A research on resting-state functional network connectivity after rt-fMRI neurofeedback in insomnia

Huan Zhang 1,a, Hui Gao 1,b, Zhonglin Li 2,c, Zhiyuan Feng 1,d, Chi Zhang 1,e, Li Tong 1,f, Bin Yan 1,g*

1Henan Key Laboratory of Imaging and Intelligent Processing, PLA Strategic Support Force Information Engineering University, Zhengzhou, Henan, China.
2Henan Provincial People’s Hospital, Zhengzhou, Henan, China
*aemail: zhanghuanvct@163.com, bemail: ysugaohui@163.com, cemail: zhonglinlixd@163.com, demail: 1513612153 @163.com, eemail: zcboluo@hotmail.com, femail: tttocean_tl@hotmail.com
*gCorrespondence: gemail: ybspace@hotmail.com

Abstract: Using resting-state functional connectivity based on regions of interest to explore connectivity changes between specific brain regions and the whole brain in insomnia patients after real-time functional magnetic resonance neurofeedback (rt-fMRI NF) therapy has the limitation that the brain information used is not comprehensive enough. While the use of functional network connectivity (FNC) can more systematically and effectively explore the effect of neurofeedback intervention on brain activity in patients with insomnia. In this paper, we used independent component analysis (ICA) method to reveal the spatial properties of brain networks in the whole brain of insomnia patients, then examined and compared the FNC before and after rt-fMRI neurofeedback. The whole-brain FNC results show that the functional connectivity between the executive control network (ECN) and salience network (SAN), default mode network (DMN) were significantly decreased, while the connectivity between the DMN and the SAN was increased. In summary, rt-fMRI neurofeedback training for insomnia patients alters intrinsic functional network connectivity, which may provide objective neuroimage evidence for emotion and sleep improvement in insomnia patients.

1. Introduction
Insomnia patients have frequent brain activity before falling asleep, and they are prone to fall asleep at night due to difficulty falling asleep and short sleep duration. Insomnia can affect daytime work and impair cognitive function, and more seriously can lead to mental illness such as depression and anxiety[1, 2]. Treatments for insomnia include both pharmacological and non-pharmacological methods, however, pharmacological treatments have the potential to have side effects and may cause patients to show dependence on drugs[3]. Non-pharmacological treatments, including cognitive behavioral therapy (CBT), physical exercise, and acupuncture, are effective in relieving insomnia symptoms, but there are no uniform standards for their implementation, the progress would be difficult and slow [4, 5].

Here we used a novel treatment modality, real-time functional magnetic resonance neurofeedback (rt-fMRI NF) method[6], to reduce the negative emotions of insomnia patients using emotion regulation strategies such as recalling positive autobiographical memory by feeding back the activation of emotion-related brain regions in their brains, which in turn relieved insomnia symptoms. However, the neural mechanisms by which NF improved sleep quality in patients were unknown, and it was necessary to
observe which physiological changes contributed to the attenuation of insomnia symptoms. Changes in brain functional connectivity are important for understanding insomnia treatment outcomes. After treatment with CBT, it has been shown that insomnia patients had decreased functional connectivity between the amygdala and the lingual gyrus[7]. And another study also showed that increased sleep quality was associated with increased functional connectivity between the DMN and the premotor/dorsolateral prefrontal cortex[8]. However, these studies similarly focused on specific regions. The functional connectivity between large-scale brain networks after interventions in insomnia patients is unknown. FNC could systematically show changes in the cognitive status of the brain in insomnia, which takes into account changes in the brain network of the whole brain[9-11]. Most studies have found abnormal connectivity between SAN[12], DMN[13] and ECN[14] leads to the abnormal emotional cognition, emotion production, and inhibition functions in insomnia patients [15].

The aim of this study was to investigate changes in connectivity in insomnia after rt-fMRI neurofeedback intervention at the large-scale brain network level using a data-driven ICA method to provide a new perspective for better understanding the neural mechanisms of rt-fMRI neurofeedback in the treatment of insomnia. We hypothesized that sleep quality improvement in patients with insomnia is associated with significant changes in connectivity between abnormal brain networks following rt-fMRI neurofeedback training.

2. Method

2.1. Participants
Twenty-four patients with insomnia (mean age 47.13 years, SD 12.76 years, 5 males and 19 females) were included in this experiment through subject recruitment advertisements and hospital outpatient clinics. All patients met the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, and they subjectively showed symptoms such as difficulty falling asleep, early awakening and hyperarousal, Pittsburgh Sleep Quality Index (PSQI) score each of them was greater than 7 or Insomnia Severity Index (ISI) score was greater than 8. They did not take any sleep-improving medication during the experimental period. Exclusion criteria included severe suicidal ideation, psychosis, serious medical and neurological disorders, and a history of alcoholism and drug abuse. All subjects signed the experimental consent form, and the Ethics Committee of Henan Provincial People's Hospital approved the experiment.

