1.5 mm or 1.5° during MRI.

Forty-four age-, sex-, and education-level-matched healthy control subjects (mean age: 39±9 years), including 11 men (mean age: 38±6 years) and 33 women (mean age: 40±10 years) were recruited from the local community. All control subjects met the following criteria: 1) good sleeping habits and good sleep onset and/or maintenance; 2) no history of swing shifts, shift work, or sleep complaints; 3) no medications/substance abuse, such as caffeine or nicotine or alcohol; and 4) fulfillment of criteria 5–10 above for the PI patients.

Questionnaires

All volunteers were asked to complete a number of questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), the Self-rating Anxiety

Scale (SAS), and the Self-rating Depression Scale (SDS) to evaluate the sleep situation and the mental status of the PI patients.

MRI data acquisition

Participants completed a 10-minute resting-state fMRI scan (240 volumes) acquired on a Philips Achieva 1.5T Nova dual MR scanner. Head motion was restricted by a belt and foam pads. During resting state fMRI scanning, subjects were instructed to close their eyes, but not to fall asleep and not to think of anything particularly. The resting-state fMRI images were obtained using a gradient-echo planar imaging sequence (interleaved scanning, repetition time/echo time =2,500 ms/50 ms, matrix =64×64, field of view =224×224 mm, flip angle =90°, section thickness =4 mm, gap =0.8 mm, 27 sections covering the whole brain).

Data processing and ALFF calculations

Data Processing Assistant for Resting-State Functional MR Imaging toolbox (<http://www.restfmri.net/forum/DPARSE>)²⁹ was used to postprocess the imaging data. Functional images at the first ten volumes were discarded so that magnetization reached steady state and subjects adapted to the MRI scanning noise. The slice timing and realignment for head motion correction and spatial normalization were conducted according to the standard Montreal Neurologic Institute template, resampled into a voxel size of 3×3×3 mm³. We then smoothed these images by convolution with an isotropic Gaussian kernel (full width at half maximum, 6 mm). To reduce the effects of low-frequency drift and high-frequency noise, the smoothed imaging data were processed to remove linear trends and be filtered temporally (band pass, 0.01–0.08 Hz). Three patients and three control subjects who showed head motion of >1.5 mm or 1.5° during image acquisition were excluded in subsequent analysis. ALFF was calculated using the toolbox previously described.¹⁹ Briefly, the time series for each given voxel was first converted to a frequency domain using a Fast Fourier Transform. The square root of the power spectrum was computed and averaged throughout 0.01–0.08 Hz at each voxel. This averaged square root was termed the ALFF for each voxel. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value of each individual. The standardized ALFF value for each given voxel reflected the degree of its raw ALFF value relative to the average ALFF value of the global brain.

Statistical analysis

The SPSS Version 20.0 (IBM Corporation, Armonk, NY, USA) was used to analyze demographic data and clinical

characteristics. Statistical parametric mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) was used to analyze fMRI data in a voxel-by-voxel fashion. To investigate ALFF difference between the two groups, we used a two-sample *t*-test on the individual ALFF maps in a voxel-by-voxel fashion, with sex, age, and education level imported as covariates. A corrected significance level of individual voxel $P < 0.01$ and the contiguous cluster volume ≥ 540 mm³ were used to determine the statistical significance (corrected for multiple comparisons with AlphaSim corrected threshold of cluster $P < 0.05$, <http://afni.nimh.nih.gov/afni/>). Sex distribution among the two groups was evaluated using the chi-square test. Differences in age, ISI, PSQI, SAS, and SDS scores between the two groups were calculated with two-sample *t*-test. Differences in education level between the two groups were compared with Mann–Whitney *U* statistic.

To identify the association between the ALFF values and the PSQI, ISI, SAS, and SDS scores and duration of PI, the mean ALFF values for all voxels in the significant areas were extracted separately using the Resting-State fMRI Data Analysis Toolkit (<http://resting-fmri.sourceforge.net>). Then, Pearson's correlation analysis was performed between the mean ALFF values in significantly different areas and the PSQI, ISI, SAS, and SDS scores and duration of PI in SPSS 20.0 ($P < 0.05$).

Results

Demographic and clinical characteristics

Table 1 provides demographic and clinical characteristics for PI patients and controls. There were no differences in sex, age, and education level between the patient and control groups ($P > 0.05$). PI patients had higher PSQI, ISI, SAS, and SDS scores than controls ($P < 0.05$).

