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IMAGE & SIGNAL PROCESSING

Discussion on Brain Structure and Function in Schizophrenia by Multimodal Magnetic Resonance Imaging

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Abstract

In order to explore the relationship between hippocampal structure changes and performance symptoms as well as cognitive function in adolescent schizophrenia, taking the brain response signals of psychiatric patients as the research object, the relationship between hippocampal volume drawn by schizophrenia and language memory of negative symptoms is explored based on morphological analysis method. It is found that the left hippocampal volume of schizophrenic patients is abnormal when the whole brain volume is returned, which is significantly lower than that of normal people. It is also found that the left hippocampus volume of schizophrenic patients is a mediator between negative symptoms and speech memory. The results show that the left hippocampus of schizophrenic patients plays an important role in the pathogenesis of schizophrenia.

Keywords Schizophrenia · Brain structure and function · Hippocampus · Magnetic resonance imaging (MRI)

Introduction

Schizophrenia is a hereditary brain disease with unknown pathogenic mechanism. The strongest genetic association of schizophrenia at the population level involves variations in major histocompatibility complex (MHC) loci, but the genetic and molecular mechanisms that explain this have been difficult to identify [1]. Adult nerves occur throughout life in the discontinuous regions of the adult mammalian brain. People know little about the mechanisms that control sequential development, leading to the integration of new neurons from adult neural stem cells into existing circuits [2]. Whether schizophrenia and bipolar disorder are clinical outcomes of discrete or shared pathogenic processes is controversial in psychiatry [3]. Patients with schizophrenia who suffer from devastating mental illness are plagued by hallucinations, strange behaviors and delusions. For example, they believe that they are controlled by malicious external forces. The basic human cognitive operations that may lead to these symptoms are the ability to maintain accurate and consistent self-referential processing over time, like occurring during real-world surveillance (distinguishing self-generation from external perception information). However, the neurological basis of this surgical interference in schizophrenia has not been fully explored. Using functional magnetic resonance imaging (MRI), clinically stable schizophrenics are asked to remember whether they produced target words during the completion of tasks in early sentences [4].

By reducing the risk of cardiac metabolism, interventions of negative symptoms and cognitive deficits can improve the typical adverse consequences of schizophrenia; all aspects of the disease are often untreated. By examining the physical or psychological effects of exercise intervention on non-affective mental disorders, 20 eligible studies are identified to extract data from all studies on research design, sample characteristics, results and feasibility data to conduct a systematic evaluation. Meta-analysis of the results of physical and mental health in randomized controlled trials is also carried out. Exercise intervention has no significant effect on BMI (Body Mass Index), but can improve physical health and other cardiovascular metabolic risk factors. The study found a significant reduction in

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psychiatric symptoms through intervention with moderate to intense exercise for about 90 min a week [5].

The molecular and cellular basis of hippocampal structural and functional abnormalities found in schizophrenia is unclear. Postnatal neurogenesis contributes to the function of the hippocampus in animal models and is associated with the volume of the hippocampus in primates. Decreased hippocampal cell proliferation has been previously reported in schizophrenia, which may lead to hippocampal dysfunction [6]. The hippocampus is involved in cognitive and emotional processes, and deficiencies in both domains are consistently described in schizophrenia. In addition, the entire volume of the anterior and posterior regions of schizophrenic patients is reported to have decreased. Although the number of oligodendrocytes in the posterior left and right corneum CA4 subarea of the hippocampus has been reported to be small, the purpose of this stereological study is to study the number of cells in the dentate gyrus (DG) or the anterior hippocampus [7].

The influence of time complexity of brain regions on adult schizophrenia patients before and after treatment is studied. The results show that there are significant differences between the time complexity of brain of schizophrenia patients after single drug treatment and the time complexity of brain of schizophrenia patients before treatment. These differences are also related to the severity of clinical symptoms, which indicates that the time complexity of brain signals in schizophrenia may be a biomarker for the diagnosis of schizophrenia.

Methodology

Research object and data acquisition

The subjects with adolescent schizophrenia were patients from January 2013 to October 2018 in The Fourth Hospital of Harbin Medical University.

