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SYSTEMS-LEVEL QUALITY IMPROVEMENT

Construction and Recognition of Functional Brain Network Model Based on Depression

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Abstract

In order to make a deep analysis of depression, the construction and recognition of functional brain network model based on depression is mainly studied. Firstly, the relevant information of the subjects is introduced in turn. The data of fMRI (functional magnetic resonance imaging) are pretreated, static and dynamic functional connections are analyzed, statistical analysis and testing are carried out, and then the results are analyzed and discussed. The results show that static functional connectivity provides a new research perspective and means for further understanding the connection patterns of brain functional networks in unipolar depression and bipolar depression. Dynamic functional connectivity analysis (DFA) extends the previous studies on unipolar depression and bipolar depression, and provides a potential biological marker for clinical identification of unipolar depression and bipolar depression.

Keywords Depression · Brain network model · Unipolar depression · Bipolar depression · fMRI

Introduction

Depression is a common mental illness in modern society. Its clinical manifestations are mainly the symptoms of decreased interest and low mood. On the one hand, depression often afflicts patients themselves with illness and even leads to suicide [1]; on the other hand, it also brings heavy financial burden to patients' families and has a serious impact on society [2]. In recent years, the incidence of depression has been increasing year by year, and more patients have developed into severe depression patients. Therefore, more and more scholars and experts in psychiatry, psychology, neuroanatomy, neurobiology and other fields pay attention to the study of depression [3–5]. The traditional research methods of depression are too single and have obvious limitations [3]. With the development of modern medical technology, more and more advanced science and technology have been applied to the study of depression, such as functional magnetic resonance imaging (fMRI) technology, positron emission tomography (PET) technology and so on. With these scientific means, more and more studies have been made on the pathogenesis and working mode of depression [6].

In recent years, the further development of deep learning and artificial intelligence has made the big data technology more and more widely applied in academia. According to these project studies, a new generation of huge human brain image database has been established worldwide, which provides powerful data support for promoting the development of neuroimaging. Exploring the connection mode of brain functional network in patients with depression has become one of the hotspots in brain imaging research in recent years [7].

Analytical methods and materials

Subject information

At present, there are 50 patients with unilateral depression and 50 patients with bipolar depression. A total of 100 patients are recruited from Qingdao Mental Health Center. All patients are interviewed by two psychiatrists with rich diagnostic experience who use structured clinical interviews with DSM-IV-TR

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(Diagnostic and Statistical Manual of Mental Disorders). According to DSM-IV-TR criteria, patients with unipolar and bipolar depression are diagnosed. Patients with schizophrenia, mental retardation or personality disorders, loss of consciousness, drug abuse, serious medical or neurological diseases are excluded. 24 items of the authoritative Hamilton Depression Scale (HAMD) are used to evaluate the condition of patients with diseases. The HAMD-24 evaluation criteria include seven factors: anxiety/somatization, weight, cognitive disorder, sleep disorder, blockade, diurnal changes and despair. The characteristic data of clinical scale scores are collected, including age of first onset, course of disease, duration of single onset, frequency of depressive onsets, etc. Drugs given to depressive patients who receive antidepressant drugs include selective serotonin reuptake inhibitors (SSRI) and serotonin thyroidectomy reuptake inhibitors (SNRI). To measure the total drug load, each psychotropic drug is coded as vacancy = 0, low = 1 (average or lower average dose), or high = 2 (greater than average dose), relative to the midpoint of the recommended daily dose range. The comprehensive measurement of the total drug load of each individual is calculated, reflecting the doses and types of different drugs, and all individual drugs are summarized.

Fifty cases in the healthy control groups (HC) are recruited from the community by sending advertisement leaflets manually. Each recruited healthy control group also receives structured clinical interviews with DSM-IV (non-patient version). None of the HC has a history of serious medical or psychiatric illness, nor do they have a family history of major psychiatric or psychiatric disorders among their first-degree relatives. The clinical and demographic data of 150 patients in the three groups are shown in Table 1.