2.2. Experimental Paradigm
There were six visits in the experiment shown in Figure 1A, each visit was separated by 1 week and insomnia patients were instructed to fill in emotion and sleep scales. At visit1, subjects were asked to fill in a demographic scale and an overnight Polysomnography test (PSG) measurement was taken; during visit2, T1 structural image, T2-weighted image and resting state of the subjects were scanned; from visit3 to visit5, there were neurofeedback sessions shown in Figure 1B, each session lasted about 55 minutes and including a pre-training run which was allowed the subjects to adapt to the experimental process, three neurofeedback training runs that fed the activation of the left amygdala back to the subjects in the form of a thermometer and allowed them to increase the height of the thermometer with the previously prepared positive autobiographical memory, and a transfer run that would not provide feedback information, in addition, the resting state before and after neurofeedback training were scanned respectively, the subjects were asked to think nothing and look at the cross in the screen; in the last visit, T1 structural image, T2-weighted image and resting state were acquired.
Figure 1. (A) The rtfMRI NF experimental process for insomnia patients, including six visits with different experimental arrangements. Visit 3 to visit 5 were three neurofeedback training sessions. (B) The NF task, 13 blocks were divided into two conditions, each condition was performed alternately.

2.3. Data Acquisition

fMRI data were collected on a 3T Siemens Prisma of Henan Provincial People's Hospital using the 64-channel head coil. High-resolution T1-weighted anatomical images were collected. Subsequently, functional images were collected using an echo-planar imaging (EPI) sequence with the following parameters: a repetition/echo time of 2000/30ms, a slice thickness of 4 mm with 27 slices, FOV of 22×22cm, and a flip angle of 90°.

2.4. fMRI Data processing

We used resting-state data of visit 3 and visit 6 to discuss the brain imaging mechanism of sleep improvement. Data were pre-processed using the Gretna toolbox[16] including slice-timing, realignment, spatial normalization to the standard Montreal Neurologic Institute (MNI) EPI template and spatial smooth with FWHM = 6 mm.

We performed ICA on the preprocessed data using the GIFT toolbox[17] to obtain a resting-state network of the whole brain and identify brain networks of interest. The number of resting-data components was estimated by using the minimum description length criterion (MDL)[18]. After data reduction, fMRI data were decomposed using the Infomax algorithm. Each independent component is converted into z-values by normalization processing. The brain networks of interest were selected by using the maximum spatial correlation, we used the brain network template in a study as the spatial template of components and selected interested networks, which were the anterior SAN (aSAN), posterior SAN (pSAN), dorsal DMN (dDMN), ventral DMN (vDMN), left ECN (LECN) and right ECN (RECN)[19]. Finally, Pearson correlations between time courses of networks were calculated and Fisher-Z transformation of correlation coefficients was performed and differences in functional connectivity between brain networks before and after neurofeedback were tested using paired T-test.
3. Results
Fifty-eight spatial components were identified using the MDL criterion in resting-state data before and after neurofeedback, representing different resting-state networks and noise, respectively. After spatial correlation analysis with our brain network templates of interest, the components of the SAN, DMN and ECN before and after neurofeedback training were sorted out by correlation values. The composition distribution of the brain network is given in Figure 2. Among them, prefrontal activation was higher in the SAN, which indicated that insomnia patients were more sensitive to external stimuli. And the cingulate and angular gyri in the DMN are also associated with hyperactivity in the brain. The ECN contains the medial prefrontal and posterior parietal lobes, which are involved in the control of emotions.

Then we performed functional connectivity analysis between brain networks before and after neurofeedback and averaged the functional connectivity values of the subjects are shown in Figure 3. The functional connectivity results are represented as a connectivity matrix of 6×6, each row represents a different brain network, and the intersection of rows and columns represents the connectivity between two networks. The significant results of the paired T-test are shown in Figure 4. After univariate t-tests (p < 0.05), we found that the functional connectivity between LECN and aSAN (t=-2.87, p=0.0086) and dDMN (t=-2.49, p=0.0201) was significantly reduced, and the functional connectivity between dDMN and pSAN (t=2.42, p=0.0236) was significantly enhanced.
Figure 3. FNC correlations are averaged across insomnia subjects before and after neurofeedback.

Figure 4. Significant effects of neurofeedback (after-before) after univariate t-tests.

4. Discussion
This study investigated the functional connectivity of resting state brain functional networks in patients with insomnia after rt-fMRI neurofeedback. It was found that LECN-aSAN and LECN-dDMN functional connectivity were significantly decreased, and dDMN-pSAN functional connectivity was significantly increased in patients with insomnia compared to before NF.

