Auditory Verbal Hallucination-Specific Functional Brain Networks in Schizophrenia: A Study Based on Graph Theory

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Abstract

Background

Although mounting previous studies have characterized auditory verbal hallucinations (AVH) related brain network abnormalities in the patients with schizophrenia, AVH related brain network alterations based on graph theory was rarely reported. In addition, the relationship between the features of AVH related brain networks based on graph theory and clinical features of schizophrenia patients with AVH is unclear. Our study to explore associations among network metrics, and clinical features in schizophrenia patients with AVH.

Method

Thirty-one schizophrenia patients without AVH, 17 patients with AVH, and 31 healthy controls were examined by functional magnetic resonance imaging. Graph theory method was performed to analyze the topological properties of functional network in three groups.

Results

Our results showed that schizophrenia patients with AVH displayed decreased local network efficiency, clustering coefficients, and nodal efficiency of the right dorsolateral prefrontal cortex. Local network efficiency was positively correlated with AVH characteristics.

Conclusion

The topological properties of brain functional networks are disrupted in schizophrenia patients with AVH, suggesting a role of functional brain networks in the pathogenesis of AVH.

Introduction

Auditory verbal hallucinations (AVH) are the perceptions of voice without corresponding external stimuli, are one of typical symptoms of schizophrenia (SZ)[1], affect about 60%-90% patients with SZ[2]. AVH can also occur in other mental disorders including bipolar and major depression disorders, as well as in the general population[3, 4]. At present, the neural basis of AVH is not fully clear. Neuroimaging studies have suggested abnormal brain structure and function in patients with AVH[5].

In recent years, functional Magnetic Resonance Imaging (fMRI) is commonly used to investigate the features of brain activity in schizophrenia patients with AVH. Extensive studies have shown that brain function of schizophrenia patients with AVH differ from those of without AVH and healthy controls[4, 6–8]. For example, a previous meta-analysis indicated that schizophrenia patients experiencing AVH showed

increased activity in Broca's area, anterior insula, precentral gyrus, frontal operculum, middle and superior temporal gyri, inferior parietal lobule, and hippocampus/parahippocampus region[8]. Another literature reported that altered brain resting-state networks between default mode network and cognitive control, salience network[9]. In addition, the abnormal functional connectivity of thalamic is correlated with hallucinations, delusions, and bizarre behavior[10]. Meanwhile, Zhuo *et al.* found that AVH-specific cerebral blood flow was increased in the auditory and striatal areas and decreased in visual and parietal cortices[11]. Structural neuroimaging studies have indicated grey matter volume reductions in the superior temporal gyrus, middle temporal gyrus, left postcentral gyrus, and posterior cingulate gyrus in SZ patients with AVH[5, 12]. Previous study found that AVH-related critical brain regions are mainly located in prefrontal cortex, auditory cortex, superior temporal gyri, insula cortex and anterior cingulate cortex. However, the current study focuses on the interaction of several brain regions, and there are still few studies on the characteristics of the whole brain network in schizophrenia patient with AVH.

Graph theoretical analyses is a powerful tool that can be used to analyze the topological properties of complex brain networks. This method describes brain networks as graphs composed of nodes and edges[13]. Previous studies have indicated that topological properties of brain networks are disrupted in schizophrenia[14]. For example, Zhu *et al.* reported the "small-worldization" and network efficiency of functional networks is decreased in patients with schizophrenia[15].

In this study, to systematically investigate associations among network metrics, and clinical features, we applied the graph theory method to quantitatively analyze functional brain connectivity. Herein, we hypothesized that global and local topological properties of functional network of schizophrenia patients with AVH would be abnormal, and the features of AVH based on graph theory in the patients with schizophrenia would be related to the clinical other features of schizophrenia.

Methods

Participants

Forty-eight patients with schizophrenia (17 with AVH, 31 without AVH) and 31 age and gender matched healthy controls were included. All patients were diagnosed using the Structured Clinical Interview for DSM-IV (SCID). Healthy controls were screened using the non-patient version of the SCID to rule out lifetime psychosis. Symptoms of psychosis were assessed using the Positive and Negative Syndrome Scale (PANSS).[16] The Auditory Hallucination Rating Scale (AHRs) was used to evaluate the severity and characteristics of AVH.[17] Exclusion criteria consisted of: (1) a history of alcohol or substance abuse; (2) MRI contraindications; (3) pregnancy; and (4) a history of brain injury, epilepsy, glaucoma, or diabetes. Our study was approved by the Ethics Committee of Tianjin Anding Hospital, and written informed consent was obtained from all subjects.