fMRI data preprocessing

Data preprocessing for static brain network model recognition. All the data preprocessing steps of fMRI are carried out in DPARSF software. Firstly, the images at the first five time points are removed to maintain the stability of the signal after the initial transient. Then, the data are corrected to obtain the difference of slice timing and to adjust it to the middle layer in space, so as to correct the movement of the scanning head. The head movements of all participants do not exceed the defined threshold (translation or rotation parameters are higher than (±1.5 mm or ± 1.5°). Subsequently, the fMRI is normalized into an EPI template and resampled to 3 mm*3 mm*3 mm. Then, the low frequency drift is removed by de-linear drift, and the uninterested covariate effect is removed by multiple regression models, including 24 head movement parameters, white matter signal and cerebrospinal fluid signal. After covariate regression, a band-pass filter is used to remove high frequency noise from 0.01 to 0.08 Hz. Finally, the method of cubic spline difference is used to clean the signal. It is worth noting that the whole brain signal is not regressed in the process of regression covariance, because studies have shown that the whole brain signal regression may lead to a negative correlation between brain regions and change the correlation differences between groups and in groups. Therefore, in order to provide more credible results, the method of non-regression of whole brain signals is adopted.

Data preprocessing of dynamic brain network pattern recognition. All the fMRI data used are processed strictly, and subjects whose head movement is greater than 3 mm are discarded. The filtered data are also wiped and cleaned by cubic spline interpolation fitting method, and the data are further revised. Specific data preprocessing steps are consistent with what described in the fMRI data preprocessing section in the second chapter.

Static and dynamic functional connection analysis

Static functional connection analysis. The functional connectivity analysis of the pre-processed fMRI data is carried out in REST software. In 264 seed regions, the time process signals

Table 1 Information statistics and clinical scale evaluation of three groups of subjects

Statistical variable	Normal health (50)	Unipolar depression (50)	Bipolar depression (50)	*P*
Age (years old)	33.6 ± 10.38	35.23 ± 10.29	33.7 ± 9.89	0.71[a]
Gender (male and female)	24, 26	25, 25	25, 25	098[b]
Educational years (years)	13.7 ± 4.19	12.88 ± 3.60	14.07 ± 2.93	0.33[a]
Handedness (left and right)	1,49	0, 50	5,45	0.13[b]
Course of disease (month)		69.25 ± 68.64	88.78 ± 75.41	0.23[c]
Age of first onset (years old)		29.78 ± 9.95	25.95 ± 8.78	0.07 [c]
Number of onsets		2.25 ± 0.87	2.73 ± 1.47	0.08 [c]
Single onset time		4.63 ± 3.33	4.03 ± 2.75	0.38 [c]
HAMD score		23.48 ± 4.63	21 ± 7.81	0.08 [c]

"±" in the table means the mean and standard deviation. One-way ANOVA, b chi square test, and c double-tailed double-sample T-test are used. HAMD score is Hamilton Depression Scale score

around the sphere with radius of 6 mm are extracted and averaged, and Pearson correlation coefficients between each seed point are calculated. In order to make the final statistical analysis conform to normal distribution, the correlation coefficients are transformed by Fisher transform to produce Z value. Finally, each person gets a 264*264 functional connection correlation matrix, from which 10 correlation matrices in the network and 45 correlation matrices between networks are extracted, respectively.

Dynamic functional connectivity analysis. Time-varying parametric regression equation is used to describe the dynamic interaction between brain regions.

$$y(t) = x(t)\beta(t) + \mu(t) \quad (1)$$

In Formula (1), $x(t)$ and $y(t)$ refer to the variables of seeds and target regions, respectively, $\mu(t)$ represents approximate errors, $\beta(t)$ indicates the coefficients of dynamic connectivity between variables x and y, and t is time.

Statistical analysis and test

Static statistical analysis and test. Covariance analysis is carried out on the group matrix data of three groups: unipolar depression, bipolar depression and normal control. The covariance analysis is made on gender, age, education years and average head movements. Bonferroni method ($p < 0.05$) is used to correct the comparison between 10 intra-network and 45 intra-network. The threshold value in the network is $p < 0.005$ and the threshold value between networks is $p < 0.001$. After correction by multiple hypothesis tests, it is found that there are significant differences in sensorimotor network (SMN), Cingulate Island cover network (CON) Fig. 1 and auditory network (AN) Fig. 2 among the three groups: unipolar depression, bipolar depression and normal control, as shown in Table 2.

Meanwhile, there are significant differences in AN to the default network (AN-DMN), the AN to the visual network (AN-VN), the visual network to the ventral attention network (VN-VAN), the visual network to the back attention network (VN-DAN), the SMN to the AN (SMN-AN), and the SMN to the visual network (SMN-VN), as shown in Table 3.

