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IMAGE & SIGNAL PROCESSING

Discussion on the Application of Multi-modal Magnetic Resonance Imaging Fusion in Schizophrenia

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Abstract

In order to study the application of multi-modal magnetic resonance imaging (MRI) fusion technology in schizophrenia, a 4-way multi-modal fusion method based on mCCA+jICA is used to fuse the local consistency and functional network connection of resting-state functional MRI, gray matter volume of structural MRI, and partial anisotropy of diffusion MRI four characteristics of large sample of schizophrenic patients in multi-site China, trying to find out the common characteristics of function and structure of significant differences between schizophrenia and healthy controls. It is found that compared with normal people, schizophrenic patients show higher local consistency, lower gray matter volume, lower functional network connectivity and decreased white matter integrity in the anterior thalamic radiation, upper bundle and other bundles in brain areas such as basal ganglia network, hippocampus and prominence network. There is a significant correlation between a thalamocortical perceptual loop and auditory hallucination in schizophrenia, and there is a high degree of spatial consistency and commonality among the three MRI features. The higher the volume of gray matter in the dorsolateral and medial prefrontal cortex is, the higher the integrity of white matter fibers such as corticospinal tract, superior longitudinal tract and anterior thalamic radiation is, the higher the digital backward score is, and the better the working memory ability of the subjects is.

Keywords MR · Multi-modal fusion · Auditory hallucination · Schizophrenia

Introduction

Schizophrenia is a common severe mental disorder, which often has many obstacles such as perception, thinking, emotion and behavior. Its clinical symptoms mainly include hallucination, delusion, social dysfunction, attention and working memory impairment [1]. The worldwide lifetime prevalence rate is about 0.3–2.0%. Brain is the most complex and efficient information processing system of human body [2]. Anatomical/structural images generally have high resolution, which can provide clear anatomical morphology, but cannot reflect the functional changes of organs; while functional images can provide accurate metabolic information, but their low resolution makes it impossible to provide clear anatomical morphology [3]. In a word, single modal imaging is difficult to reflect the complete information of a specific object of study, but they are complementary to each other. Recent studies have shown that multi-modal images can not only understand the brain from multiple perspectives, but also have certain complementarity. For brain diseases, it is possible to find the commonality between multi-modal images. Combining multi-modal data, the changes of brain connections can be described more comprehensively. To sum up, the use of advanced multi-modal fusion technology can help to mine the crossover information of different modal image data. Multi-modal MRI (Magnetic Resonance Imaging) includes structural MRI, fMRI and diffusion tensor imaging, which can provide clear gray cortex image, functional activity information and white matter fiber image [4]. It opens up a new way for the study of mental disorders, thus finding the commonality among different modes of schizophrenia and can increase

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the understanding of the pathological mechanism of schizophrenia in many ways.

Methodology

According to the use of assumptions or not, multi-modal fusion methods can generally be divided into model-driven methods and data-driven methods. These multi-modal fusion methods are described in detail below [5].

Hypothesis-based method

As the name implies, hypothesis-based methods are based on certain hypothetical conditions, such as the specific impact of one brain area on another brain area, to establish a mathematical model, and then carry out simulation experiments and clinical experiments for verification. According to different hypothesis conditions, there are three main hypothesis-based multi-modal fusion methods: general linear model, dynamic causal model/state space model, and structural equation model. They have some obvious advantages: being able to test hypotheses related to interactions between different networks or regions; being able to evaluate multiple connections at the same time, rather than just one-to-one covariance [6].

General linear model: In machine learning used for fMRI data analysis, general linear model is a common choice because of the high ratio of data features (voxels) to samples (scanned subjects). A standard linear model can be expressed as:

$$o = y(x, w) + \varepsilon \tag{1}$$

In Formula (1), $y(x, w)$ is a deterministic input-output mapping part and εrepresents measurement noise. The deterministic mapping can be modelled as follows:

$$y(x, w) = w^T \phi(x) \tag{2}$$

In Formula (2),ϕ:$R^V \rightarrow R^M$ indicates the mapping from the V-dimensional space of x to the M-dimensional space, w represents the M-dimensional parameter vector, and T represents matrix transpose transformation.