MRI data acquisition and preprocessing

Subjects were scanned using a 3T Magnetom Skyra scanner (Siemens, Erlangen, Germany). During the scans, participants were required to relax and to close their eyes and without falling asleep. In addition, sponge pads were used to limit head motion. Resting-state functional magnetic resonance imaging (fMRI) was conducted using an echo-planar imaging sequence (repeat time = 750 ms, echo time = 30 ms, slice thickness = 3, flip angle = 54°, field of view = 222×222 mm, voxel size = 3×3×3 mm³; 480 volumes). All images were visually examined by an experienced radiologist to exclude visible artifacts.

fMRI data preprocessing was performed by Statistical Parametric Mapping software (SPM12, <https://www.fil.ion.ucl.ac.uk/spm>) and GRETNA.[18] Preprocessing included removal of the initial ten images; slice timing correction; realignment to the middle image; spatial normalization of the image to the Montreal Neurological Institute template; re-sampling to 3×3×3 mm³; spatial smoothing with 6 mm³ Gaussian kernel; and band-pass filtration (0.01–0.08 Hz). Finally, white matter, cerebrospinal fluid, and 24-parameters of head motion were regressed out. To minimize the effect of head motion, subjects with a maximum head motion > 2 mm or > 2° were excluded.

Network construction

Construction of functional brain networks and graph theoretical analyses were performed using GRETNA[18]. We utilized the atlas of Dosenbach to parcel the brain into 160 cortical and sub-cortical regions of interest (ROI)[19] that act as network nodes. The atlas has been widely used in the study of brain networks[20, 21]. Averaging time series were extracted from each ROI. Pearson correlation coefficients between each pair of ROI time courses were considered as the edges of functional networks, and represented inter-ROI functional connectivity strengths. This process produced a 160×160 correlation matrix for each participant (Fig. 1).

Brain networks of different subjects differ in the number of significant edges[22]. To ensure that each graph had the same number of edges, we defined a wide range of network cost thresholds. Sparsity is the actual number of edges divided by the maximum possible number of edges in the network[23]. The selection of sparsity is based on the following criteria: (1) the average degree (the degree of a node is the number of edges linked to the node) of overall nodes in each threshold network was larger than $2 \times \log(N)$, where N is the number of nodes; and (2) the small-worldness of the threshold networks was larger than 1.1 for each subject[24]. According to these criteria, cost thresholds ranged from 0.03 to 0.30, with step = 0.01.

Network metrics

We calculated both global and local characteristics of functional networks at each sparsity threshold. The network metrics included: (1) small-world characteristics involving small-worldness (σ), clustering coefficient (C_p), characteristic shortest path length (L_p), normalized clustering coefficient (γ), normalized characteristic pathlength (λ), (2) network efficiency related global efficiency (E_{global}), and local efficiency (E_{local}). The local characteristics included node efficiency (E_i), nodal clustering coefficient (C_i), and node degree (S_i)[25, 26]. C_p measures the local cliquishness of network, and quantified the local

interconnectivity of a network. L_P represents the overall routing efficiency of a network. γ is C_P of real network divided by C_P of random network; λ is L_P of real network divided by L_P of random network. The global efficiency measures the ability of parallel information transmission over the network. The local efficiency indicated the network fault tolerance, reflecting the communication efficiency between the first adjacent nodes when it is eliminated. E_i characterizes the efficiency of parallel information transfer of that node in the network. C_i measures the likelihood its neighborhoods are connected to each other. S_i reflects its information communication ability in the functional network. Finally, we calculated the area under the curve (AUC) for all network metrics at each cost threshold, providing an overall value for the topological characterization of functional brain networks independent of the selected sparsity threshold.