Inclusion criteria: two psychiatrists, schizophrenia patients confirmed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV); total score of PANSS (Positive and Negative Symptoms Scale) more than 60; those who with first onset and course of disease less than two years; Han nationality, right-handed; age range from 12 to 18 years old;

Exclusion criteria: organic brain diseases or other serious or uncontrolled physical diseases; recent alcohol and drug abuse or past drug dependence history; mental retardation; any contraindication of MRI scans; incomplete questionnaires; a total of 35 persons, 19 males and 16 females, as shown in Table 1.

All the subjects are scanned by Siemens 3 T Trio scanner (Siemens Medical System in Ellangen, Germany) in the Second Affiliated Hospital of Xinxiang Medical College, using 8-channel phased array coil.

The T1-weighted three-dimensional images are obtained with the following scanning parameters: repetition time/echo time (TR/TE) = 1900/2.52 ms, 256*256 matrix, flip angle = 9 degrees, voxel size = 1*1*1mm^2 and 158 axial sections, without interlayer gap.

Functional images are captured and used with the following parameters: TR/TE = 2000/30 ms, layer number 33, matrix 64*64 flip angle 90 degrees, FOV = 220*220 mm^2, interlayer gap = 0.6 mm, voxel size = 3.44*3.44*4mm^3. For the subjects, functional magnetic resonance scans last 480 s and 240 whole brain images are obtained.

Clinical symptom evaluation: PANSS is used to evaluate the symptoms. At least one professional psychiatrist is required to complete the scale according to the patient's specific conditions on the same day of the case's MRI scan.

In the health group, volunteers of Han nationality who volunteered through poster information are scanned with patients at the same time. Inclusion criteria: direct relatives such as fathers and children do not have a history of mental illness; do not meet the diagnostic criteria for mental illness in DSM-IV; Han nationality, right-handed; age ranges from 12 to 18 years; data quality problems. A total of 29 participants are enrolled, including 13 males and 16 females, as shown in Table 2.

All participants and guardians need to sign the informed consent after they have a detailed understanding of the study, which is approved by the Ethics Review Committee of The Fourth Hospital of Harbin Medical University.

Introduction to FreeSurfer brain volume calculation

FreeSurfer is a fully open toolkit developed based on Linux platform. It is a software package developed for magnetic resonance data and specially used for data analysis. It is developed by Harvard University in conjunction with other schools. FreeSurfer is also a software package for analyzing and visualizing structural and functional data [8]. It provides a complete set of automatic processing procedures for analyzing structural data of MRI, including image segmentation, registration and three-dimensional reconstruction. The specific processing procedures include skull removal, B1 bias field correction, volume data registration, gray and white matter segmentation, and reconstruction of cortical surface model, subcutaneous and super-cutaneous structures numbering, non-linear registration, and statistics of morphological differences. It is a software of human connection project designated analysis structure MRI, which is widely used in brain structure analysis. It can process brain MRI images conveniently and generate high-precision gray and white matter segmentation interface and segmentation interface between

Table 1 Demographic, clinical data and volume statistics of hippocampus between patients and control groups

	Enrolled Participants				Difference	
	Schizophrenia		Normal Person			
	Mean	Variance	Mean	Variance		
Demographics						
Age	15.57	1.82	1.32	1.22	T = 0.45	$P = 0.66$[a]
Gender: Male Female)	19/16		13/21		$X^2 = -0.567$	$P = 0.45\ 1$[b]
Course of Disease (Month)	5.97	6.33				
Hand (Right/Left)	35/0		29/0			
L Land Bed Symptoms						
Positive Symptoms	21.23	5.65				
Negative Symptoms	19.21	7.44				
General Score	43.22	5.98				
Total Score	31.32	10.54				
Speech Memory	23.43	5.22				
Simple Visual Memory	54.22	5.89				
Brain Structure Volume						
Left Hippocampal Volume	4321.11	396.41	4297.74	345.42	T = 0.76	P = 0 .23[a]
Whole Brain Volume	1,283,627.111	150,499.63	1,430,120.62	128,049.46	T = 0.72	P = 0 .24[a]
Left Hippocampal Volume (Return To The Whole Brain)	−72.22	319.04	90.16	299.62	T = 2.13	$P = 0.019$[a]

a means double sample T test and b means chi-square test

gray matter and cerebrospinal fluid. Based on these two surfaces, the software can calculate the cortical thickness, outer surface area, curvature and gray matter volume at any location on the cerebral cortex. The surface of cerebral cortex can be visually displayed by white matter structure expansion algorithm. In addition, Freesurfer also has the function of analyzing the differences between groups of data features and visualizing the results. In image processing, Freesurfer can transform the images into visual images that users can intuitively feel.