Table 1 Characteristics of subjects

Parameter	PI (55)	HC (44)	P-value
Sex*			0.086 ^a
Male	24	11	
Female	31	33	
Age (year)	39.18±10.34	39.91±9.43	0.72 ^b
Education (year)	7.47±3.58	8.30±4.21	0.24 ^c
Insomnia duration (month)	46.04±29.63	N/A	N/A
PSQI	12.51±3.25	5.93±2.27	0.00 ^b
ISI	19.69±3.28	5.36±1.14	0.00 ^b
SAS	52.05±10.73	42.33±5.21	0.00 ^b
SDS	54.62±8.71	42.32±6.35	0.00 ^b

Notes: Unless otherwise indicated, data are mean ± standard deviation. ^aData are number of patients or control subjects. ^bThe *P*-values were obtained by using the chi-square test. ^cThe *P*-values were obtained by using a two-sample *t*-test. ^dThe *P*-values were obtained by using Mann–Whitney *U* statistic.

Abbreviations: ISI, Insomnia Severity Index; PI, primary insomnia; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; N/A, not applicable; HC, healthy controls.

Table 2 Brain regions showing significant differences of ALFF in PI patients compared with healthy controls

Location	Voxel size	MNI coordinates			T-value	Brodmann area
		X	Y	Z		
Right cerebellum	3,213	15	-60	-48	-4.10	N/A
Left cerebellum	1,107	-15	-57	-48	-3.60	N/A
Left orbitofrontal cortex/inferior frontal gyrus	729	-21	33	-21	-3.62	11, 47
Right middle frontal gyrus	594	33	3	48	-3.95	6, 9
Left inferior parietal lobule	648	-42	-39	33	-4.08	40
Right middle/inferior temporal gyrus, occipital lobe	567	57	-63	-3	4.32	19, 37

Abbreviations: ALFF, amplitude of low frequency fluctuations; PI, primary insomnia; MNI, Montreal Neurological Institute; N/A, not applicable.

Regional brain ALFF values comparison

We found significantly abnormal spontaneous regional brain activity in six clusters in the PI patients compared with the control group (Table 2 and Figure 1). PI patients displayed lower ALFF values in the left orbitofrontal cortex/inferior frontal gyrus, right middle frontal gyrus, left inferior parietal lobule, and bilateral cerebellum posterior lobes, while higher ALFF values in the right middle/inferior temporal that extended to the right occipital lobe.

Correlation between ALFF values and PSQI, ISI, SAS, and SDS scores and duration of PI

Figure 2 shows the results of correlation analysis. The duration of PI negatively correlated with ALFF values in the left orbitofrontal cortex/inferior frontal gyrus ($r=-0.492$, $P=0.001$). The PSQI score negatively correlated with ALFF values in the left inferior parietal lobule ($r=-0.324$, $P=0.016$). Current study did not detect significant correlation between ALFF values in abnormal regions and ISI, SAS, and SDS scores.

Discussion

Using resting-state fMRI with ALFF algorithm, we explored differences in spontaneous regional brain activity between a group of PI patients and a group of healthy controls. Statistical analysis indicated that compared with controls, the PI patients showed significantly lower ALFF values in some brain regions associated with alertness, attention, and higher-order cognitive processes, while PI patients showed significantly higher ALFF values in auditory-related and vision-related regions. Additionally, the ALFF values of some regions showed a significant correlation with the clinical features of PI patients. Current study may play an important role in precisely figuring out the abnormal brain regions and provide evidence for hyperarousal hypothesis.

Consistent with previous studies, we detected lower ALFF values in the prefrontal lobe, including the left orbitofrontal cortex/inferior frontal gyrus and right middle frontal gyrus (Table 2 and Figure 1).^{11,13,23-26,30} The prefrontal cortex is thought to be involved in alertness, attention, and higher-order cognitive processes.²⁶ Using task fMRI, Altema et al¹¹ found that chronic insomnia patients showed hypoactivation of the medial and inferior prefrontal cortical areas during the performance of a category and a letter fluency task, which recovered after sleep therapy. This findings suggested that chronic insomnia can damage prefrontal cortex function. Using [¹⁸F]-fluorodeoxyglucose positron emission tomography, Nofzinger et al²³ also found PI patients showed reduced relative metabolism in the prefrontal cortex while awake, and they speculated that daytime fatigue may reflect decreased activity in the prefrontal cortex resulting from inefficient sleep. Brain morphological studies also demonstrated structural abnormalities in the prefrontal cortex in PI patients. Using voxel-based morphometry, Joo et al³⁰ found that PI patients displayed significantly reduced gray matter concentrations in dorsolateral prefrontal and pericentral cortices, superior temporal gyrus, and cerebellum and decreased gray matter volumes in medial frontal and middle temporal gyri compared with controls. Evidences from sleep deprivation also support our findings. For example, a recent resting-state fMRI study with ALFF algorithm found that healthy people who underwent sleep deprivation showed decreased ALFF in the right inferior parietal lobule, bilateral orbitofrontal cortex, and dorsolateral prefrontal cortex.¹³