Dynamic causality model: The dynamic causality model used in the field of neuroimaging is originated from the state space model in the field of control. It was first proposed by Friston et al. in 2003 [8], and then widely used to fuse fMRI with EEG or MEG data, thus helping to understand the brain network dynamics in various functional systems.

In neuroimaging research, dynamic causal model is often used to fuse EEG/MEG and fMRI data. It combines hemodynamic model with neurodynamic model to accurately describe the process of neuron activation to BOLD (Blood Oxygenation Level Dependent) signal. By measuring the fMRI data, the parameters of the nerve system can be estimated and adjusted. The optimal model can be obtained by optimally fitting the measured fMRI data and hypothesis model, and then the optimal model can be used to verify the theoretical hypothesis [7].

The state equation of neurons is:

$$\dot{z} = F(z, u, \theta) \tag{3}$$

In Formula (3), F is a non-linear function that describes the neurophysiological effects of the activity z and input u of all brain regions on other changes. It is a partial differential of time of $z^{\bullet}$ and θ is a model parameter of the system.

Structural Equation Model (SEM): It is an index for the measurement of hemodynamics and metabolism to assess the effective connections between cortical areas in the nervous system. Covariance represents the degree of correlation between activities between two or more regions. SEMs consist of a set of linear structural equations, which contain observed variables and parameters defining causal relationships between them. Consider a set of variables (expressed as mean deviation) with N observations. SEMs can be expressed as:

$$y = By + \tau x + \varepsilon \tag{4}$$

In the above formula, y denotes m*1 dimension factor (endogenous) variable vector, x denotes n*1 dimension factor (exogenous) variable vector, εrefers to the error vector of dimension equation (random distribution), B is m*m endogenous variable coefficient matrix andτ suggests n*n exogenous variable coefficient matrix.

As mentioned earlier, parameter estimation is usually performed by minimizing the covariance matrix function of an observation value and an implicit value. The most widely used objective function for structural parameter models is maximum likelihood (ML) function:

$$F_{ML} = \log|\Sigma_{\text{mod}}| + tr\left(\Sigma_{\text{mod}}\Sigma_{\text{mod}}^{-1}\right) - \log|\Sigma_{obs}| - p \tag{5}$$

In the formula, tr(.) denotes the trace of the matrix and p denotes the number of observed variables. Σ_{mod} and Σ_{obs} are the covariance matrix implicit in the model and the covariance matrix of the observed values, respectively.

Data-driven method

Although there are many data-driven methods, they are divided into two categories according to whether or not using prior knowledge: Blind method without using any prior knowledge and Semi-blind method with partially using prior knowledge.

Blind method: It is assumed that the multi-modal data set X_k(k = 1, 2 or more, representing the number of modes) is a linear combination of M_k given sources S_k, and that each mixed coefficient matrix (or loading

parameters) A_k is non-singular, satisfying the following linear systems:

$$X_k = A_k S_k, k = 1, 2... \quad (6)$$

mCCA. For the sum of two variables, in order to find the corresponding relationship between them, Hotelling put forward the so-called canonical correlation analysis (CCA) in 1936. Its basic idea is to find the linear combination of sum separately, so that the correlation between them is the greatest, namely:

$$\max_{w1,w2} W_1^T X_1^T X_2 W_2 \quad (7)$$

Supposing that there are m variables, ${}_jX^{'} = ({}_jX_1, {}_jX_2, ..., {}_jX_{pj})(j = 1, 2, ...m)$. Finding the linear relationship among m variables usually involves several stages, and m variables are obtained in each stage.

$$Z^{(S)} = \left({}_1Z^{(S)}, {}_2Z^{(S)}, ...{}_mZ^{(S)}\right) \quad (8)$$

In the formula, ${}_1Z^{(S)}$ is a linear combination, and the variance is 1, the right superscript represents the stage, and the left subscript represents the variable; the variable is obtained by maximizing or minimizing its correlation matrix.

jICA. In order to find the correspondence or add constraints between different modes on the correlation matrix A of CCA, another method calculates on the source according to the idea of blind source separation, such as ICA (Independent Component Analysis). jICA is, based on ICA, firstly to carry out dimension reduction of the data of each mode, then to arrange the dimension-reduced data matrix horizontally, and then to make ICA analysis.

mCCA+jICA. Sui et al. combined the advantages of CCA and jICA, proposed CCA + jICA suitable for the fusion of two modes, which not only guarantees the correspondence between different modes, but also guarantees the independence between the decomposed source components [1]. Subsequently, Sui et al. proposed N-way multi-modal fusion method: mCCA + jICA, which can fuse data of more than two different modes.

