

Effective Prediction of Neurofeedback based on Functional Connection Characteristics of Brain Network in Insomnia

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Abstract: Real-time functional magnetic resonance imaging neurofeedback (rt-fMRI-nf) is a new means of emotion regulation in insomnia, however, due to personal physiological and psychological differences, the effect of neurofeedback training on different patients is significantly different. Using brain imaging data to predict the curative effect is of great significance to improve the individual adaptability of clinical application of neurofeedback training, reduce the treatment cost and reduce the burden of patients. In this article, we raise a neurofeedback training effectiveness prediction method based on brain network functional connection. In this method, network connection matrices of the default mode network (DMN), salience network (SAN), executive control network (ECN), basal ganglia (BG), sensorimotor (SM) et.al. in insomnia are used as features to construct the prediction model, so as to predict the training effect of patients' neurofeedback by using machine learning method. The experimental results through the cross validation of CatBoost model with leave one method show that, the prediction accuracy of whether an insomnia patient can benefit from emotion regulation method produced by rt-fMRI-nf is 75%. This method can initially provide a reference basis for insomnia patients to choose treatment methods.

1 INTRODUCTION

The drug treatment effect of patients with mental diseases such as insomnia, depressive disorder and anxiety shows that more than 50% of patients have not been relieved after treatment (Li 2007). In recent years, rt-fMRI-nf has become a conventional method for the treatment of mental diseases. Due to the large differences in individual treatment success rates, some participants did not learn to control their brain responses, resulting in "ineffective neurofeedback". Ineffective regulation reduces the overall efficiency of neurofeedback training and hinders its transformation into clinical interventions (Haugg 2020). In neurofeedback studies, these participants are often referred to as "non-responders", accounting for 30% to 50% of the total population in study (Alkoby 2017). For example, in 2021, Direito (Ramos 2019) et al. explored whether a personalized fMRI neurofeedback framework will have a positive impact on the success of neurofeedback, the adjustment threshold is defined for every subject according to the maximum change of blood oxygen

level dependency (BOLD) area during positioning operation in visual motion, it is found that 40% of the subjects can successfully adjust the activation of visual motor area, while 60% of the subjects do not. Therefore, exploring the prediction model of the effectiveness of neurofeedback therapy is of great significance to guide individual clinical treatment decisions.

In recent years, brain imaging indexes, combined with traditional machine learning approach such as support vector machine and random forest, have been widely used to predict the prognosis of diseases. In 2017, Kesler et al. (Kesler 2017) used rt-fMRI data and random forests to predict the long-term cognitive ability of breast cancer patients after drug therapy. It was found that the prediction accuracy of the training model could reach 100% in the network and attention network. In 2019, Zhutovsky et al. (Zhutovsky 2019) used the functional connectivity of resting state brain network components and Gaussian process classifier to predict the treatment response of psychotherapy to patients with post-traumatic stress disorder. It was found that the network centered on auxiliary motor

area before treatment contributed the most to the classification of non-responders and responders. Using the characteristics of resting state brain activity to establish machine learning prediction model plays an important role in improving the efficiency of treatment and reducing the cost of treatment. It can be seen that the resting state brain activity characteristics of functional magnetic resonance imaging can effectively predict disease treatment.

Recent studies have shown that the DMN, ECN, SAN and other connection modes of resting state are abnormal in insomnia, depressive disorder and other diseases (Ma 2018, Albert 2018). These networks are closely related to emotion processing, executive function and attention, and the regulation between brain networks affects the behavior of patients. For insomnia patients, not only the weak connection between the SAN responsible for discovering the surrounding sensory and emotional stimuli and the DMN related to self-reference and meditation may lead to the over processing of negative information, but also the enhanced connection between the ECN responsible for attention control and advanced cognitive control tasks and the DMN may be related to the large cognitive load (Zhang 2021). Research has pointed previously that the internal brain functional network connection based on fMRI can be used to predict the performance of remission of major depressive disorder after drug treatment (Korgaonkar 2020). Researchers used a fully connected group method to explore the internal brain function network that can predict the treatment outcomes of antidepressants in patients with depression before the treatment, which found that patients with high connectivity among DMN, frontal parietal and motor network were most likely to benefit from antidepressant treatment. Chin et al. (Fatt 2019) found that depressive disorder patients with high connectivity between DMN and ECN support the treatment of antidepressants. Therefore, the brain network connection model before neurofeedback training is expected to become a potential feature to predict the training effect, and plays an important role in predicting which patients may be effective for neurofeedback training in insomnia.