Dynamic statistical analysis and test. Data of dynamic functional connectivity network variability connection matrix are extracted from three groups: unipolar depression, bipolar depression and normal control. Covariance analysis is performed at SPSS 20.0. Regression analysis is made with gender, age, education years and average head movements as co-variants. Bonferroni method ($p < 0.05$) is used to correct 10 inter-network and 45 intra-network. The threshold of each network is $p < 0.005$ and that of each network is $p < 0.001$. After correction by multiple hypothesis tests, it is found that there are significant differences in SMN among three groups: unipolar depression, bipolar depression and normal control group (statistical test p value is 0.0018) and there is significant difference between 45 dynamic functional connectivity networks (Figs. 3).

Table 2 Intranet differential network

Intranet differential network	*P*
SMN	0.0013
CON	0.0023
AN	0.0020

Results and discussion

Recognition and classification of static brain network model

The feature data extracted from each group are analyzed by SVM (Support Vector Machine) classifier, "leave one to cross validation" (LOOCV), permutation test and other pattern recognition methods [8] in three groups: unipolar depression, bipolar depression and normal control. The detailed analysis process is as follows:

Step 1: extract static functional connectivity significant difference network of three groups of people by statistical analysis, which makes each group have three characteristics in the network and six characteristics among the networks.
Step 2: standardize the extracted feature data with Z-score.
Step 3: use SVM classifier with linear kernel function to construct and classify the model. The parameters c and g use the default values.
Step 4: use the cross validation method to validate the model. It divides the data set with N samples into test set and training set, in which each sample is taken as test set and the remaining N-1 sample is taken as training set. In this way, N test classification results are obtained and the average of N test classification results is taken as the final classification result.
Step 5: verify the reliability and stability of classification results by permutation test, i.e. keep all features

Table 3 Inter-network differential network

Inter-network differential network	*P*
AN-DMN	0.0010
AN-V N	0.0010
VN-VAN	0.0004
VN-DAN	0.0002
SMN-AN	0.0002
SMN-VN	0.0001

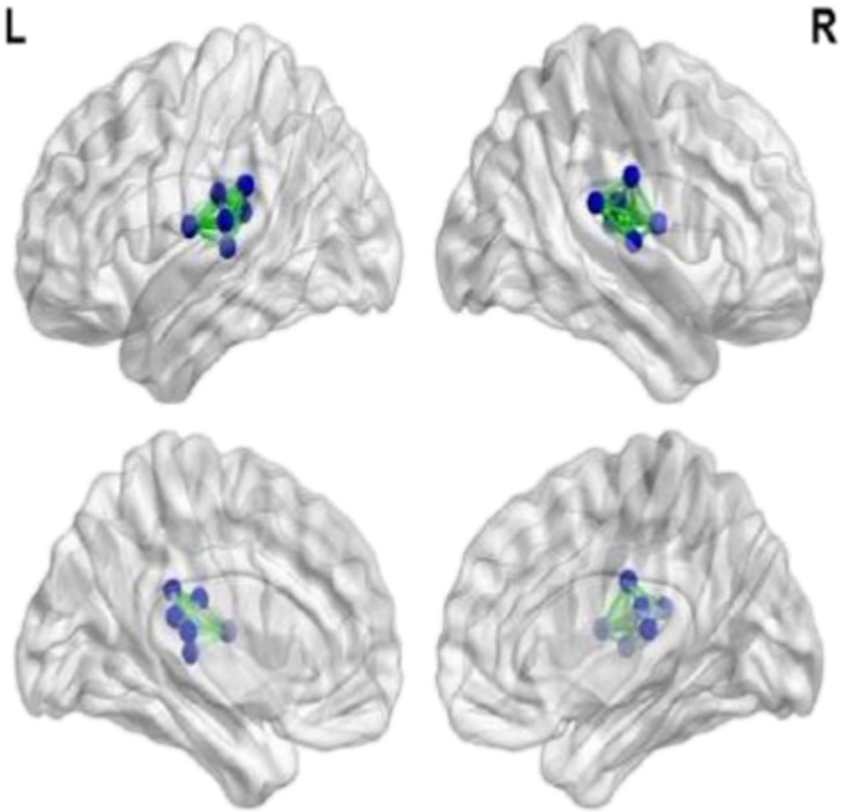

Fig. 1 Static functional connection in AN

unchanged, randomly disrupt sample labels, do 1000 times of LOOCV, and obtain 1000 classification results. Statistics greater than the number of times of the original label classification results divided by 1000 values is taken