Semi-blind method: Semi-blind method mostly uses the second-level fMRI data (3D contrastmap) as input, mainly including parallel independent component analysis (parallel ICA), coefficient-constrained independent component analysis (CC-ICA), PCA with reference (PCA-R) and informed multi-modal partial least squares (PLS) method.

Results and discussion

Multi-modal image data acquisition and processing

There are 605 subjects in this experiment, including 307 schizophrenics and 298 healthy controls, aged between 18 and 45 years old, right-handed, Han nationality, from 4 hospitals in China, The First Affiliated Hospital of Harbin Medical University (Station 1), The First Specialized Hospital of Harbin (Station 2), The School of Basic Medicine at Ningxia Medical University (Station 3) and The Fourth Hospital of Harbin Medical University (Station 4). The study was approved by the ethics committees of the above hospitals, and all the subjects signed the informed consent.

All subjects collected fMRI, dMRI and sMRI data, of which stations 1, 2 and 3 used 3.0 T Siemens TrioTim scanner, while station 4 uses 3.0 T Siemens Verio scanner, and both adopt 8-channel coil of sensor head. To ensure balanced and high quality data acquisition, all four stations use the same scanning protocols developed by experienced experts. The scanning parameters of each modal MRI data are summarized as shown in Table 1.

Feature extraction of each modal image

ReHo calculation: The pre-processing of fMRI data includes: eliminating the first 10 time point images of each subject; time correction; head motion correction; spatial standardization; removing covariates such as head motion parameters; filtering. Next, using the REST toolkit v1.8 (Resting State fMRI Data Analysis Toolkit; http://restfmri.net/forum/REST_V1.8) to calculate the Kendall's coefficient of concordance (KCC) for each individual, also known as regional homogeneity ReHo, which measures the KCC value of each given voxel and its nearest neighbour voxel time series. The formula is as follows:

$$W = \frac{\sum (R_i)^2 + n(\bar{R})^2}{\frac{1}{12}K^2\left(n^3 - n\right)} \quad (9)$$

In the formula, W represents the KCC value of a given voxel, ranging from 0 to 1; R_i denotes the rank sum of the i-th time point; $\bar{R}$ indicates the mean value, K refers to the number of time series in the measured cluster (27 is chosen here, that is, a given voxel plus 26 adjacent voxels); and n suggests the total rank number. Then, an isotropic 8 mm Gauss kernel is used to smooth the ReHo image in order to improve the signal-to-noise ratio (SNR).

Functional network connection calculation based on group ICA: According to the literature of functional network connection analysis based on group ICA, the following data preprocessing is needed before group ICA analysis: deleting the first 10 time point images of each subject; time correction; head motion correction; spatial standardization; space smooth. Then, for the pre-processed fMRI data, group ICA is performed using GIFT (Group ICA Of fMRI Toolbox) software package (http://mialab.mrn.org/software/gift) (Figs. 1).

Table 1 Summary of scanning parameters of modal MRI data

Stations			Station 1	Station 2	Station 3	Station 4
Scanner type	Supplier		Siemens			
	Model		Trio			Verio
Scan parameters	fMRI	Sequence	Single-shotfull k-space EPI			
		TR (ms)	2000			
		TE (ms)	30			
		Time node	240			
		Matrix size	64*64			
		FA (°)	90			
		Layer thickness (mm)	4			
		Layer spacing (mm)	0.6			
		FOV (mm^2)	220			
		Voxel size (mm)	3.44*3.44*4.60			
	dMRI	TR (ms)	7000			8400
		TE (ms)	92		91	
		Voxel size (mm)	2*2*3			
		Layer spacing (mm)	0			
		FA (°)	90			
		FOV (mm^2)	256			
		Matrix size	128*128			
	sMRI	Sequence	MPRAGE			
		TR (ms)	2530			
		TE (ms)	3.44			2.43
		TI (ms)	1100			
		Voxel size (mm)	1			
		FA (°)	7			
		Layer thickness (mm)	1			
		Layer spacing (mm)	0			
		FOV (mm^2)	256			
		Direction	Sagittal			
		Matrix size	256*256			