The ECN mainly includes the frontoparietal lobe and is involved in multiple cognitive tasks. After rt-fMRI neurofeedback, LECN in patients with insomnia reduces cooperative relationships with the dDMN, which may be associated with diminished functional connectivity between the hippocampus and dorsolateral prefrontal cortex, and previous studies have shown that poor sleep is associated with abnormal responses to emotions in these brain regions. This information further illustrates that insomnia patients are attenuating rumination of memories, which facilitates their entry into sleep. In addition, the SAN is responsible for attention allocation and cognitive control processing, and it has been shown that when insomnia patients receive negative stimuli, the SAN regulates the ECN to increase internal...
cooperation and attenuates the activity of the DMN to reduce internal resource consumption, which increases the patient's processing burden for negative stimuli. Rt-fMRI neurofeedback training attenuated the processing of negative stimuli in insomnia patients, and the performance in brain activity was a weakening of SAN and ECN connectivity, and an enhancement of connectivity with the DMN.

Our research has some limitations. First, only a few of the connections between the four networks were significantly altered in our FNC results, which is likely because the small number of patients included in the experiment leads to differences in statistical analysis. Second, the gender distribution of insomnia patients is uneven, but according to previous studies found that after middle age due to psychological and physical reasons, the female insomnia population will be relatively large, caused by the realistic basis of the study. Thirdly, a healthy group lacking the same control variables may limit the interpretation of FNC changes after neurofeedback interventions. Finally, changes of brain FNC may be useful biomarkers for effective disease treatment based on the results, in future studies, we can predict the treatment effect of patients before intervention in combination with machine learning and brain imaging characteristics, which is very important to promote individualized treatment of diseases.

5. Conclusion

The functional connectivity between networks suggests that changes in functional connectivity between cognitive control networks and emotion-related networks are associated with improvements in insomnia after rt-fMRI neurofeedback training in insomnia patients. With amygdala-based rt-fMRI neurofeedback training, abnormal brain network connectivity changes in insomnia patients and enhancing control of emotions. These changes may be a biological marker for the successful application of neurofeedback training in insomnia and may provide research evidence for rt-fMRI neurofeedback method to become a clinical treatment for insomnia.

Acknowledgements

This research was funded by the National Key Research and Development Plan of China under grant 2017YFB1002502 and the National Natural Science Foundation of China under grant 82071884.

References

[1]. Roth, T., Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med, 2007. 3(5 Suppl): p. S7-10.

[2]. Hertenstein, E., et al., Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. Sleep Med Rev, 2019. 43: p. 96-105.

[3]. Asnis, G.M., M. Thomas and M.A. Henderson, Pharmacotherapy Treatment Options for Insomnia: A Primer for Clinicians. Int J Mol Sci, 2015. 17(1).

[4]. van Straten, A., et al., Cognitive and behavioral therapies in the treatment of insomnia: A meta-analysis. Sleep Med Rev, 2018. 38: p. 3-16.

[5]. de Zambotti, M., et al., Insomnia disorder in adolescence: Diagnosis, impact, and treatment. Sleep Med Rev, 2018. 39: p. 12-24.

[6]. Weiskopf, N., Real-time fMRI and its application to neurofeedback. Neuroimage, 2012. 62(2): p. 682-92.

[7]. Lee, Y.G., et al., Changes in subcortical resting-state functional connectivity in patients with psychophysiological insomnia after cognitive-behavioral therapy: Changes in resting-state FC after CBT for insomnia patients. Neuroimage Clin, 2018. 17: p. 115-123.

[8]. Park, H.Y., et al., Changes in resting-state brain connectivity following computerized cognitive behavioral therapy for insomnia in dialysis patients: A pilot study. Gen Hosp Psychiatry, 2020. 66: p. 24-29.

[9]. Dong, X., et al., Rest but busy: Aberrant resting-state functional connectivity of triple network model in insomnia. Brain Behav, 2018. 8(2): p. e00876.

[10].Malhi, G.S., et al., Resting-state neural network disturbances that underpin the emergence of emotional symptoms in adolescent girls: resting-state fMRI study. Br J Psychiatry, 2019.
215(3): p. 545-551.

[11]. Yokoyama, S., et al., Effects of behavioral activation on default mode network connectivity in subthreshold depression: A preliminary resting-state fMRI study. J Affect Disord, 2018. 227: p. 156-163.

[12]. Uddin, L.Q., Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci, 2015. 16(1): p. 55-61.

[13]. Raichle, M.E. and A.Z. Snyder, A default mode of brain function: a brief history of an evolving idea. Neuroimage, 2007. 37(4): p. 1083-90; discussion 1097-9.

[14]. Seeley, W.W., et al., Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci, 2007. 27(9): p. 2349-56.

[15]. Khazaie, H., et al., Functional reorganization in obstructive sleep apnoea and insomnia: A systematic review of the resting-state fMRI. Neurosci Biobehav Rev, 2017. 77: p. 219-231.

[16]. Wang, J., et al., GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. Front Hum Neurosci, 2015. 9: p. 386.

[17]. Calhoun, V.D., et al., A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp, 2001. 14(3): p. 140-51.

[18]. Li, Y.O., T. Adali and V.D. Calhoun, Estimating the number of independent components for functional magnetic resonance imaging data. Hum Brain Mapp, 2007. 28(11): p. 1251-66.

[19]. Shirer, W.R., et al., Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex, 2012. 22(1): p. 158-65.