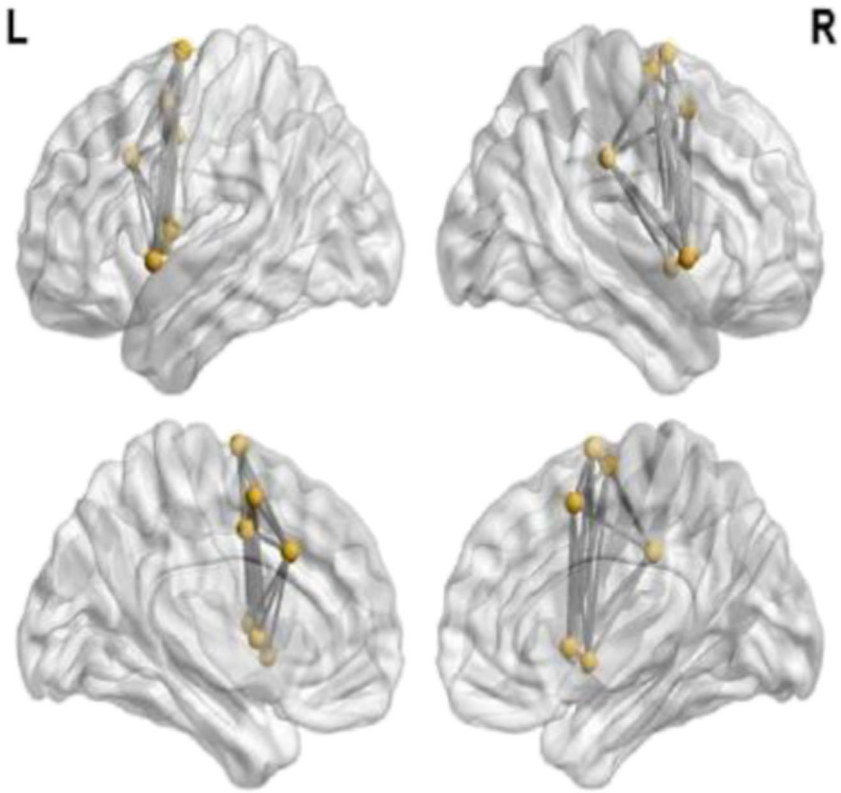

Fig. 2 Static functional connection in CON

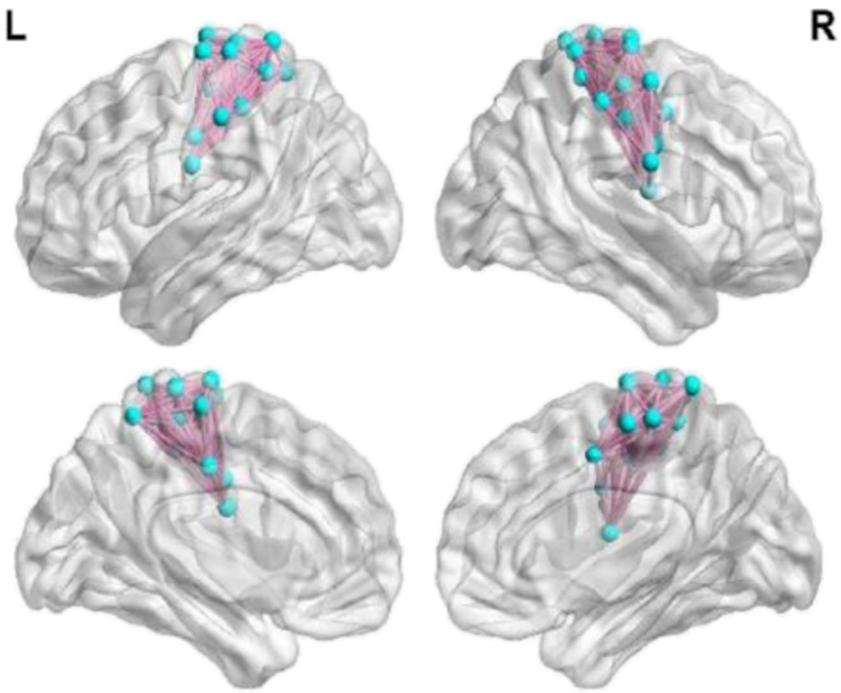

Fig. 3 Dynamic functional connection in SMN

as the threshold of permutation test. When the threshold value is less than 0.05, it shows that the classification accuracy of the construction model is stable and reliable.