Note: The First Affiliated Hospital of Harbin Medical University (Station 1), The First Specialized Hospital of Harbin (Station 2), The School of Basic Medicine at Ningxia Medical University (Station 3) and The Fourth Hospital of Harbin Medical University (Station 4); FA: flip angle; TR: repetition time; TE: echo time; TI (inversion time); FOV (field of view)

Standardization and station image correction

After extracting ReHo, FNC, FA (Fractional Anisotropy) and GM (Gray Matter) features from three modal MRI (fMRI, dMRI and sMRI) data, for each feature, each participant obtains a multidimensional brain image (three-dimensional ReHo, FA and GM images, and two-dimensional FNC matrix), which is then drawn into one-dimensional row vectors, and then stacked into a matrix according to the participants, whose dimension is 605*[voxel number or the number of functional connections] so that a total of four feature matrices can be obtained.

Multi-modal fusion analysis based on mCCA+jICA

Fusion analysis: A multi-modal fusion method based on 4-waymCCA + jICA is used and the complementary advantages of two BSS (Blind Source Separation) models: CCA and ICA. Firstly, mCCA is used to find the flexible connection between the features, and then jICA is used to separate the "source components" more accurately and find the common mixing profiles.

By modifying the minimum description length (MDL) algorithm, the number of components of the four features (ReHo, FA, GM and FNC) estimated here is 15, 12, 16 and