Notably, the most recent animal study performed by Bellesi et al²⁵ further deepened our understanding of hypoactivation or hypoperfusion in prefrontal cortex in PI and individuals experienced sleep deprivation. They found that the noradrenaline level in prefrontal cortex declined after extended prolonged wakefulness. This result suggests that locus coeruleus neurons, the primary source of

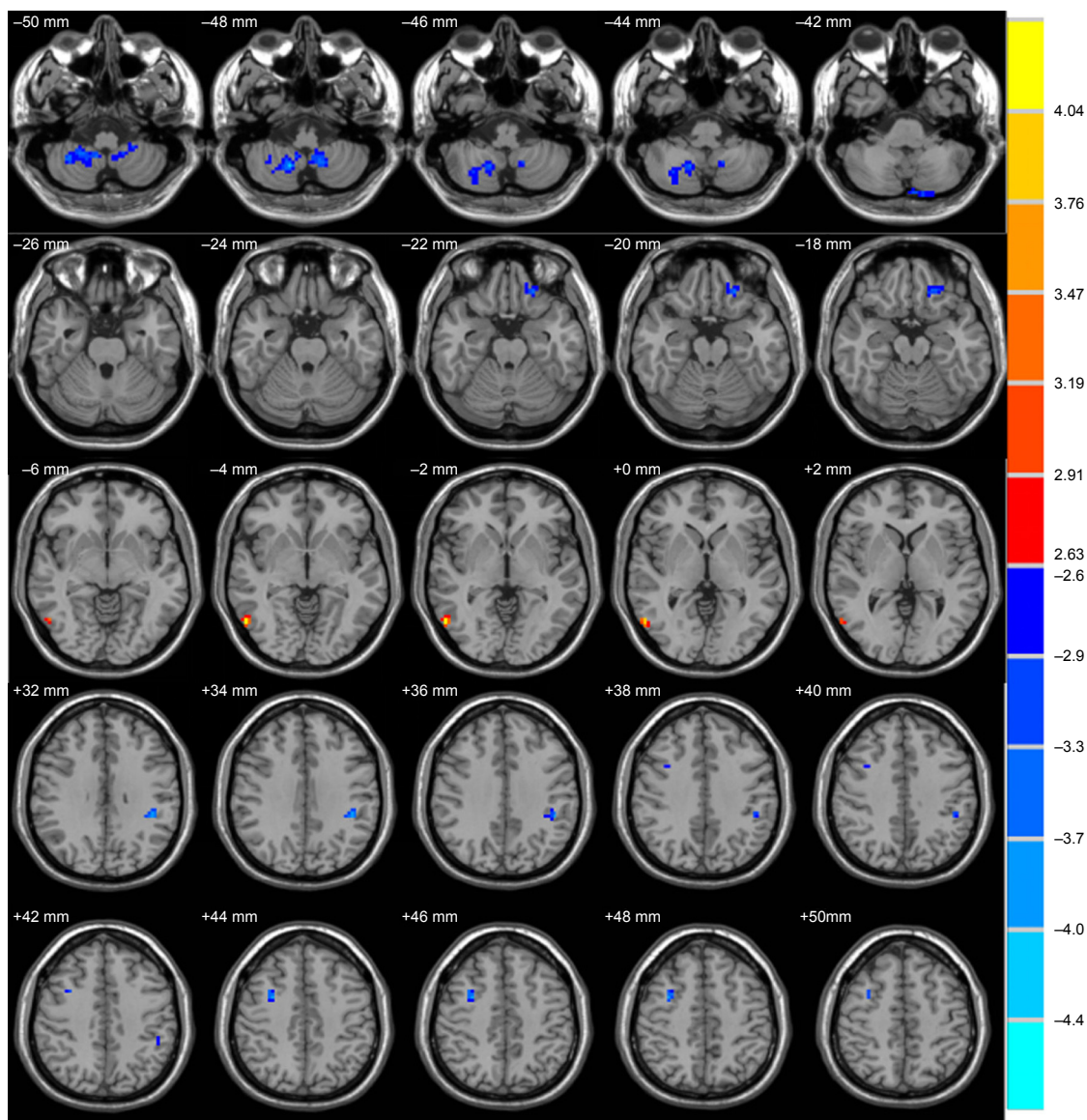


Figure 1 Clusters showing statistically significant different ALFF values in patients with PI compared with the controls ($P < 0.01$, corrected). Numbers indicate z slice and are displayed in MNI coordinates.