Two groups of people in the three groups of unipolar depression, bipolar depression and normal health control are combined, i.e. bipolar depression and normal health, unipolar depression and bipolar depression, and unipolar depression and normal health control. The final classification results after a series of analysis such as data pretreatment, feature selection, model construction, cross-validation and permutation test are shown in Tables 4 and 5, Figs. 4, and 5.

Recognition and classification of dynamic brain network model

Through the analysis of the results of dynamic functional network connection, it is found that there are significant differences among the three groups in SMN. In order to verify whether SMNs may be abnormal connectivity characteristics of brain dynamic functional networks in patients with unipolar depression and bipolar depression, the connection matrices of SMNs of three groups of people with unipolar depression, bipolar depression and normal control are extracted as characteristics [9]. The feature data extracted from each group are averaged. SVM classifier, LOOCV and permutation test are used to analyze three groups of patients with unipolar depression, bipolar depression and normal control. The detailed analysis process is shown as follows:

Step 1: extract the significant difference network of three groups of people's dynamic functional connectivity through statistical analysis, and then average it so that each group has a feature in the network.
Step 2: standardize the extracted feature data with Z-score.
Step 3: use SVM classifier with linear kernel function to construct and classify the model. The parameters c and g use the default values.

Table 4 SVM classification results in significant difference networks

Classification results in static networks				
Groups	Accuracy rate (%)	Specificity (%)	Sensitivity (%)	Permutation test *P* value
Bipolar depression and normal health	68.89	64.00	75.00	0.0450
Unipolar depression and bipolar depression	75.00	72.50	77.50	0.0030
Unipolar depression and normal health control	71.11	68.00	75.00	0.0130

Table 5 SVM classification results among significant difference networks

Classification results among significant difference networks				
Groups	Accuracy rate (%)	Specificity (%)	Sensitivity (%)	Permutation test *P* value
Bipolar depression and normal health	74.44	68.00	82.50	0.0370
Unipolar depression and bipolar depression	78.75	80.00	77.50	0.0280
Unipolar depression and normal health control	72.22	66.00	80.00	0.0130

Step 4: use the cross validation method to validate the model. It divides the data set with N samples into test set and training set, in which each sample is taken as test set and the remaining N-1 sample is taken as training set. In this way, N test classification results are obtained and the average of N test classification results is taken as the final classification result.

Step 5: verify the reliability and stability of classification results by permutation test, i.e. keep all features unchanged, randomly disrupt sample labels, do 1000 times of LOOCV, and obtain 1000 classification results. Statistics greater than the number of times of the original label classification results divided by 1000 values is taken as the threshold of permutation test. When the threshold value is less than 0.05, it shows that the classification accuracy of the construction model is stable and reliable.

Two groups of people in the three groups of unipolar depression, bipolar depression and normal health control are combined, i.e. bipolar depression and normal health, unipolar depression and bipolar depression, and unipolar depression and normal health control. The final classification results after a series of analysis such as data pretreatment, feature selection, model construction, cross-validation and permutation test are shown in Table 6 and Fig. 6.

Discussion on connections in static networks

The SMN includes bilateral central anterior, posterior gyrus and auxiliary motor areas. The AN includes bilateral middle temporal gyrus, superior temporal gyrus, transverse temporal gyrus and temporal pole. Both SMN and AN belong to primary perception network. Previous studies have found that functional connections in the right posterior central gyrus and bilateral lenticular nucleus of the SMN are weakened in patients with unipolar depression. This indicates that the primary perception network system of patients with unipolar depression is abnormal. It is found that unipolar depression patients have less connectivity in SMNs and ANs, which is consistent with previous studies. In addition, it also found that bipolar depression patients have lower connectivity in the cingulate insular network than normal healthy controls, but no significant difference between bipolar depression patients and unipolar depression patients. The study suggests that the CON is associated with attention and executive control. It shows that bipolar depression patients show more attention and lower executive control than unipolar depression patients.