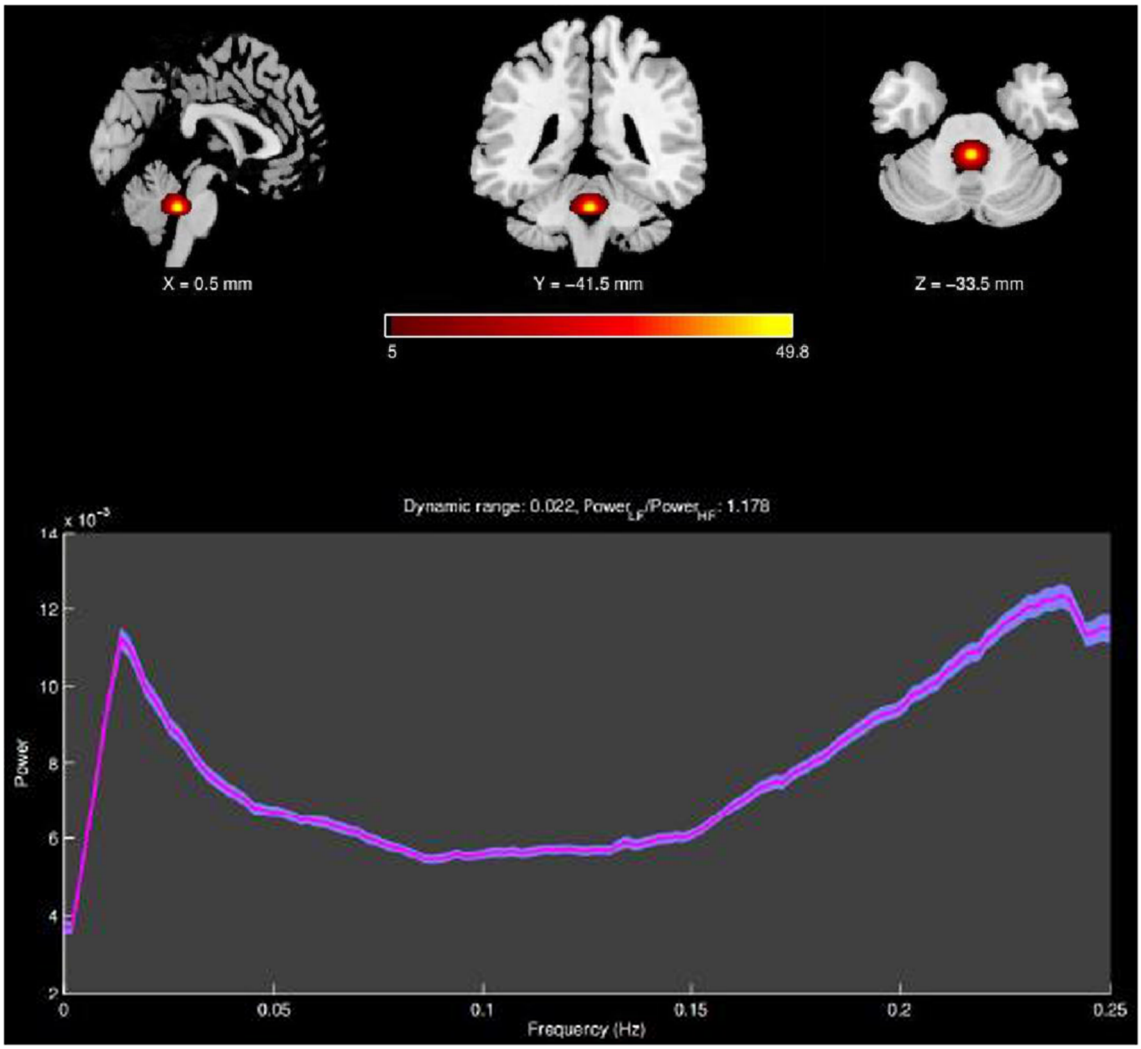

Fig. 1 Excluded independent component cases

12, respectively. The results show that the slight overestimation of the number of components found in the simulation will not affect the results, so the maximum of the four feature estimation components (M = 16) is chosen as the number of independent components.

Post-hoc statistical analysis: After BSS of four features of three MRI modes based on 4-waymCCA+jICA multi-modal fusion method, each feature produces independent components and mixing matrices, which provides us with a variety of methods to analyze the correlation between features and the differences between groups.

Research findings

Results of inter-group differences: After post-hoc statistical analysis of the results of multi-modal fusion, a combined independent component (IC12) is obtained. That is to say, IC12 of the four characteristics ReHo, GM, FA and FNC shows significant mixing coefficients among groups. The two-sample t-test P values of their mixing coefficients are p = 7.7e-15, 1.0e-14, 0.0019, and 1.3e-12, respectively, and all of them pass multiple comparison correction of false detection rates. The abnormal brain areas in the combination of ReHo and GM are mainly located in the hippocampus, parahippocampal gyrus, anterior cingulate zone and spindle gyrus. For the characteristic components of ReHo, the schizophrenic patients show higher ReHo in the basal ganglion network including caudate nucleus, putamen and globus pallidus, as well as in the dorsolateral prefrontal cortex. For the characteristic components of GM, the patients have lower GM volume in insula, superior temporal gyrus, temporal pole and inferior parietal lobule than the healthy controls. For the characteristic components of FA, the main white matter bundles, especially the anterior thalamic radiation, forceps, right cingulate and right superior longitudinal bundle, have lower FA values in the patient group.

Result related to symptom score: Among the independent components with significant difference between groups, the

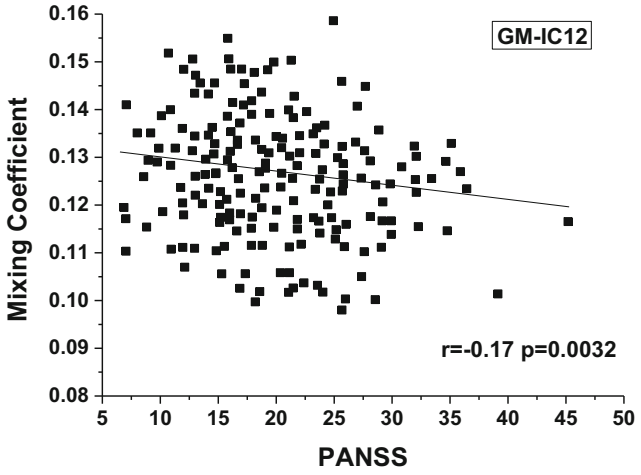

Fig. 2 Scatter plots of components significantly associated with negative symptoms

gray matter component is negatively correlated with the negative symptom score in PANSS (Positive and Negative Symptoms Scale) ($r = -0.17$, $p = 0.0032$, corrected by FDR multiple comparison), as shown in Fig. 2.