Results and discussion

Computation and analysis of hippocampal volume by FreeSurfer

Many evidences have shown that there are abnormal changes in the brain structure of schizophrenic patients, including hippocampus, which seriously affect their cognitive function and hinder their normal life. At present, the relationship between the volume changes of hippocampus and the symptoms and

Table 2 Demographic and clinical data

	Normal people ($n = 38$)	Therapeutic ($n = 34$)	After treatment (n = 34)	Statistics	
Demographics					
Age	24.76 ± 4.56	25.76 ± 4.39	1.32	−0.48	0.635[a]
Gender (Male, Female)	25/13	21/13	13/21	0.13	0.723[c]
Course of Disease (Month)	38	34			
Hand (Right/Left)		7.90 ± 2.56	29/0		
L Land Bed Symptoms					
Positive Symptoms		92.76 ± 22.34	66.86 ± 10.34	−10.09	<0.001[a]
Negative Symptoms		26.59 ± 3.52	29.34 ± 3.21	−10.75	<0.001[a]
General Score		19.23 ± 5.67	17.13 ± 5.11	−1.80	0.087[a]
Total Score		51.90 ± 4.76	31.22 ± 5.71	−10.30	<0.001[a]

a means double sample T test

cognitive function of schizophrenic patients is still unclear. Therefore, the role of hippocampus in the pathogenesis of schizophrenia is further explored by studying the relationship between structural abnormalities of hippocampus in adolescents with schizophrenia and their symptoms and cognitive function.

In order to measure the volume of hippocampus, FreeSurfer software (running on Linux system) is used for automatic segmentation of T1 data and probabilistic region of interest (FreeSurfer 5.2.0, http://surfer.nmr.mgh.harvard.edu/).

In short, the pre-processing includes image head-movement correction, standardization to Talairach space, and removal of non-brain tissue. Next, based on the probability information estimated from the training set, the neuroanatomical label is automatically assigned to each voxel in the volume of the MRI. In order to obtain the linear optimal transformation, the program uses the spectrum constructed by the manual labeled image to maximize the probability of the output image, thus calculating the linear transformation. The maximum posterior estimate of the label is determined by Bayesian segmentation. The estimated volume of each brain region is stored directly in the aseg. Stats file. The volume of the hippocampus studied is also extracted from it. The estimated total intracranial volume is recalculated using the talairach. Xfml file.

FreeSurfer divides the image by automatic segmentation and the segmentation process is divided into two processes. First, it classifies the image based on intensity information. Next, it checks the volume and marks the area containing the same tissue type for further processing. Then, according to each of these "boundary" voxels, the plane orientation is calculated to minimize the intensity change in the plane. Finally, if the in-plane strength shows that the strength of the wrong label or voxel itself is critical, the segmentation decision is adjusted, and the label is modified and mapped to other categories. Based on this idea, three strength-based constants WM_LOWC90WM_HIGH (140) and GRAY_HIGH (100) are defined. These designated white matter minimum strength and maximum strength, and white matter and gray matter overlapping area are processed through GRAY_HIGH greater than WM_LOW. In fact, a series of ambiguous intensity are defined, but not enough to distinguish white matter and non-white matter tissue. Nevertheless, only based on WM_LOW and GRAY_HIGH constants for preliminary segmentation is to obtain the white matter tissue value from WM_LOW to GRAY_HIGH, and the expression $I_0(X)$ of skull removal is obtained as follows:

$$I_1 = \begin{cases} 1, & I_0(x) \in WM\,LOW\,W, M\,LHIGH \\ 0, & otherwise \end{cases} \tag{1}$$