In order to verify whether the significant difference network found can be used as a marker significant network to distinguish the brain function network of patients with unipolar depression from that of patients with bipolar depression, model recognition analysis method is used and it is found that

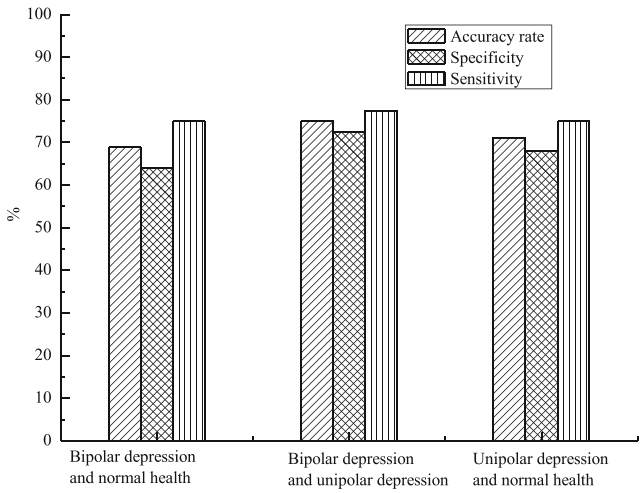

Fig. 4 Classification results in static networks

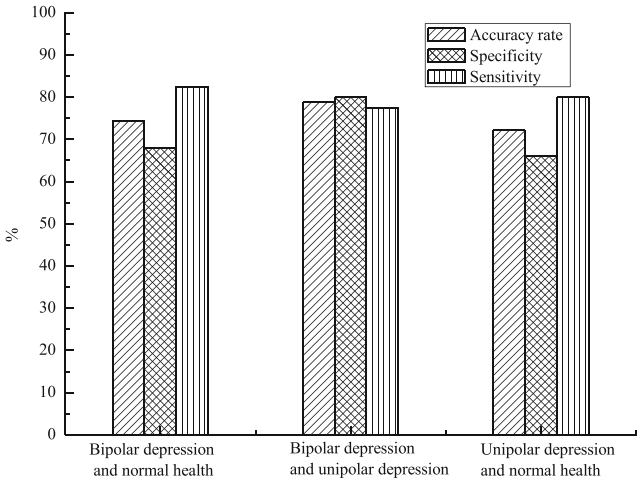

Fig. 5 Classification results among static networks

Table 6 SVM classification results in significant difference networks

Classification results in dynamic networks				
Groups	Accuracy rate (%)	Specificity (%)	Sensitivity (%)	Permutation test *P* value
Bipolar depression and normal health	58.89	58.00	60.00	0.0207
Unipolar depression and bipolar depression	67.50	64.50	69.50	0.0001
Unipolar depression and normal health control	59.34	56.00	63.41	0.0040

the accuracy of model classification based on significant difference network is 75%. To some extent, the results indicate that the three networks with significant differences can be used as a landmark feature to distinguish patients with unipolar depression from those with bipolar depression.

Discussion on connections among static networks

In the discussion section of the network, it has been pointed out that SMN and AN belong to primary perception network. Previous studies have suggested that VNs also belong to primary perception networks. The study shows that unipolar depression patients have decreased connectivity from AN to VN, SMN to AN, and SMN to VN. This is consistent with the results of previous studies. At the same time, it is also found that the connectivity between VNs and VANs is also reduced in patients with unipolar depression. Previous studies have found abnormal connections in patients with severe depression in the ventral attention network, which involves emotional processing of special events. The results further demonstrate that abnormal connections also exist in patients with unipolar depression. Default network and dorsal attention networks involving internal or external attention have been found to have abnormal connections in previous studies of depressive disorders. However, the study of unipolar depression and bipolar depression has not been found. The study shows that bipolar depression patients have increased visual to dorsal attention network connectivity compared with unipolar depression patients, but there is no significant difference between bipolar depression patients and healthy controls. At the same time, the connection between AN and default network is decreased in patients with unipolar depression compared with healthy controls, but there is no significant difference between patients with bipolar depression and patients with unipolar depression. The results of this study further complement the previous research results, and provide new research content for further understanding the connection mode of brain functional network in patients with unipolar depression and bipolar depression.

