Granger Causality Changes during Rt-fMRI Neurofeedback Training of Emotion Regulation for Insomnia Patients

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Abstract: The amygdala is a key brain region in the emotional network. Studies have shown that emotion regulation neurofeedback training targeting amygdala based on real-time functional magnetic resonance can effectively improve the symptoms of insomnia patients. However, the brain mechanism for this improvement remains unclear. In this paper, Granger causality model was constructed to analyze the difference of causality between different brain regions before and after neurofeedback training. Firstly, the brain regions related to emotion regulation with significant differences in ReHo before and after neurofeedback training were selected as regions of interest. Secondly, the time series of the regions of interest were extracted to establish the Granger causality model. Finally, through group level analysis, the difference of effective connection before and after neurofeedback training was used as a biomarker to evaluate the effect of emotion regulation. The results have shown that rt-fMRI neurofeedback training targeting the amygdala significantly regulated the activity of brain regions related to emotion regulation in insomnia patients. And the effective connections from the right triangle inferior frontal gyrus to the left amygdala, the left precuneus to the left middle frontal gyrus, and the right middle cingulate gyrus to the left middle frontal gyrus were significantly enhanced. While the effective connection from the left middle frontal gyrus to the left precuneus was significantly reduced. Moreover, these changes were consistent with the scale evaluation results and clinical psychiatric studies, which further demonstrated that real-time fMRI neurofeedback training can change the effective connectivity of brain regions related to emotion regulation, and these changes could be used as a potential biomarker to evaluate the effect of neurofeedback training.

1 INTRODUCTION

Insomnia is a common clinical disorder characterized by difficulty falling asleep or maintaining sleep for more than three months. With the development of brain science, non-invasive methods have become a hot topic in the field of insomnia research (Christopher and Decharms 2008). Among them, the neurofeedback technology based on real-time functional magnetic resonance imaging(rt-fMRI) detects the changes in blood oxygen caused by the enhancement of neuronal activity in a specific area of the brain to measure the neuronal activity of the brain indirectly, and feedback relevant information to the subjects in real time. It has been used in the diagnosis and intervention of various psychiatric diseases because it can target the brain regions related to patients' neurological defects and has high spatial and temporal resolution (Brühl 2015). Recent studies have shown that rt-fMRI neurofeedback emotion regulation training can effectively improve the symptoms of insomnia patients (CHEN 2021, Zhang and Gao 2021).

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At present, neurofeedback emotion regulation technology based on rt-fMRI has been successfully applied as an adjunctive treatment for major depression (Bodurka and Jerzy 2017; Mehler D and Sokunbi 2018, Bruce and Doré 2018), anxiety disorder (Abraham and Kaufmann 2013), schizophrenia (Zweerings and Hummel 2019) and other diseases related to emotion regulation disorders. A number of studies have also shown that sleep supports continuous changes in neuronal representation of emotional experiences, and insomnia disorder may be related to the inability of patients to eliminate emotional distress (Bonnet and Arand 2010). There are also data suggesting that insomnia and depression may share a common pathology, that is, the diagnosis of insomnia and the severity of sleep disorders are both related to high cortisol secretion (Young and Korszun 2010). These studies have proved pathologically that insomnia patients can be treated by emotion regulation training.

How to analysis the effectiveness of rt-fMRI neurofeedback is focus of attention. In addition to the evaluation method of clinical scale, the evaluation of training effect by using brain image features has become one of the focuses of scientific research and clinical attention. The brain connectivity analysis of fMRI functional data is mainly divided into two types: functional connectivity and effective connectivity. From the direction of connection, functional connection only emphasizes whether there is a connection between brain regions, and does not study the direction of the connection, that is, undirected connection. In order to explain the coupling relationship between neural activities in different brain regions more accurately, scholars put forward the concept of effective connection, which refers to the influence exerted by the activity of one brain region on the activity of another brain region, revealing the causal effect of non-adjacent brain regions in finger spac2 (Friston and Frith 2010). For the analysis of effective connections, model-driven methods are generally adopted to reflect the changes of neural activities by establishing the causal relationship between neurons. The commonly used methods are as follows: psychophysiological interaction (PPI), structural equation model (SEM), dynamical causal model (DCM) and Granger causality analysis (GCA) (Liang X and Wang J H, 2010). GCA is one of the most widely used effective connection analysis methods in current research.