Abbreviations: ALFF, amplitude of low frequency fluctuations; MNI, Montreal Neurological Institute; PI, primary insomnia.

noradrenaline in brain, projecting to prefrontal cortex are not able to maintain noradrenaline release for long periods of time. Based on previous studies mentioned above, we speculate that the lower ALFF values in the prefrontal cortex may represent locus coeruleus neural fatigue.²⁴ In other words, the lower ALFF values in the prefrontal cortex may be caused by extended hyperactivity in these areas in view of the hyperarousal hypothesis.^{27,28} Our speculation was also supported by our correlation analysis that the duration of PI negatively correlated with ALFF values in the left orbitofrontal cortex/inferior frontal gyrus. Thus, the longer the duration of PI, the lower would be the spontaneous activity in the prefrontal cortex.

We also observed significantly decreased ALFF values in the left inferior parietal lobule, which is consistent with previous studies.^{12,13,31} Using task fMRI with working memory paradigm, Drummond et al¹² found that PI patients showed reduced activation of task-related working memory regions (main effect of group) compared with controls, including bilateral inferior parietal lobes. Gao et al¹³ also detected lower ALFF values in the inferior parietal lobule in those who experienced sleep deprivation. Inferior parietal lobule is main node of the Default Mode Network³² characterized by more energetic metabolic and neural activity at rest. A proposed function for sleep is brain energy restoration.³³ PI patients with poor sleep quality will probably disturb this