Then, the difference of adjacent voxel labels on images is analysed. Especially those in 3*3*3 neighbourhood which are not the same as central voxel labels, they need to be further processed and analyzed. It is necessary to judge whether further analysis is needed by taking a wide range of threshold values, and the change range of threshold values is 0.2. That is to say, the voxels whose adjacent voxels have different labels are more than 20% of the voxels whose labels are ambiguous than the labels. Further analysis of the voxels at this location deserves our attention. In these cases, most of the voxels are located at the critical positions in different regions. Generally speaking, the voxel A set of fuzzy classification is derived from the following expressions:

$$A = \left\{ X_i \frac{\#\{X \in N | (I_1(x) \neq I_1(x))\}}{\#N(X)} > 0.2 \right. \tag{2}$$

N(x) represents the relative position of adjacent voxels. It divides voxels into two categories, one is that which category has been determined, and the other is that which category is undetermined. Next, the following classification is carried out by using local geometric information, in particular, to classify by determining the maximum plane direction of the local strength value, and using the values and initial labels of the plane containing central voxels. If this location is not at the junction of gray matter and white matter, then their local strength will not be in such a definite direction.

Finally, a complete label is formed by reversing the previously ambiguously classified voxels. The formula is as follows:

$$I_1 = \begin{cases} 1, & I_0(x) \in WM\,LOW\,W, M\,LHIGH \\ 0, & otherwise \end{cases} \tag{3}$$

In the formula, $\tau(X)$ represents the classification of given voxel X, and $I_1(X)$ refers to binary logic negation. Therefore, all voxels are clearly labelled, that is, they are segmented into different categories.

In the data of MRI, the structures of cortical gray matter and subcutaneous gray matter in brain tissues are accurately identified and segmented, and their morphological quantitative analysis is carried out. In order to construct brain area maps of cerebral cortex areas more accurately, foldable cortical models and other tools are put forward in relevant studies, which promotes the further study of brain nerve activity. The current trend is to make further analysis based on the surface features of anatomy.

FreeSurfer often uses recon-all command to restore the brain image. It plays an important role in the cortical reconstruction and restoration of FreeSurfer. The purpose of data reconstruction is to convert the format of original MR data into a format that is easily recognized by FS-FAST software, so as to prepare for image generation and statistical analysis. Reconstruction of cortical surface is a complex process, so it is divided into several self-tasks. Firstly, the non-uniform changes of magnetic field intensity need to be corrected and normalized according to high-resolution T1 data and morphological 3D MRI data. Next, the exocerebral voxels are removed by removing skulls, and then the exfoliated skulls are segmented based on the geometric structure of gray and white matter. The image is normalized again, and then the cutting surface is calculated to separate the cerebral hemisphere and the subcortical structure is separated from the cortical part. This requires that the initial segmentation of the image is used to represent that the empty space in the part representing white matter is filled, so as to obtain the filling image of each cortical hemisphere. The final image obtained is smoothed to make the final image more complete.

Statistical analysis

Under the SPSS 20.0 software environment, the age of the two groups is tested by double-sample T test, and the gender difference between the two groups is tested by x^2 test, and $P < 0.05$ indicates that the difference is significant. Similarly, the structure and volume of left hippocampus of schizophrenic patients and normal people are compared by double-sample T test, and the difference between the two groups is significant when $P < 0.05$. The correlation analysis is made between the left hippocampus and age and clinical scale, and $P < 0.05$ is set as having statistical significance. Considering the effect of whole brain volume, the left hippocampal volume used in the statistical analysis process is regressive to the whole brain volume.

Difference analysis and comparison

After statistics, the results show that the age of the patients and the normal group match each other, that is, $P > 0.05$. By comparing the two groups, it is found that the left hippocampal volume of the patients with adolescent schizophrenia is significantly smaller than that of the normal people ($t [35, 29] = -2.115$, $P < 0.05$) (Fig. 1).