Many researchers have analyzed brain connectivity abnormalities in insomniacs using different functional connectivity methods. For example, in 2018, Li C et al. (Li and Dong 2018) used Granger causality model to analyze the effective brain connectivity between patients with primary insomnia and healthy subjects, and found that patients with insomnia had reduced effective connectivity from the right anterior insula to bilateral precuneus, left posterior central gyrus and bilateral posterior cerebellum, and decreased effective connectivity from bilateral orbitofrontal cortex to the right anterior insula. Dai X J et al. (Dai and Wang 2021) used Granger causality analysis and mediating causality analysis to study the relationship between chronic insomnia and the seeking system and value-driven attention network, and found that the value-driven attention network reduced the mediating effect of sleep regulation and the seeking system reduced the mediating effect of negative emotions after insomnia. However, the interaction between these brain regions with abnormal functional connectivity and the change of the interaction relationship after treatment remains unclear. In this study, a GCA model based on resting state fMRI data of insomnia patients was established to compare and analyze the differences of effective brain connections of insomnia patients before and after neurofeedback training. This study provides a new perspective for understanding the pathological mechanism of insomnia patients, thus promoting the development of brain network imaging markers for early diagnosis and treatment evaluation of insomnia.

2 MATERIALS AND METHODS

2.1 Participants

This experimental design is described in detail in Zhang's research (Zhang and Gao 2021). The original study recruited 32 healthy subjects for the experimental group and 36 healthy subjects for the control group. Among them, the experimental group received neurofeedback signals from the amygdala during training, while the healthy control group received only one baseline scan but didn't participate in neurofeedback training. The two studies have been approved by the Ethics Committee of Henan Provincial People's Hospital, and all volunteers signed the informed consent to participate in this study.

2.2 Experimental Paradigm

The experimental design is described in detail in Zhang's research paper (Zhang and Gao 2021). In this experiment, the experimental group completed 6 stages of experiment, while the control group completed 2 stages of experiment. The experiment was conducted once a week. During stage 1, general demographic characteristics of the experimental group were collected. During stage 2, baseline scans were performed for both experimental and control subjects. Stage 3 to 5 were three neurofeedback sessions for insomnia patients, with each session lasting 50 minutes. Stage 6 was the follow-up period.

The specific steps of the three neurofeedback training sessions are shown in Figure 1. Each run consisted of 7 "rest" blocks and 6 "happy" blocks alternately, lasting for 6min30s. In the "happy" block, participants upregulated the height of the thermometer on the screen by recalling the specific positive autobiographical memory they had written down, and the feedback signal was updated every repetition time (TR=2s). In the "resting" block, the "+" appears on the screen and the subject looks at the "+" calmly to return their brain activity to baseline levels.

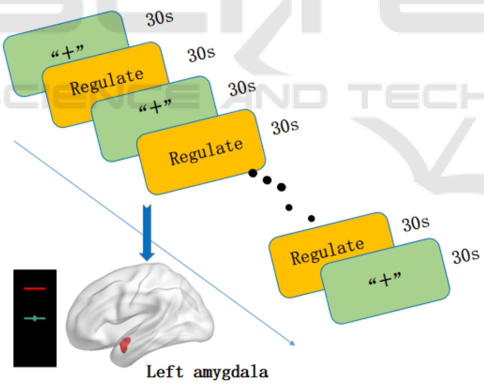

Figure 1: Experimental paradigm of rt-fMRI neurofeedback training for amygdala.

2.3 Data Acquisition

Behavioral data and related experimental results from the same sample have been published in an earlier study. The data analyzed in this paper are resting state functional images of insomnia patients collected before Session3 and after Session5 during neurofeedback training.