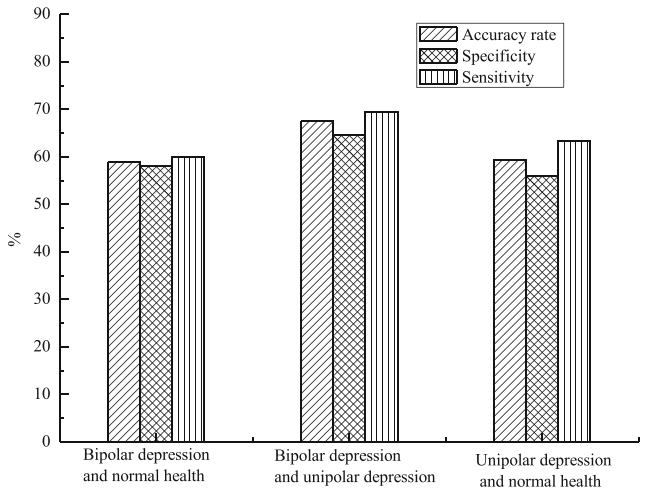

Fig. 6 Classification results in dynamic networks

Using the method of pattern recognition, the result shows that the accuracy of model classification between networks based on significant difference network is 78.75%.

Discussion on intranet connections in dynamic networks

SN belongs to primary perception network, which mainly includes bilateral central anterior and posterior gyrus and auxiliary motor areas. Scholars, through static functional connectivity analysis, found that functional connectivity was weakened in the right posterior central gyrus of SMN in patients with unipolar depression. This weakening of functional connectivity is an abnormal connection in the SMN of patients with unipolar depression, but the brain is a complex organizational network system, which is flexible in the process of processing information. Rapidly changing functional connectivity patterns can achieve cognitive control across multiple tasks. The results reveal an increased variability of dynamic functional connectivity in SMNs in patients with unipolar depression compared with bipolar depression and healthy controls, which has not been found in previous studies. Previous studies have shown that the variability of brain functional network connections reflects rapidly changing functional connectivity patterns. The increased variability of functional connectivity in SMNs in patients with unipolar depression can well depict the changes of functional connectivity in SMNs in patients with unipolar depression over a period of time. Patients with depression show mental agitation clinically, which may be due to the increased variability of functional connections in the SMN of the brain in depressive patients. At

the same time, in order to verify the increased variability of dynamic functional connectivity in the SMN of patients with unipolar depression and whether it can be used as a significant marker network to distinguish the brain functional network of patients with unipolar depression from that of patients with bipolar depression, patterns classification analysis is carried out from the perspective of significant difference network and data driven. The analysis results show that the classification accuracy based on significant difference network is 67.5%.

Discussion on connection between dynamic networks

There are no significant abnormal changes in the variability of dynamic functional connections among the three groups of patients with unipolar depression, bipolar depression and normal control. Because the subjects used are all treated with medication, and Zhao et al. found that medication may play a specific role in functional connectivity, but it has not yet been confirmed. This may lead to no significant difference in the variability of the three groups of people's functional network connections. Secondly, it may be due to the small sample size analyzed and the fact that the template used to divide the network is not based on voxel level, which makes it impossible to capture more information about the dynamic functional connections among the three groups of people. In the future, the analysis of functional connectivity between networks at voxel level by enlarging the sample size may achieve better results. The results extend the understanding of connectivity variability between brain functional networks in patients with unipolar depression and bipolar depression.

Conclusion

Static functional connectivity and model recognition analysis are used to detect the connection mode of whole brain functional networks in patients with unipolar depression and bipolar depression. The abnormal intra-network and inter-network connections found extend previous studies on brain functional networks in patients with unipolar depression and bipolar depression. It provides a new research perspective and means for further understanding the connection mode of brain functional network between unipolar depression and bipolar depression.

At the same time, the dynamic functional connectivity analysis method is used to explore the variability patterns of the whole brain functional network connections in patients with unipolar depression and bipolar depression, and to depict the dynamic evolution process of the whole brain functional network in patients with unipolar depression and bipolar depression. The results of previous studies on unipolar depression and bipolar depression are extended. It provides a potential biological marker for clinical identification of unipolar depression and bipolar depression.

Compliance with Ethical Standards

Conflict of Interest Author Lin Wen declares that he has no conflict of interest. Author Shan Liu declares that he has no conflict of interest. Author Yurong Cao declares that he has no conflict of interest. Author Guiling Li declares that he has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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