Aiming at the rt-fMRI neurofeedback emotion regulation training in insomnia, this paper constructs a resting state brain network functional connectivity feature set based on reflecting emotion correlation, and proposes a neurofeedback training effectiveness prediction method based on brain network connection. The results show that this method can accurately predict the training effect of insomnia

patients, and provide an important basis for patients' treatment decision-making.

2 MATERIALS AND METHODS

2.1 Participants

The subjects of this experiment were recruited by Henan Provincial People's hospital through outpatient and advertising. A total of 24 patients with right-handed insomnia (average age 47.13 ± 12.76 years, 5 males and 19 females) were enrolled, which met the criteria of DSM (American 1994). The degree of insomnia of all patients was consistent with the Pittsburgh sleep quality index (PSQI) total score of more than 10 or the insomnia severity index (ISI) score of more than 8 (PSQI > 10 and ISI > 8 showed insomnia disorder. The higher the score, the more serious insomnia). They subjectively showed symptoms such as difficulty in getting in and out of sleep, dreaminess and easy to wake up, depression and emotional abnormalities. The exclusion criteria included serious suicidal ideation, history of mental or cardiovascular diseases, drinking or taking drugs affecting brain function during the experiment, and MRI contraindications.

2.2 Experimental Paradigm

The neurofeedback training of insomnia disorder requires subjects to complete six stages of experiments, once a week, and fixed on weekends. At visit1, insomnia patients asked to fill in a demographic scale and took an overnight Polysomnography test (PSG) measurement. At visit2, subjects underwent baseline scans, including T1 structural images and a resting state scan of 6min20s. During visit2 to visit6, subjects were asked to fill in six scales to evaluate sleep, depression and emotional status before and after the experiment, including Pittsburgh sleep quality index (PSQI), insomnia severity index (ISI), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), positive and Negative Emotion Scale (PANAS) and Baker Depression Scale (BDI). From visit3 to visit5, each subject underwent three neurofeedback training runs, each session lasted about 50 minutes, including the formal experimental run and the rest time between each run.

Before neurofeedback training, the subjects were asked to write down three or more specific positive autobiographical memories, and explain the specific tasks of the experiment to the subjects. Each rt-fMRI

neurofeedback experiment session included functional localization before training and 7 min resting state scanning. Before the formal neurofeedback training, there will be a pre-training lasting for 6 min and 30s and subjects will train without feedback signal. Then, three formal neurofeedback trainings composed of seven 30s "rest" blocks and six 30s "emotion regulation" blocks guided by the prompt "happy" were conducted, each lasting for 6 min and 30s. In the "rest" block, the patient is required to look at the cross on the screen to calm their emotions. In the "emotion regulation" block, the activity signal of the left amygdala of the insomnia patient is fed back to the subjects in the shape of a bar column, and the patient is instructed to adjust the height of the bar column on the screen by specifically recalling positive autobiographical memory. Each repetition time of the feedback signal (TR = 2S) update once. Then a transfer training run without feedback signal but the same as the formal feedback run experimental paradigm was carried out, which also lasted for 6 min and 30s. Finally, a 7 min resting state scan was performed. Visit 6 is the follow-up period, during which the T1 structure image and resting state of the subjects were scanned again. The neurofeedback process is shown in Figure 1:

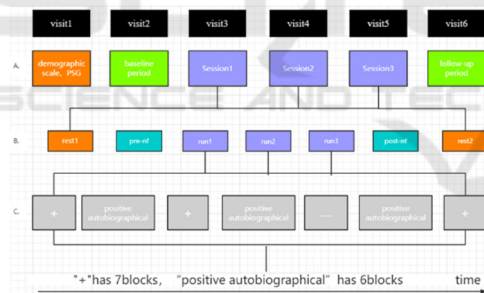


Figure 1: The process of neurofeedback training in insomnia

2.3 Experimental Acquisition

All fMRI data in this experiment are from the medical imaging center of Henan people's hospital. The data collection is completed through their magnetic machine (Siemens prism 3T). The head coil is 64 channels. Before the experiment, we first fixed the subject's head with a sponge pad, and then pasted medical tape laterally on the subject's forehead to both sides of the coil for fixation to prevent excessive head movement from affecting the experimental results. This paper uses the resting state data of insomnia patients before and after neurofeedback.

2.4 Data Processing

The DPABI is used to process resting state fMRI data, including converting DICOM raw data to NII data (deleting the first 10 time points), slice timing, realignment, reorientation, coregister, brain component segment, smooth, detrending, filter, etc.

This paper performed group ICA analysis by gift v3.0b toolbox (Calhoun2010) on the preprocessed data to gain the resting state brain network components of the whole brain. The minimum description length criterion (MDL) (Li 2007) was used to calculate the optimal number of resting state components in the whole brain, and the INFOMAX algorithm was used to decompose the fMRI data. The reliability and robustness of component analysis are improved through repeated calculation for 20 times by ICASSO (Himberg 2003). Then, the simplified data of principal component analysis (PCA) is inversely reconstructed and decomposed into a series of spatially independent components and their corresponding time processes. Normalization converts each independent component to a z-value.

The brain network of interest is selected by the method of maximum spatial correlation, and the brain network template is used as the spatial template of the component. We single out 10 brain networks involved in emotional cognitive processing and sensory motor in the resting brain network template proposed by Stanford cognitive and System Neuroscience Laboratory in 2012 (Shirer 2012), anterior salience network (ASN), posterior salience network (PSN), dorsal default mode network (DDMN), ventral default mode network (VDMN), left executive control network (LECN) and right executive control network (RECN), basal ganglia(BG), sensorimotor(SM), precuneus and auditory. The Pearson correlation between each network time series is calculated, and the correlation coefficient is transformed by fisher-z transform. Finally, the functional connection matrix of the brain network before neurofeedback is used as the characteristic input of the prediction model.

2.5 Machine Learning Model for Treatment Effect Prediction

In recent years, people are increasingly interested in the application of machine learning technology in the diagnosis, classification and effect prediction of clinical diseases such as depression, schizophrenia, bipolar disorder and autism disorder. We use machine learning method combined with brain image characteristics to predict the effect of neurofeedback

training for insomnia patients, further promote the decision-making of individual treatment plan for insomnia, and accelerate the clinical transformation and application of rt-fMRI neurofeedback technology.

In this paper, 10 functional brain networks and 68 network sub-components of 24 insomnia patients were analyzed in time, and twenty-four 78×78 functional connection matrix were generated within and between brain networks. We select 3003 non-repeated function connection values in the generated function connection matrix as features. The machine learning method is adopted, and CatBoost, RandomForest, LightGBM, XGboost, ExtraTrees, KNeighbors and other models are used for secondary classification. Label 0 represents the ineffective

neurofeedback treatment, and label 1 represents the effective neurofeedback treatment.

3 RESULTS

Referring to the common segmentation proportion of machine learning, 24 patients are divided into 14 patients for training and 10 patients for testing. Using automatic machine learning technology, the recognition accuracy of 11 machine learning models under this data set is investigated.

For the generated 10 test sets, the prediction of each model is shown in Table 1.