The restplus toolbox based on MATLAB was used to preprocess data (Jia and Wang 2019). The data preprocessing mainly includes: dicom to nifti, remove first 10 time points, slice timing, realign/head motion correction, normalization and smooth (FWHM: 6mm). Subjects with head movements greater than 2.5mm and 2.5° were excluded in this experiment.

2.4 Analysis of fMRI Data

2.4.1 Choice of ROI

Firstly, Regional Homogeneity (ReHo) analysis were performed on resting state data before and after neurofeedback training to study the difference in effective connection of emotion-related brain regions in insomnia patients before and after neurofeedback training. Through the paired T-test of ReHo results, we found that 10 brain regions related to emotion regulation were significantly changed in insomnia patients after neurofeedback training. The results are shown in Table 1, where: Right precuneus (10, -47, 18), right posterior cingulate gyrus (12, -47, 30), left precuneus (-5, -47, 15), right middle cingulate gyrus (-4, -12, 32), left insula (-42, 15, 9), right triangle inferior frontal gyrus (52, 25, 19), opercular part of inferior frontal gyrus (48, 18, 9), left middle frontal gyrus (-51, 24, 33), right middle frontal gyrus (36,39,39), right dorsolateral prefrontal cortex (24, 6, 57). Therefore, these brain regions were selected as ROI with a radius of 7 mm for the next GCA analysis. In addition, since BOLD signal of the patient's left amygdala was provided to the subjects during the experiment, the left and right amygdala were used as ROI, where: left amygdala (-24, -1, -17) and right amygdala (26, 1, -18), and the radius was 7 mm.

Table 1: Significant differences in brain regions analyzed by Reho before and after neurofeedback training.

	Brain regions	Coordinates	Cluster size	Peak intensity
1	Right precuneus	(10, -47, 18)	115	4.795
2	Right posterior cingulate gyrus	(12, -47, 30)	32	4.394
3	Left precuneus	(-5, -47, 15)	24	4.916
4	Right middle cingulate gyrus	(-4, -12, 32)	56	3.165
5	Left insula	(-42, 15, 9)	36	-5.1656
6	Right triangle inferior frontal gyrus	(52, 25, 19)	51	-3.184

7	Opercular part of inferior frontal gyrus	(48, 18, 9)	45	-4.4361
8	Left middle frontal gyrus	(-51, 24, 33)	28	-4.4819
9	Right middle frontal gyrus	(36, 39, 39)	21	-3.8115
10	Right dorsolateral prefrontal cortex	(24, 6, 57)	27	-4.0626

2.4.2 GCA Analysis

The GCA method was first applied to fMRI data for effective connection analysis by Goebel et al. in 2003(Goebel and Roebroeck 2013). Granger causality tends to be multi-variable, that is, the causal relationship between two time series under the influence of multiple additional time series. GCA tests whether the current and past values of the first sequence can better predict the results of the second sequence by building a linear model. If so, then these two sequences constitute a causal relationship.

Specifically, In the Granger causality model, we take and as generalized prediction errors. Then we predict two time series and by linear projections of their respective past values respectively. According to Geweke's feedback model (Jiao and Zou 2014), the time dynamics of two time series and with length T can be described as,

$$X_1(t) = \sum_{k=1}^{p} a_{1,k} X_1(t-k) + e_1(t) \quad (1)$$

$$X_2(t) = \sum_{k=1}^{p} a_{2,k} X_2(t-k) + e_2(t) \quad (2)$$

Where p is the maximum number of lagged observations included in the model (model orderp < k). $a_{1,k}$ and $a_{2,k}$ are autoregressive coefficients. $\varepsilon_1(t)$ and $\varepsilon_2(t)$ are the autoregressive residuals of each time series respectively.

