Original Article

Abnormal Degree Centrality of Bilateral Putamen and Left Superior Frontal Gyrus in Schizophrenia with Auditory Hallucinations: A Resting-state Functional Magnetic Resonance Imaging Study

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Abstract

Background: Dysconnectivity hypothesis of schizophrenia has been increasingly emphasized. Recent researches showed that this dysconnectivity might be related to occurrence of auditory hallucination (AH). However, there is still no consistent conclusion. This study aimed to explore intrinsic dysconnectivity pattern of whole-brain functional networks at voxel level in schizophrenic with AH.
Methods: Auditory hallucinated patients group ($n = 42$ APG), no hallucinated patients group ($n = 42$ NPG) and normal controls ($n = 84$ NCs) were analyzed by resting-state functional magnetic resonance imaging. The functional connectivity metrics index (degree centrality [DC]) across the entire brain networks was calculated and evaluated among three groups.
Results: DC decreased in the bilateral putamen and increased in the left superior frontal gyrus in all the patients. However, in APG, the changes of DC were more obvious compared with NPG. Symptomology scores were negatively correlated with the DC of bilateral putamen in all patients. AH score of APG positively correlated with the DC in left superior frontal gyrus but negatively correlated with the DC in bilateral putamen.
Conclusion: Our findings corroborated that schizophrenia was characterized by functional dysconnectivity, and the abnormal DC in bilateral putamen and left superior frontal gyrus might be crucial in the occurrence of AH.

Key words: Auditory Hallucinations; Degree Centrality; Functional Magnetic Resonance Imaging; Resting-state; Schizophrenia

Introduction

Schizophrenia is a severe psychotic disorder, which mainly shows disorder in cognition, thinking, perception, emotion, and behavior.[1,2] 70–80% schizophrenia patients suffer from auditory hallucinations (AHs),[3] which deeply affects their social functions and often results in emotional and behavioral dysfunctions. After decades of neuroimaging studies, evidence concerning with AH has shown that functional abnormalities in distributed networks include voice recognition,[4,5] voice processing,[6] cognitive processing, attention, memory, and emotion.[7,8] However, it is regrettable

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that it still lacks consistent results and remains controversial issue in the neuroimaging bases of AH in schizophrenia.

In recent years, the resting-state functional magnetic resonance imaging (fMRI) has been used as hot neuroimaging techniques in the study of mental disease. The commonly used analysis methods that mainly reflect local or global changes in brain function networks include regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), region-of-interest (ROI) analysis, and independent component analysis (ICA).[9] However, ReHo and ALFF can only reflect local brain neural activity but fail to reflect functional connection (FC) mode. ROI analysis can only reflect two (or some) brains interval FC mode and the ICA fails to reflect the FC strength. Though these methods have been widely used in schizophrenia research, they still cannot sufficiently describe the characteristic of brain network. The graph theory technology has been used to study the topological properties of brain networks, which has provided powerful mathematical tools to study the behavior of complex brain systems of interacting elements.[9]

Based on graph theory, we can process complex brain network analysis such as "small world" properties of brain network. The latest researches show that specific graph metrics can provide new insight into either the local or the distributed interactions occurring in the whole-brain networks.[10] Based on voxel level, degree centrality (DC) technology takes each element as a node, and then calculates the amount of each node connecting with other nodes, indirectly reflecting the position and importance of the node or brain regions in the whole-brain networks.[11,12] Converging evidence indicates that DC, as one of the main measured topological properties in graph theory analysis, is an effective index, which has been widely used to find changes in resting-state functional networks in mental illness.[13-15] A previous DC study also showed that sex-specific patterns of functional aberration existed in schizophrenia, and these patterns were associated with the clinical features both in male and female patients.[13]

In this study, we measured functional connectivity metrics index (DC) across the entire brain networks to get a better understanding of the intrinsic dysconnectivity patterns of the whole-brain functional networks in schizophrenic with AH. We considered that DC, as a novel resting-state fMRI parameter in the voxel-wise whole-brain functional networks, might provide an appealing alternative approach to explore further the neuroimaging mechanism of AHs from a new insight.

Methods

Participants

Eighty-four in patients with Diagnostic and Statistical Manual of Mental Disorder 4th edition (DSM-IV) diagnosis of schizophrenia were recruited from the Mental Health Centre of Renmin Hospital of Wuhan University (Wuhan, China). We used the patient version of Structural Clinical Interview for DSM-IV to determine compliance with diagnostic criteria and the Positive and Negative Syndrome Scale (PANSS)[16] to evaluate clinical features. The patient group was further subdivided into those with and without AHs (42 APG/42 NPG). The standard of classification depended on the score of PANSS as well as detailed information regarding past and present symptoms, which were acquired through examination of patient's medical records and face-to-face interview. In particular, the patients were assigned to the APG group if they scored >4 on item P3 (hallucination) and had been suffering from clinical AH for at least 1 month.[17] The clinical AH was assessed using Hoffman auditory hallucination scale[18] from seven aspects: Frequency, reality, loudness, number of voices, length, attention dedicating to the hallucinations, and hallucination-induced arousal. Then, we calculated the scores of total items to evaluate the general AH severity. By contrast, these NPG individuals never experienced AH during the course of illness. Although the two patient groups had different hallucination ratings, they were matched with PANSS total score, PANSS positive and negative scores. Eighty-four normal controls (NCs) were all right-handed native Chinese speakers, matched on age and gender level. They were carefully examined to exclude the following conditions: A history of neurological disorder, severe medical disorders, substance abuse or dependence, and prior electroconvulsive therapy or head injury resulting in loss of consciousness. The above process was evaluated by a psychiatrist attending physician. The study was approved by the local Research Ethics Committee. Written informed consent was obtained from all participants after a complete description of the study. Detailed clinical and demographical data are presented in Table 1.