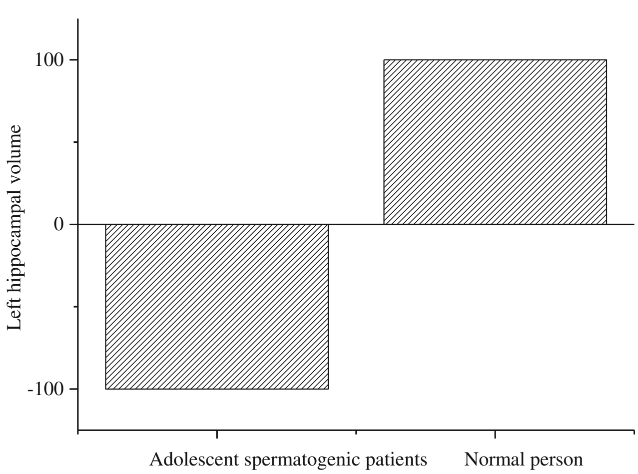

Fig. 1 Difference of left hippocampal volume (returning to whole brain volume) between adolescent schizophrenic patients and normal people

Correlation analysis

The study is conducted to investigate the morphological changes of hippocampus and their relationship with symptoms and cognitive changes in adolescents with schizophrenia who have not taken any drugs for the first time. The results show that the left hippocampal volume of the patients is smaller than that of the normal subjects. It is found that the hippocampal volume of the patients is negatively correlated with age, while the hippocampal volume of the normal subjects is positively correlated with age. Unfortunately, there is no significant correlation. At the same time, it is found that the left hippocampal volume of the adolescent schizophrenic patients is significantly correlated with negative symptoms and speech recordings. The size of hippocampus is inversely proportional to negative symptoms. That is, the more serious the negative symptoms are, the smaller the size of hippocampus is. The size of hippocampus is positively correlated with speech memory. That is to say, the stronger the speech memory is, the larger the volume of hippocampus is. Finally, the relationship among the size of hippocampus, negative symptoms and speech memory is observed through intermediary analysis. It is found that negative symptoms can be significantly correlated with speech memory through hippocampus, a mediator variable, in which the volume of hippocampus returns to the volume of the whole brain.

Similarly, after statistical analysis, it is found that the left hippocampal volume of patients decreases, while the left hippocampal volume of normal people increases with age, as shown in Fig. 2. With the increase of age, it shows an upward trend.

Brain hippocampus is a part of the limbic system of the brain. Its function mainly includes memory, emotional triggering and spatial localization. Two years of random interviews and tests on schizophrenia in early childhood show that the volume of hippocampus of patients changes significantly,

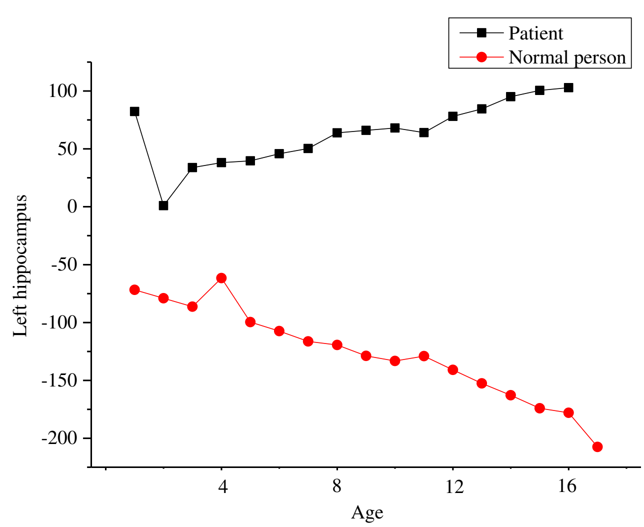

Fig. 2 The correlation between left hippocampal volume (returning to whole brain volume) and age in adolescent schizophrenia

which is significantly lower than that of normal people. Another study is about hippocampal structure in early-onset schizophrenia and it is found that the volume of hippocampus in patients with early-onset schizophrenia is lower than that in normal subjects. It is also found that the volume of hippocampus in patients with early-onset schizophrenia is negatively correlated with the course of the disease. Similarly, it is also found that the left hippocampal volume of adolescents with schizophrenia decreases, and the statistical significance is also obvious. The relationship between the hippocampal volume and age is explored. The results show that the change trend of the hippocampal volume of patients and normal people is different with the change of age. With the increase of age, the hippocampal volume of patients becomes smaller and smaller, while that of normal people becomes higher and higher, but there is no significant correlation. This may be due to the small sample size. In future studies, more sample size brain imaging data may be needed to explore the relationship between structure and age of early-onset schizophrenia patients. To sum up, like previous studies, it is also found that the abnormal volume of left hippocampus of schizophrenia decreases with age through the study of hippocampal morphology in adolescents with schizophrenia. That is to say, the abnormal volume of hippocampus of schizophrenia patients is also related to the age of patients, which may indicate that schizophrenia is a developmental psychiatric disorder, and the brain structure of patients changes with the increase of age.