Statistical analysis

One-way analysis of variance was used to examine significant AUC differences between the three groups, and to regress out gender and age. *Post hoc* analyses were performed to test inter-group differences. Multiple comparison correction was used by false discovery rate (FDR, $p = 0.05$). We further evaluated the association between network metrics and AVH by using Spearman's correlation analysis. The above steps were completed with GREYNA[18] and SPSS 23.

Results

Demographic and clinical features

Demographic and clinical features of the three groups are summarized in Table 1. There were no significant differences in age ($F = 2.903$, $p = 0.061$) and gender ($\chi^2 = 0.407$, $p = 0.816$) between the three groups. The AVH and non-AVH (nAVH) groups did not differ significantly in duration of illness ($t = -1.161$, $p = 0.252$) and PANSS total scores ($t = -0.366$, $p = 0.716$).

Table 1

Demographic and clinical characteristics of schizophrenia patients with AVH, schizophrenia patients with nAVH, and healthy controls.

Characteristics	AVH(n = 31) Mean $\pm$ SD	nAVH(n = 17) Mean $\pm$ SD	HC(n = 31) Mean $\pm$ SD	<i>p</i> value
Gender(male/female)	15/16	7/10	12/19	0.82
Age	33 $\pm$ 4.76	35.67 $\pm$ 6.25	32.19 $\pm$ 5.83	0.06
Duration of illness (years)	12.06 $\pm$ 5.24	9.83 $\pm$ 6.83	-	0.25
PANSS total score	52.88 $\pm$ 14.38	51.03 $\pm$ 17.76	-	0.72
Positive symptoms score	14.88 $\pm$ 5.93	10.22 $\pm$ 4.50	-	0.01
Negative symptoms score	14.88 $\pm$ 4.69	15.44 $\pm$ 8.18	-	0.75
AHRS total score	29.59 $\pm$ 6.33	-	-	-
nAVH, no auditory verbal hallucinations; HC, healthy controls; SD, standard deviation; PANSS, positive and negative syndrome scale; AHRS, auditory hallucination rating scale				

Intergroup differences in network metrics

Significant alterations of functional network metrics occurred primarily in E_{local} , C_{net} , and in the nodal efficiency of the right dorsolateral prefrontal cortex (DLPFC) (FDR corrected, $p < 0.05$) (Fig. 2). Furthermore, the AVH group showed lower E_{local} and nodal efficiency of the right DLPFC compared to nAVH groups. Compared with healthy controls, the AVH group displayed decreased E_{local} , C_{net} , and efficiency of the right DLPFC. In addition, decreased E_{local} and nodal efficiency of the right DLPFC was a common abnormality in patients with and without AVH. Reduced C_{net} was the only specific change in patients with AVH. Other network metrics were not significantly different among the three groups.

Relationship between network metrics and AVH severity in AVH group

There were no statistical associations between network metrics and AVH total scores. We further examined the correlation between network metrics and the AHRS checklist, and found that low nodal efficiencies of the right DLPFC correlated with increased amount of distress ($r = -0.743$, $p = 0.001$) and intensity of distress ($r = -0.571$, $p = 0.017$) (Fig. 2).

Discussion

Our study explored the topological organization of whole-brain level functional networks of schizophrenia patients with AVH. Our results indicated that: (1) network metrics including E_{local} , C_{net} , and nodal efficiency of the right DLPFC were decreased in the AVH group; and (2) local network efficiency is negatively correlated with the severity of distress caused by AVH.

Graph theory provides a powerful paradigm for the analysis of the topological organization of complex brain networks in health and in psychiatric diseases[13]. We computed Pearson correlations between different brain regions to act as undirected and unweighted binary graphs for each participant, and compared the network metrics of functional brain networks between the three groups. Schizophrenia patients with AVH had lower C_P and E_{local} than healthy controls. C_P was used to measure the extent of the local connection or cliquishness in a network, thus representing network segregation[27]. The E_{local} indicated the network fault tolerance, reflecting the communication efficiency between the first adjacent nodes when it is eliminated[28]. Our results are consistent with a previous study that showed that schizophrenia patients with and without AVH displayed disruption of “small-world” characteristics and lower network efficiencies relative to healthy controls[15]. A task-related EEG study demonstrated decreased clustering coefficients in patients with schizophrenia, which correlated with increased negative and cognitive symptom scores[29]. Similarly, Liu *et al.* reported decreased C_{net} and E_{local} of functional networks in schizophrenia patients[30]. In contrast, Yu *et al.* found that C_{net} and E_{local} are increased in patients with schizophrenia[31]. In this study, group-independent component analyses were used to deconstruct the brain into independent components and to treat the components as network nodes. The partial correlation coefficients between different components were considered as network edges. Different methods of constructing functional networks may lead to the opposite result. In addition, our study showed that E_{local} is correlated with AVH characteristics. This study further proved that schizophrenia is a disorder of brain connectivity[14, 32].

