Altered regional brain and subjective sleep deficits in chronic primary insomnia:a resting-state fMRI study with ALFF

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Introduction: Patients with chronic primary insomnia (PCPIs) undergo the subjective experience of chronically disturbed sleep, sleep loss, non-refreshing sleep, and heightened arousal in bed. Only a handful of studies have directly addressed the structural bases of PCPIs trait with voxel based morphometry (VBM) and manual volume measurements methods, however, too many disputes have been left unclear. Amplitude of low-frequency fluctuations (ALFF) is an index in which the square root of the power spectrum was integrated in a low frequency range, for detecting the regional spontaneous neuronal activity in BOLD signal[1-2]. Previous study have demonstrated that the ALFF showed good to moderate test-retest reliability[3-4]. Recently, the use of ALFF measurements have been successfully applied to explore the functional modulations and to characterize the pathophysiological changes of several diseases. However, it has not yet been used to explore the pathophysiological changes in CPI. In the current study, we employed ALFF as an index to investigate potential mechanisms of CPI traits and to investigate whether alterations in intrinsic brain activity amplitude could index the subjective sleep deficits and disturbed mood status.

Materials and methods: Thirty patients (21 females and 9 males; 19 PCPIs with medication history and 11 without) with CPI(PCPIs) and thirty (16 females and 14 males) good sleepers (GSs) were recruited. The mean signal values of altered ALFF areas were analyzed with receiver operating characteristic curve. Simple linear regression was performed to investigate the relationships between the different areas and behavioral performances,including Pittsburgh Sleep Quality Index, Insomnia Severity Index, Self-Rating Depression Scale, Self Rating Anxiety Scale, Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale, Self-Rating Scale of Sleep and Profile of Mood States.

Results: Two-way ANOVA analysis showed that none of differences in brain areas were found in main effect of gender, main effect of medicine, and interaction of gender and medicine. Compared with GSs, PCPIs disturbed subjective sleep quality, splitted positive mood and exacerbated negative mood. Compared with female GSs, female PCPI showed significant higher ALFF areas in left fusiform gyrus (BA37), bilateral limbic lobe(posterior cingulate cortex (PCC), parahippocampal gyrus, corpus callosum) and bilateral primary visual cortex (BA17), and lower ALFF areas in left limbic lobe (orbitofrontal cortex, BA11; subgenual cortex,BA25). Compared with male GSs, male PCPI only showed significant higher ALFF values in left temporal gyrus (BA21, BA38) and bilateral medial frontal gyrus (BA10). Compared with all GSs, all PCPIs group only showed significant higher ALFF areas in left temporal gyrus and bilateral PCC (BA30). Compared with GSs, PCPIs without medication only showed significant higher ALFF areas in left fusiform gyrus (BA37). Compared with GSs, medicated PCPIs showed significant higher ALFF areas in right PCC (BA30), and lower ALFF in left medial frontal gyrus and left supplementary motor area (BA6).The details are presented in Fig1. All different areas showed high values of area under curve and high degree of sensitivity and specificity for discriminating PCPIs from GSs (Table 1), and showed substantial linear correlations with behavioral performances.

ALFF Index	ROC curve		
	The area under curve	Sensitivity	Specificity
Result 1	0.815	73.3%	76.7%
Result 2	0.754	70%	80%
Result 3	0.777	60%	86.7%
Result 4	0.925	85.7%	92.9%
Result 5	0.823	66.7%	92.9%
Result 6	0.932	85.7%	92.9%
Result 7	0.844	76.2%	92.9%
Result 8	0.968	100%	92.9%
Result 9	0.849	77.8%	92.9%
Result 10	0.967	90.9%	100%
Result 11	0.909	89.5%	89.5%
Result 12	0.878	78.9%	89.5%

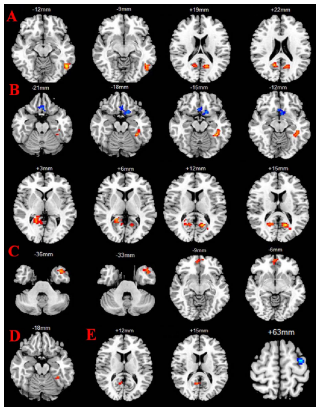

Table 1 *ROC curve anslasis for the different ALFF areas.*

Fig1 *Brain regions showing ALFF differences between PCPIs and GSs(A), between female PCPIs and female GSs(B), berween male PCPIs and male GSs (C), between PCPIs without medication history and GSs (D), and between PCPIs with medication history and GSs (E).*

Discussion and Conclusions: The ALFF method may be a useful non-invasive imaging tool and symbolistic early biomarker for the detection of cerebral changes and indexing the extent of insomnia, duration of insomnia and mood state, which may be helpful in the development of imaging biomarkers for the detection of cerebral changes. The inability to fall asleep may be related to a arousal mechanisms to increase in activities in temporal cortex and the interacting neural networks in the neurobiology of insomnia, including an emotion-regulating system (hippocampus and PCC), a cognitive system (prefrontal cortex), and a visual system (lingual gyrus, middle occipital gyrus and cuneus). These changes in emotional circuits may contribute to the ultimate development of comorbidities such as stress, depression, fear and anxiety disorder, and may decrease arousal thresholds and/or increase perceptions of wakefulness in CPI.

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