In addition, there is a significant negative correlation between the three components and the score of auditory hallucination scale (Reho_IC8: $r = -0.21$, $p = 0.02$; GM_IC13: $r = -0.25$, $p = 0.005$; FNC_IC1: $r = -0.18$, $p = 0.0045$), as shown in Figs. 3, 4 and 5. It can be found that the spatial map of ReHo and GM components is very consistent with the key nodes of functional connectivity network, that is, the abnormal brain areas (nodes) are mainly located in the prefrontal cortex, thalamus, insula and superior temporal gyrus. These regions are found to be related to the production of hallucinations. It can also be found that the lower the ReHo of prefrontal cortex is, the lower the volume of GM is, the weaker the functional connectivity is, and the more serious the auditory

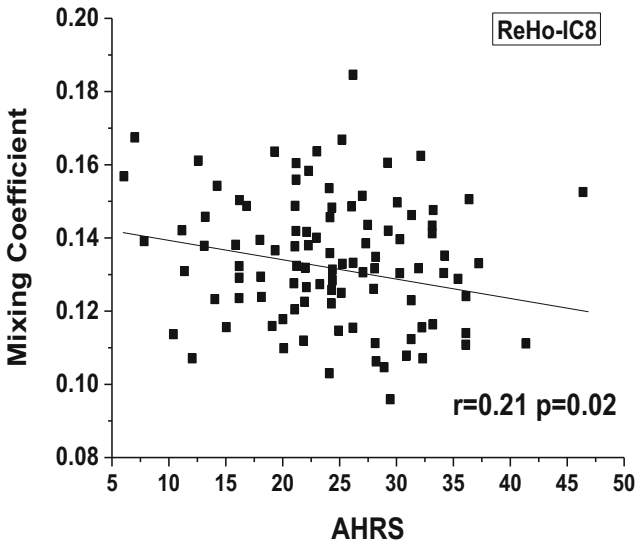

Fig. 3 Components of ReHo-IC8 related to auditory hallucination score

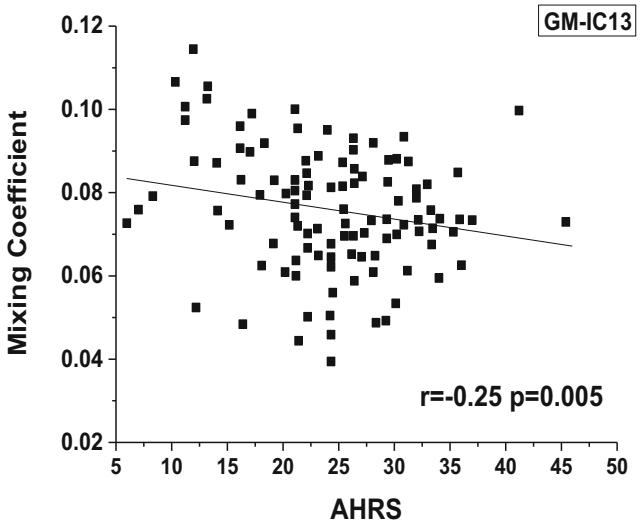

Fig. 4 Components of GM-IC13 related to auditory hallucination score

hallucination is (the higher the auditory hallucination score is); this is also related to the higher ReHo and stronger functional connectivity of thalamus and superior temporal gyrus, and the lower volume of GM in superior temporal gyrus. It is noteworthy that in the paired modal correlation analysis of the three components of interest, it is found that the ReHo-GM modal correlation is the most significant ($r = 0.14$, $P = 6.1e\text{-}4$).