Our results revealed that schizophrenia patients with AVH exhibited decreased nodal efficiency of the right DLPFC. These findings support previous reports that the functional connectivity of the DLPFC is impaired in schizophrenia[33, 34]. DLPFC is an important part of PFC and plays a role in monitoring speech production in language processing, especially in schizophrenia patients with AVH[35]. Numerous neuroimaging literature demonstrated that the resting-state brain function abnormalities of DLPFC is observed in schizophrenia patients with AVH[36–38]. Cui *et al.* reported that schizophrenia patients with AVH showed increased regional homogeneity in the right DLPFC, and increased in functional connectivity (FC) between left DLPFC and right putamen [39]. Moreover, a previous study indicated that reduced FC between left DLPFC and superior temporal cortex in schizophrenia patients with AVH[36]. Consequently, our results revealed that DLPFC abnormalities might be the underlying neural mechanism of AVH.

Conclusions

Graph theory analysis were performed to examine abnormalities of functional networks in schizophrenia patients with AVH. Schizophrenia patients with AVH exhibited reductions of “small-worldization,” local network efficiency, and nodal efficiency of the right DLPFC. Importantly, the nodal efficiency of the right DLPFC was positively correlated with C_{net} only in schizophrenia patients with AVH. These findings suggest that abnormal functional brain networks constitute the neural basis of AVH in schizophrenia patients.

Limitations

Several limitations of this study should be considered. First, because most patients were medicated, the potential effects of antipsychotic medications on functional brain networks have not been ruled out. Second, because we conducted a cross-sectional study, the evolution of functional network abnormalities over time is unclear. Third, because the duration of illness of all patients was more than two years, some patients may have had AVH that had resolved before study enrollment. Finally, in the sub-group analysis, the number of patients with AVH was small. The sample size should be increased in future studies to improve statistical power.

Abbreviations

SZ

schizophrenia; Auditory verbal hallucinations:AVH; fMRI:functional Magnetic Resonance Imaging; PANSS:Positive and Negative Syndrome Scale; AHRS:Auditory Hallucination Rating Scale; ROI:regions of interest; AUC:under the curve; DLPFC:dorsolateral prefrontal cortex

Declarations

Acknowledgments

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Data availability statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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Author contributions

Weiliang Yang designed the study, writing of the manuscript. Yongying Cheng, Jiayue Chen and Haiyan Cao: recruitment of patients. Yan Li and Shuli Xu: processed the fMRI data, performed the analysis. Wen Qin and Jie Li: reviewed and revised the article.

Ethics approval and consent to participate

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. And the study was approved by the Ethics

Committee of Tianjin Anding Hospital. All subjects provided written informed consent prior to inclusion in the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Design flow chart. First, whole brain was divided into 160 ROIs, and each ROI was considered as a node. Second, we computed the Pearson correlation coefficients between each pair of ROIs, resulting in 160×160 correlation matrices. Finally, the binarization of the correlation matrix was used for graph theoretical analysis.

Figure 2

First row: Clustering coefficients, normalized characteristic pathlengths, and local network efficiencies of functional networks in schizophrenia patients with AVH, schizophrenia patients without AVH, and healthy controls at different cost thresholds. Second row: Comparison of local network efficiencies among the three groups. Third row: Correlation between local network efficiency and AVH characteristics. The red, green, and gray lines represent healthy controls, schizophrenia patients without AVH, and schizophrenia patients with AVH, respectively. AVH, auditory verbal hallucinations. AUC, area under the curve. * represent $p < 0.05$ after false discovery rate correction.