That is, if the inclusion of X_2's past observations can reduce the prediction error in the linear regression model of X_1 and X_2 compared to a model containing only previous observations of X_1 , then X_2 cause to X_1. For time series $X_1(t)$ and $X_2(t)$, we assume that both $X_1(t)$ and can be described as binary autoregressive models (Jiao Z-Q and Zou L, 2014),

$$X_1(t) = \sum_{k=1}^{p} A_{11,k} X_1(t-k) + \sum_{k=1}^{p} A_{12,k} X_2(t-k) + e_1(t) \quad (3)$$

$$X_2(t) = \sum_{k=1}^{p} A_{21,k} X_1(t-k) + \sum_{k=1}^{p} A_{22,k} X_2(t-k) + e_2(t) \quad (4)$$

Where p is the model order. $A_{12,k}$ and $A_{22,k}$ are signed path coefficients. and are autoregressive coefficients respectively. $e_1(t)$ and $e_2(t)$ are residuals of and $X_2(t)$, respectively.

GCA is a data-driven method, which overcomes the limitations of SEM and DCM. The GCA method does not require a prior hypothesis model, and the model is relatively simple with low computational complexity, which can be used to analyze the effective connection of large brain networks (Roebroeck and Formisano 2005).

In this study, the time series of the above 12 ROIs related to emotion regulation was extracted to establish a GCA model based on fMRI. Then the GCA results of subjects before and after neurofeedback training were statistically analyzed at group level, so as to detect the effect of neurofeedback training on the effective connection between emotion-related brain regions of subjects.

3 RESULT

The results of GCA-paired T test before and after neurofeedback training for insomnia patients were shown in Table 2 and Figure 2. It was found that after neurofeedback training, the effective connections from the right triangle inferior frontal gyrus to the left amygdala, the left precuneus to the left middle frontal gyrus, and the right middle cingulate gyrus to the left middle frontal gyrus were significantly enhanced. The effective connection from the left middle frontal gyrus to the left precuneus was significantly reduced. In figure2, Red ‘→’ represents a significant increase of the effective connection, and blue ‘→’ represents a significant decrease of the effective connection. Render visualized using BrainNet Viewer (Xia and Wang 2013).

Table 2: Significant differences in brain effective connections before and after neurofeedbacktraining through Granger causality analysis.

	ROI A→ROI B	t	p
1	Right triangle inferior frontal gyrus→Left amygdala	2.470863	0.019598
2	Left precuneus→Left middle frontal gyrus	2.587577	0.014944
3	Left middle frontal gyrus→Left precuneus	-2.685914	0.011842
4	Right middle cingulate gyrus→Left middle frontal gyrus	2.413076	0.022365

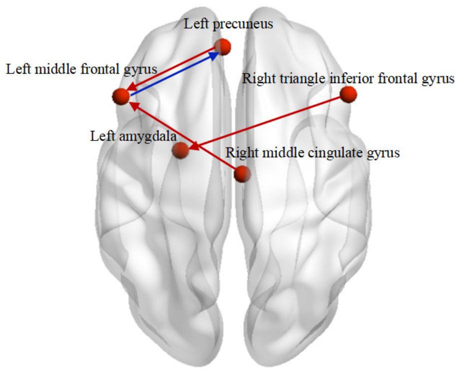

Figure 2: The changes of effective connections between emotional brain regions in insomnia patients before and after neurofeedback training.

4 DISCUSSION

The prefrontal cortex can respond to positive emotional faces, pleasant stimulating images and happy memories, which is an atypical reward mechanism (Vijayakumari and Menon 2020). These responses can be used to guide emotion and may play an important role in emotion regulation. The results of GCA showed that after neurofeedback training, the effective connection of the right triangle inferior frontal gyrus to the left amygdala was enhanced, suggesting that the activity of the prefrontal lobe directly affects and controlls the amygdala. This is similar to the previous results of rt-fMRI neurofeedback emotion regulation by Paret et al. (Paret and Ruf 2016) in healthy subjects in 2016. Similar results have been obtained in the drug treatment for patients with depression and other psychiatric diseases, that is, antidepressants enhance the activities of the prefrontal lobe in cognitive control and other tasks, thus promoting the top-down control of emotions. In 2018, Guo et al. (Guo and Liu 2018) also found that functional connectivity between amygdala, medial prefrontal cortex and inferior frontal gyrus decreased in Alzheimer's disease patients with depression compared with healthy controls, proving that the functional connectivity between amygdala and prefrontal lobe may be an important feature of AD patients with depression.