Result related to cognitive score: There is a significant positive correlation between the two components and digital breadth backward score (GM_IC13: $r = 0.14$, $p = 0.00096$, FA_IC5: $r = 0.15$, $p = 0.00062$). Higher digital breadth backward score indicates better working memory performance. It is worth noting that, taking patients and healthy controls as covariate regression, after partial correlation analysis, the correlation is still obvious (GM: $r = 0.13$, $P = 0.004$; FA: $r = 0.175$, $P = 5.9e\text{-}05$). It can be found that the GM components are negatively correlated with auditory hallucination scores

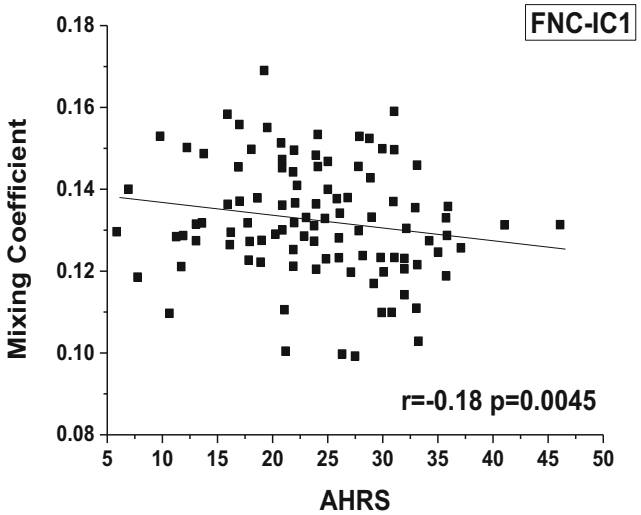

Fig. 5 Components of FNC-IC1 related to auditory hallucination score

and positively correlated with digital breadth inverted back scores. The brain areas involved are mainly located in the dorsolateral prefrontal cortex and medial prefrontal cortex, while the FA components are covariant in white matter fibers such as corticospinal tract, superior longitudinal tract and thalamic anterior radiation, i.e., the better the white matter integrity of these fibers is, the higher the digital breadth inverted back scores are (corresponds to better performance of working memory). Interestingly, the modal correlation between the two components is very high and significant ($r = 0.22$, $P = 2.6e\text{-}08$).

Analysis and discussion of multi-modal fusion results

Commonality of function and structure: Compared with healthy control group, schizophrenia patients have increased ReHo, reduced GM volume and lower white matter integrity. The findings support the widespread hypothesis of functional and structural disconnection in schizophrenia. This study also found a significant correlation between the GM components in the combined components and the negative symptom scores, as well as the significant correlation between the different characteristic modes of the combined components, indicating that the coexistence of multiple imaging modes is related to the clinical symptoms of schizophrenia. In the widely distributed brain network, the subcutaneous network including hippocampus, putamen and caudate nucleus shows the most serious damage, and a variety of imaging features are abnormal. It is also found that the medial prefrontal lobe, as part of the default network, also shows significant differences between schizophrenic patients and healthy controls. Therefore, the functional coupling of hippocampus and prefrontal lobe in resting state indicates that they together lead to confusion in cognitive process of schizophrenic patients.

Secondly, the basal ganglion network, mainly the striatum, receives the afferent signals from different cerebral cortex regions and sends the mapping back to the cerebral cortex through the thalamus. This nerve loop is the basis of various functions of the basal ganglion, including motion, cognitive control, motivation and emotional processing. In different states, schizophrenic patients are frequently reported with abnormal functions of this loop. The study shows that schizophrenic patients have increased ReHo in striatum. In addition, recent studies have shown that striatal dopamine receptors regulate the information transmission of fronto-parietal network (FPN). The FPN consists mainly of the dorsolateral prefrontal cortex and the inferior parietal lobule. The characteristics of ReHo and FNC are also found to be abnormal. In addition to the subcutaneous network, significant functional and structural abnormalities are also found in the salient network composed of insula and anterior cingulate.

Multi-modal co-generative discussions related to auditory hallucination: Although the results of early structural MRI studies on auditory hallucination are quite inconsistent, this may be due to the limitations of the research methods themselves, later studies using more advanced analytical techniques have shown that schizophrenics with auditory hallucinations appear in auditory and speech perception areas, especially in the left temporal transverse/superior gyrus. The volume of GM decreases obviously. Similarly, studies have found that the severity of auditory hallucinations is associated with a decrease in GM volume in these typical areas. In addition to the left temporal transverse/superior gyrus, the areas of GM volume decline associated with auditory hallucination are mainly distributed in two networks: FPN and prominence network, in which FPN is composed of dorsolateral prefrontal cortex and lateral parietal cortex (i.e., inferior parietal lobule), which play an important role in cognitive control and adaptive realization of task requirements. The prominent network composed of islands and anterior cingulates is mainly responsible for controlling and selecting behavior-related events for further processing.