Table 1: Prediction of 10 subjects under each model.

model	Light-GBMLarge	Light-GBMXT	XG-Boost	Light-GBM	Cat-Boost
accuracy	90%	70%	50%	70%	60%
Random-ForestEntr	KNeighborsUnif	KNeighborsDist	Random-ForestGini	Extra-TreesEntr	Extra-TreesGini
40%	30%	30%	30%	20%	20%

Considering that the sample size of this experiment is relatively small, the left one method (LOOCV) is used for cross validation, that is, the functional connection matrix of each subject is recycled as the test set, and the brain network

characteristics of the other 23 subjects are input into the automatic machine learning model as the training set for training, with a total of 24 cyclic evaluations. The prediction results of each model are shown in Table 2.

Table 2: The prediction of each model of 24 subjects under LOOCV.

model	Cat-Boost	Random-ForestEntr	Random-ForestGini	Light-GBMXT	Light-GBM
accuracy	75%	71%	71%	63%	63%
Extra-TreesEntr	Light-GBMLarge	XG-Boost	KNeighborsDist	KNeighborsUnif	Extra-TreesGini
63%	58%	54%	54%	54%	54%

From table2, CatBoost, RandomForestEntr and RandomForestGini models have higher prediction

accuracy among all models.

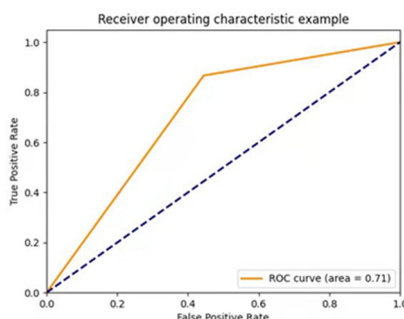


Figure 2: ROC curve of CatBoost under LOOCV.

As shown in Figure 1, the area is 0.84 under the ROC curve of CatBoost, the accuracy of this model is high. Compared with other models, CatBoost model solves the problems of gradient deviation and prediction offset, so the occurrence of over fitting is reduced and the accuracy and generalization ability of the algorithm are improved. Randomforestnr and RandomForestGini belong to random forest models, which can be over fitted by reducing randomness, so their prediction accuracy is high. However, due to the high randomness of their parameters, their accuracy is lower than CatBoost. Xgboost model uses approximate algorithm to improve operation speed. Kneighborsdist and Kneighborsunif are too simple in structure, resulting in insufficient fitting of data. Extratreesgini model adopts randomization for model structure and model parameters, resulting in too strong randomization of model. Therefore, the prediction accuracy of Xgboost, Kneighborsdist, Kneighborsunif and Extratreesgini are lower.

4 DISCUSSION

The results of machine learning prediction model based on the functional connection characteristics of brain network show that the effectiveness of neurofeedback in insomnia patients is significantly higher than the random probability. The clinical practical significance of the model can be explained as whether an individual with insomnia can be predicted to be suitable for neural feedback training after resting state MRI scanning and brain network data analysis, which provided a reliable basis for the selection of treatment schemes for insomnia patients.

However, our study has some limitations. On the one hand, the degree of each subject is different in insomnia, and there are individual differences in the treatment effect after neurofeedback training. For the ineffective treatment of patients after neurofeedback, whether it is caused by internal factors or external factors such as errors in the experimental process, these problems need to be further discussed. For example, we can divide the subjects' disease degree more carefully, explore the impact of different severity of insomnia on the effect of neurofeedback training, or adjust the neurofeedback experimental design by changing the neurofeedback target area. On the other hand, due to the limited experimental conditions and the limited number of samples included in the experiment, 24 subjects participated in neurofeedback training. With the development of more clinical experiments, this method is expected to achieve more accurate prediction.

5 CONCLUSIONS

In the paper, we propose a neurofeedback effectiveness prediction method based on the functional connectivity of resting state brain networks. The functional connections of brain networks such as DMN, ECN, SAN and SM et.al. before neural feedback in insomnia are extracted as features, and a prediction model based on automatic machine learning is constructed to predict the neural feedback training effect of insomnia patients, so as to realize the prediction of the effectiveness of neural feedback training of insomnia patients based on machine learning. The experimental results show that the highest prediction accuracy of all machine learning models reaches 75%, which provides an important support for insomnia patients to make decisions in the treatment plan.

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