The precuneus, located in the posterior medial parietal lobe, is an important structure of the posterior default mode network and is associated with cognitive functions (self-related information processing, consciousness, episodic memory extraction and visuo-spatial imagination) (Cavanna and Trimble 2006). Research by Quinten Van Geest et al. (Van Geest and Westerik 2017) has shown that people with insomnia have reduced FC in the thalamus, anterior cingulate cortex and precuneus. A study of 18 healthy women by K Helmbold et al. (Helmbold and Zvyagintsev 2016) showed that acute consumption of tryptophan (a precursor of 5-HT synthesis) led to reduced FC in precuneus and DMN. Therefore, the decrease of FC in precuneus and DMN was related to the decrease of 5-HT level. The results of this study showed that after neurofeedback training, the sending ability of left precuneus to left middle frontal gyrus was enhanced while the receiving ability was decreased, suggesting that the improvement of effective connection between left precuneus and left middle frontal gyrus was related to the improvement of insomnia symptoms.

The cingulate gyrus is located between the corpus callosum sulcus and cingulate sulcus, and is an important part of the limbic system. It was first defined and named by Professor Broca (Broca 1878), who divided the cingulate gyrus into three parts by making vertical lines for the center. The anterior cingulate gyrus (ACC), the middle cingulate gyrus (MCC) and the posterior cingulate gyrus (PCC), among which the anterior cingulate gyrus and the middle cingulate gyrus have similar functions, so most experiments have studied them as a functional region. Moreover, studies have found that the cumulative and negative memories of objective objects and experiences can activate the anterior cingulate gyrus and the middle cingulate gyrus. Li et al. (Li and Yan 2018) used Dartel-VBM technology to evaluate the changes of gray matter in 53 healthy subjects and 60 patients with primary insomnia, and found that the gray matter volume in the lateral prefrontal cortex and anterior cingulate cortex in patients with insomnia was lower than that in healthy subjects, and was negatively correlated with the scores of anxiety scales such as SAS and SDS, which leads to higher levels of negative emotions such as anxiety and depression. Wang et al. (Shi and Wang 2021) observed under fMRI plain scanning that brain activities in bilateral brainstem, left parahippocampal gyrus, frontal lobe and right anterior cingulate gyrus of 15 insomnia patients were significantly more active than before acupuncture at Shenmen, Sanyinjiajie and Baihui points 5 weeks after acupuncture. The results of this study showed that the effective connection between the left middle cingulate gyrus and the left middle frontal gyrus was enhanced after neurofeedback training in insomnia patients, suggesting that the enhancement of the effective connection between the left middle cingulate gyrus and the left middle frontal gyrus was correlated with the improvement of anxiety, depression and other symptoms, and thus improved their sleep quality.

5 CONCLUSIONS

In this paper, Granger causality model was constructed to analyze the difference of causality between different brain regions before and after neurofeedback training. The results showed that rt-fMRI neurofeedback training significantly regulated the activity of brain regions related to emotion regulation in insomnia patients. The effective connections between the prefrontal lobe to the amygdala, the prefrontal lobe and the precuneus, and the cingulate gyrus to the prefrontal lobe also changed. These conclusions were consistent with the results of the scale before and after the experiment and were consistent with the results of clinical psychiatric studies. These results further indicated that rt-fMRI neurofeedback training can alter the effective connectivity of brain regions related to emotion regulation, and this change could be used as a potential biological marker to evaluate the effect of neurofeedback training.

Although rt-fMRI neurofeedback training of amygdala emotion regulation has been studied from the perspective of effective connection of brain regions related to emotion regulation, and preliminary results have been achieved, there are still some limitations. Due to time constraints, the control group experiment of neurofeedback training for insomnia patients is still in progress. The data of the experimental group and the control group can be compared and analyzed in the future to further explore the feasibility of this method in disease treatment.

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