Another important finding is that the brain regions associated with auditory hallucinations have high spatial overlap in functional and structural modes. However, unlike the consistent decrease in GM volume in schizophrenics, the ReHo of schizophrenics shows an opposite trend in different brain regions: the prefrontal lobe decreases, while the temporal lobe and thalamus increase. In addition, when covered with the surface mapping of ReHo feature components, the key nodes of FNC feature components exhibit high spatial consistency with those functional and structural areas significantly associated with auditory hallucination, i.e. the weakened functional connectivity of the prefrontal lobe and the enhanced functional connectivity of the temporal parietal region correspond to more severe auditory hallucination symptoms (higher Auditory Hallucination Scale scores).

Multi-modal confluences related to working memory impairment: A GM component, mainly located in the prefrontal cortex, anterior cingulate, insula and thalamus, is found to be correlated not only with auditory hallucination score, but also with digital breadth backward score. In addition, the brain areas with decreased GM volume are mainly located in the dorsolateral prefrontal cortex, as the core component of the rated network, which is widely believed to be related to the impairment of working memory in schizophrenia.

A FA component including corticospinal tract, superior longitudinal tract and anterior thalamic radiation is also found to be associated with the digital breadth backward score. Interestingly, the bundles found connect the frontal cortex with different subcutaneous or cortical areas, such as the pons/spinal cord through the corticospinal tract, the thalamus through the anterior thalamic radiation, and the temporal and parietal lobes through the upper longitudinal tract. This suggests that the impairment of frontal GM in schizophrenic

patients is mainly involved in cognitive impairment and associated with white matter bundle injury. It is noteworthy that in addition to the upper longitudinal bundle, the bundles found to be related to the digital breadth reversed back fraction have a lateral lesion on the right side of schizophrenia patients larger than that on the left side.

Considering the fact that schizophrenic patient generally needs longer response time and have worse working memory ability, partial correlation analysis is also done. The correlation between GM and FA components and digital breadth score is calculated by using diagnosis as control variable. The results show that their correlation is still significant. In addition, the pairwise modal correlation between the mixing coefficients of the two components which are significantly correlated with the digital breadth backward fraction is also significant. All these indicate that the decrease of frontal GM volume and the damage of white matter fiber bundles are covariant and correlated with the performance of working memory measured by digital breadth backward test. The higher the volume of GM is, the better the integrity of white matter is, and the better the performance of working memory is.

Conclusion

Firstly, schizophrenia patients have higher ReHo of brain function than normal people in subcutaneous nuclei such as caudate nucleus, putamen nucleus, hippocampus and inferior frontal gyrus; lower volume of GM in prominent network including insula and anterior cingulate cortex; lower white matter integrity in anterior thalamic radiation, upper bundles and other fiber bundles; and lower functional network connectivity in basal nucleus network.

Secondly, there is a significant correlation between a thalamocortical perception loop and auditory hallucination score in schizophrenia, and there is a high degree of spatial consistency and coexistence among the three MRI features.

Thirdly, by calculating the correlation between the digital breadth score and the mixing coefficient of multimodal components, GM and FA components are found to be significantly positively correlated with working memory ability. That is to say, the higher the volume of GM in the dorsolateral and medial prefrontal cortex is, the higher the integrity of white matter fibers radiated in the corticospinal tract, the superior longitudinal tract and the anterior thalamus is, the higher the backward score of the digital breadth test is, and the better the working memory ability is.

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Compliance with Ethical Standards

Conflict of Interest Author Xiaohong Wang declares that he has no conflict of interest. Author Na Zhao declares that he has no conflict of interest. Author Jingjing Shi declares that he has no conflict of interest. Author Yuhua Wu declares that he has no conflict of interest. Author Jun Liu declares that he has no conflict of interest. Author Qiang Xiao declares that he has no conflict of interest. Author Jian Hu 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.

This article does not contain any studies with animals performed by any of the authors.

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

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