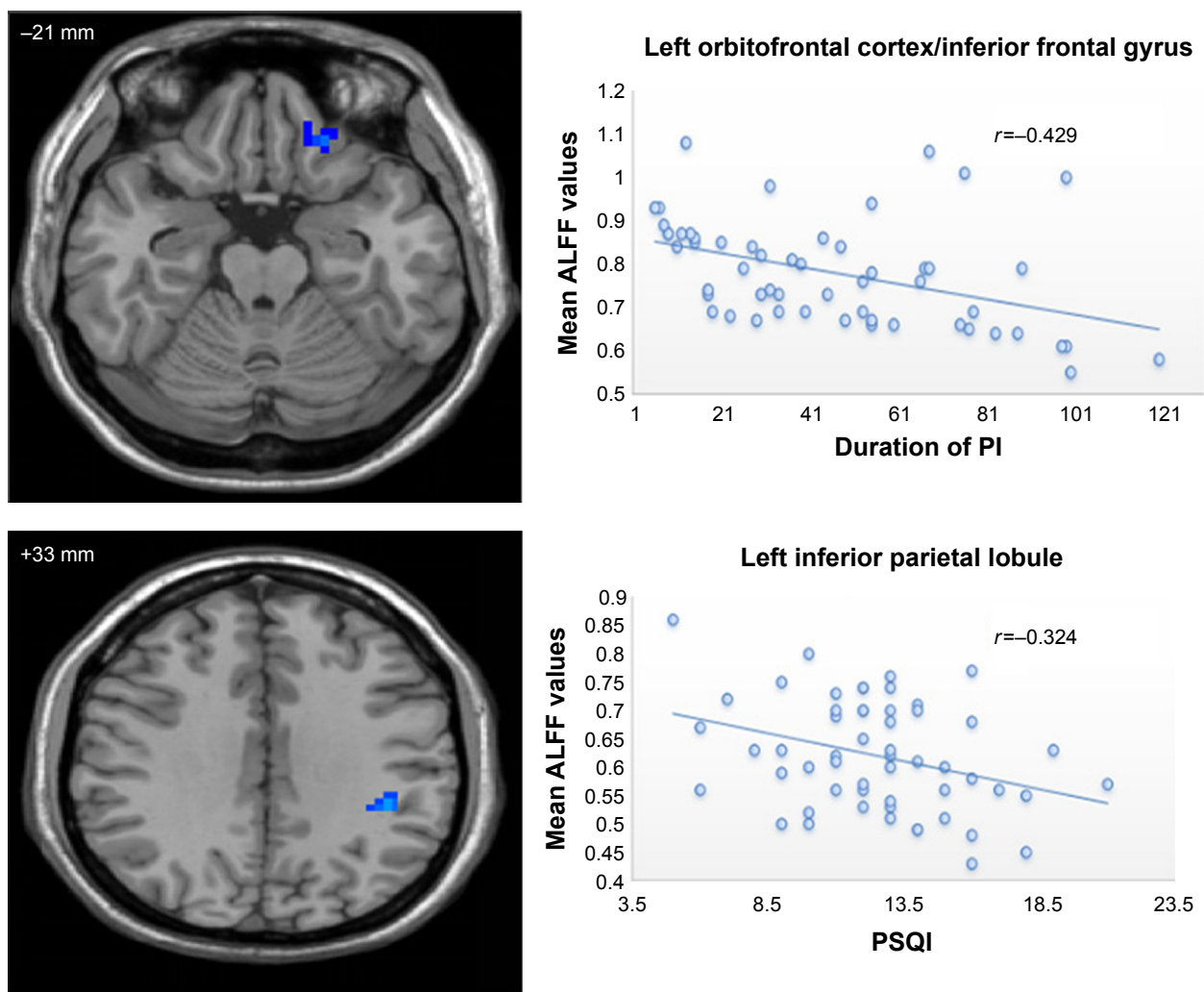


Figure 2 Scatter plot of the mean ALFF values in the left orbitofrontal cortex/inferior frontal gyrus and left inferior frontal gyrus changing with the duration of PI and PSQI, respectively.

Abbreviations: ALFF, amplitude of low frequency fluctuations; PI, primary insomnia; PSQI, Pittsburgh Sleep Quality Index.

energy restoration process. Consequently, based on previous findings, the lower ALFF values in the left inferior parietal lobule may result from disturbance of energy restoration process caused by poor sleep quality. Our proposal was supported by previous study³¹ and our correlation analysis. Sexton et al³¹ found that greater rate of atrophy in left parietal lobe in community-dwelling adults was associated with poor sleep quality represented by higher PSQI score. Current study also found that lower ALFF values in left parietal lobe was associated with poor sleep quality. Thus, both structure and function of parietal lobe are impaired by poor sleep quality.

The bilateral cerebellum posterior lobes of PI patients in our study showed decreased ALFF values. Although the traditional view is that the cerebellum is responsible for motor control,³⁴ there is growing evidence that the cerebellum has other high order function,³⁵ such as sensory acquisition

and discrimination.³⁶ Recently, it has been found that the cerebellum is involved in the regulation of sleep.³⁷ For example, Joo et al³⁰ found that chronic PI patients had reduced gray matter concentrations in cerebellum gray matter, and Dai et al⁷ found that female chronic PI patients showed lower ALFF in bilateral cerebellum. Similar to above findings, we also found PI patients showed lower ALFF in bilateral cerebellum, which further proves that the cerebellum may be involved in the regulation of sleep.

The temporal lobe and occipital lobe are auditory-related and vision-related regions. Our study detected higher ALFF values in these two regions, include the fusiform gyrus (BA 37) and associative visual cortex (BA 19), in PI patients. These results support hyperarousal hypothesis.²⁷ According to hyperarousal hypothesis, PI patients often showed hyperperfusion in cortical and subcortical structures²³ and increased beta EEG activity²⁸ in the central nerve system. Dai et al⁷ also

found PI patients showed higher ALFF values in the temporal lobe and occipital lobe. Together with previous studies, our results demonstrated that PI patients had higher spontaneous brain activity in auditory-related and vision-related regions.

We acknowledge several limitations of our study. First of all, we did not explore the sex differences in ALFF values in PI patients. However, our research motivation mainly came from the fact that only a few studies have explored the spontaneous regional brain activity of PI and results of these studies were far from consistent. Second, we did not detect the resting-state fMRI data of PI patients during sleep. Future researches could investigate the ALFF of PI patients during sleep so that researchers can directly look insight resting-state brain activity during sleep. Third, the prefrontal cortex and inferior parietal lobe are the regions responsible for higher-order function, such as attention and working memory.³⁵ However, we did not design a relevant scale to test PI patients. Fourth, this was a case-control study. A longitudinal study measuring ALFF in PI patients before and after treatment, especially cognitive behavioral therapy, is necessary to test whether ALFF can be used as a biomarker for curative effect.

Conclusion

We detected both lower and higher amplitude of spontaneous regional brain activities in PI patients. The brain regions associated with higher-order cognitive processes, alertness, attention, auditory, and vision should be paid special attention to. Current study provided evidence for hyperarousal hypothesis in PI. These results, together with limited previous studies and future studies on functional specialization in PI patients, may eventually figure out those precise regions where the spontaneous brain activities were abnormal.

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Disclosure

The authors report no conflicts of interest in this work.

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