Next, the volume of the hippocampus is correlated with the negative symptoms, and it is found that the volume of the left hippocampus is negatively correlated with the negative symptoms, as shown in Fig. 3.

In schizophrenia, negative symptoms are a common symptom, which includes indifference to the people around and rigid expression. The severity of negative symptoms is directly related to the patient's illness. The deeper the patient's illness is, the more obvious the symptoms will be. However, some studies have found that the more serious the condition is, the more abnormal changes in hippocampal structure will be, and the memory ability of the brain will be reduced. It is found that the smaller the volume of left hippocampus of schizophrenia is, the more serious the negative symptoms are. This shows that the larger the abnormal volume of hippocampus is, the more serious the patient's condition is, which confirms the previous conclusion. At the same time, it is also found that the abnormal volume of left hippocampus has a significant correlation with the ability of speech memory. The more abnormal the morphological structure of hippocampus changes, the weaker the cognitive and memory function of the patients is, which shows that there is a close relationship between hippocampus and cognitive function.

Finally, by exploring the relationship among negative symptoms, hippocampal structure and memory function, it is found that the negative symptoms of schizophrenia patients are associated with brain memory, and this association is achieved by using hippocampal structure as a mediating variable. This study is the first time to link symptoms, structures and cognition to the brain, and it is found that the symptoms of disease affect the cognitive function related to the structure through abnormal changes in morphological structure, which may provide a new way for the clinical diagnosis and treatment of schizophrenia.

In adults with schizophrenia, the research results show that the complexity of different regions is different (Fig. 4). After drug treatment, the time complexity of the left dorsolateral middle frontal gyrus, left superior temporal gyrus, right inferior temporal gyrus, right posterior superior temporal gyrus, right anterior cuneiform lobe and left thalamus increases in schizophrenic patients compared with that before treatment. In schizophrenic patients, the time complexity of the left dorsal middle frontal gyrus, right anterior central gyrus, left cingulate gyrus and right striatum decreases compared with that before treatment. The abnormal complexity of these regions

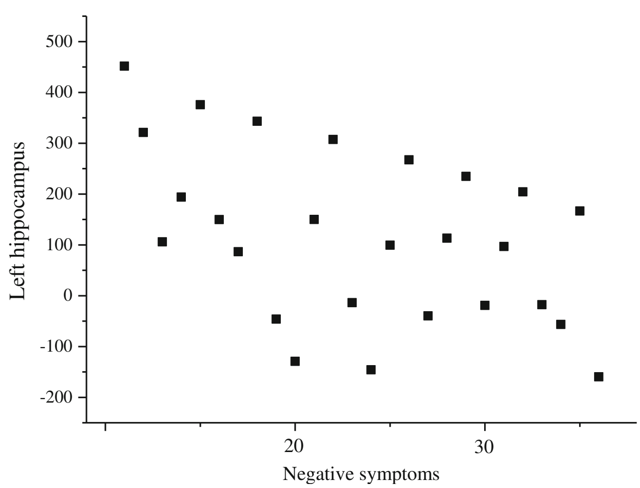

Fig. 3 The correlation between left hippocampal volume (returning to whole brain volume) and negative symptoms in adolescent schizophrenia

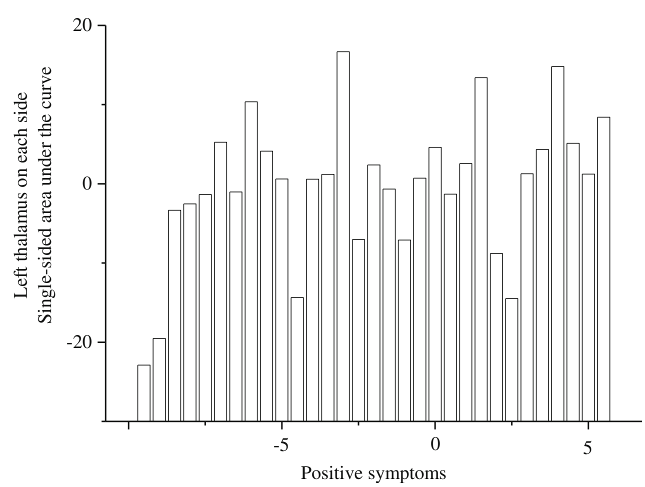

Fig. 4 Changes of left thalamic complexity in adult schizophrenics

indicates that the effects of drugs on the time complexity of the brain in schizophrenics are different for different brain regions. Previous studies of schizophrenia have found that the left thalamus plays an important role in regulating sensory input and is associated with information transmission in the prefrontal cortex and marginal structures. Visual, auditory and somatosensory pathways mainly pass through the ventral posterior and geniculate nuclei, and the anterior and dorsal thalamic nuclei are in the same loop. Many MRI studies have found that the sensory signals flowing to the cerebral cortex are filtered through the thalamic region, indicating that the thalamus plays an important role in sensory information processing, and is abnormal in schizophrenia. Recent PET-related studies have found that thalamic metabolic levels in patients with schizophrenia are lower than those in normal subjects.

Morphological studies have also shown that the thalamic volume of male patients has also decreased, and Sasa et al. found that after four weeks of risperidone treatment, the volume of left and right thalamus of schizophrenic patients has increased significantly, and is significantly related to positive symptoms (mainly auditory hallucinations, hallucinations and thinking disorders). Similarly, the research results also show that patients with schizophrenia have abnormal changes in the thalamic region before treatment. It is found that the time complexity of thalamic region in patients is lower than that in normal subjects. After eight weeks of treatment, the complexity of thalamic region is significantly higher than that in normal subjects. Complexity is an indicator showing signal complexity. Before treatment, the patients with schizophrenia show a significant decrease compared with the control group. This indicates that the disease is the complexity of BOLD signal in the thalamus of patients, that is, the fluctuation of signal is suppressed. This may be because schizophrenia makes the thalamus which filters and processes sensory signals abnormal, which leads to some symptoms of schizophrenia. After eight weeks of one-way treatment with risperidone, it is found that the complexity of the thalamic region in schizophrenic patients increases significantly, which may indicate that risperidone improves the abnormality of the thalamic region, restores its function, filters and processes sensory information normally, and enables the higher cognitive cortex to obtain real and effective information. Moreover, it is found that the time complexity of left thalamus in adult schizophrenic patients increases with the difference of positive characteristics between schizophrenic patients after treatment and before treatment. It is lso found that the time complexity of left thalamus in schizophrenic patients changes with difference of total scores of clinical symptoms between pre-treatment and post-treatment of adult schizophrenia after 8 weeks of treatment with risperidone. These correlations may explain the influence of risperidone on the left thalamic regional complexity and the existence of symptoms in adult schizophrenic patients after thalamic monotherapy.

Conclusion

From the structure of adolescent schizophrenia, hippocampal structure is detected to be abnormal, especially the left hippocampal volume of patients is less than that of normal people. The results show that the left hippocampal volume of normal people is positively correlated with age, and that the left hippocampal volume of schizophrenia patients is negatively correlated with age. At the same time, it is also found that the abnormal hippocampal volume becomes the mediating variable between negative symptoms and speech memory. That is to say, the negative symptoms of schizophrenic patients can affect speech memory indirectly through the change of hippocampal volume, which may indicate that the relationship between schizophrenic patients' symptoms and cognition is established by the change of brain structure. This result proves that the changes of hippocampal morphology in schizophrenic patients may help people better understand the effect of schizophrenia on hippocampal structure. At the same time, this study helps people to understand the relationship among hippocampal morphology, symptoms and memory in schizophrenia, so that people can have a deeper understanding of the role of hippocampus in the pathogenesis of schizophrenia.

Compliance with ethical standards

Conflict of interest Author Xiaohui Zhi declares that he has no conflict of interest. Author Lin Cai declares that he has no conflict of interest. Author Na Guo declares that he has no conflict of interest. Author Xuejia Liu 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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