Magnetic resonance imaging acquisition

Functional MRI data were acquired from the Radiology Department of Renmin Hospital of Wuhan University by using General Electric HDxt 3.0T Scanner. Whole-brain functional scans were collected in 32 axial slices using an echo-planar imaging (EPI) sequence (time points = 240, repetition time = 2000 ms, echo time = 30 ms; flip angle = 90°; matrix = 64 × 64; field of view = 220 mm × 220 mm; slice thickness = 4 mm; and slice gap = 0.6 mm). All participants were instructed particularly not to focus their thoughts on anything and to keep their eyes closed during the resting state MRI acquisition (8 min and 10 s).

Data preprocessing

All the data preprocessing was performed in MATLAB (MathWorks, USA) using Data Processing Assistant for Resting-State fMRI (R2012a),[19] which is based on Statistical Para-metric Mapping (SPM8) and Resting-State fMRI Data Analysis Toolkit (REST 1.8) (State Key Laboratory of Cognitive Neuroscience and Learning Beijing Normal University, China).[20] The first 5 time points were discarded. Thereafter, the images were corrected for slice timing and head motion. The subjects should have no more than 3 mm maximum displacement in x, y, or z and 3° of angular motion during the scan. The original number of cases was 132. About 48 subjects were excluded due to head motion and 84 subjects were included in the study. Then, functional images were normalized to EPI template (voxel

Table 1: Demographics and clinical characteristics of the participants

Characteristics	NCs (n = 84)	APG (n = 42)	NPG (n = 42)	P
Age (years)	24.69 ± 4.66	24.64 ± 5.24	24.67 ± 5.61	0.999[†]
Sex (male/female)	84 (42/42)	42 (19/23)	42 (21/21)	0.867[‡]
Education (years)*	13.99 ± 1.98	12.33 ± 2.66	11.62 ± 3.18	0.000[†]
Chlorpromazine dose (mg)	–	408.33 ± 220.01	425.60 ± 203.51	0.710[§]
Illness-duration (months)	–	39.24 ± 42.09	49.02 ± 52.16	0.347[§]
P3*	–	5.05 ± 1.08	1.52 ± 0.76	0.000[§]
PANSS total score	–	86.048 ± 12.10	86.048 ± 10.22	0.372[§]
PANSS positive score	–	23.24 ± 3.56	22.74 ± 4.37	0.382[§]
PANSS negative score	–	20.45 ± 5.15	20.55 ± 5.67	0.663[§]
Hoffman score	–	24.83 ± 2.77	–	–

Groups were matched for age, gender. Data were shown as mean ± SD or n.*Patients with AH have significantly higher P3 symptom scores than patients without AH; Normal controls show higher education level than two patient groups. [†]The P values were obtained by one-way ANOVA tests; [‡]The P values for gender distribution in the three groups were obtained by Chi-square test; [§]The P values were obtained by two sample t-test. (*P<0.001). APG: Auditory hallucination patient group; NPG: Nonauditory hallucination patient group; NC: Normal control group; P3: Hallucination score; ANOVA: Analysis of variance; PANSS: Positive and Negative Syndrome Scale; AH: Auditory hallucination.

size: 3 mm × 3 mm × 3 mm).[21] Finally, the normalized images were smoothed with a three-dimensional isotropic Gaussian kernel (full-width at half-maximum: 6 mm). A temporal filter (0.01–0.10 Hz) was applied to reduce low-frequency drifts and high-frequency physiological noise. Recent researches have demonstrated that higher-order models benefit from the removal of head motion effects,[22,23] Therefore, we further characterized the mean frame-wise displacement (FD), which considers measures of voxel-wise differences in motion in its derivation, as a measure of the micro-head motion of each subject.[16] Nuisance regression was performed using white matter, cerebrospinal fluid, global signal, and the mean FD as covariates.[23]

Degree centrality

The DC is a measure to compute the total number of connections. Therefore, it depends on the direct neighborhood of the node, but it is independent of the overall topology of the rest of the network. DC was processed with software REST.[20] An undirected adjacency matrix was then obtained by threshold each correlation at $r > 0.25$.[12,15] Then, DC was computed as the sum of the weights of the significant connections (weighted) for each voxel.[12] Finally, the individual-level voxel-wise DC was converted into a DC Z-score (zDC) map by subtracting the mean DC across the entire brain and dividing by the standard deviation of the whole-brain DC.[23]

Statistical analysis

The zDC maps were entered into SPM8 for group comparison. One-way analysis of variance (ANOVA) was performed to examine differences among NC, APG, and NPG. We computed the mean FD for our data, which provided the temporal derivative of the motion parameters. These mean FD parameters were applied as covariates at the group level comparisons. Meanwhile, taking the difference of education into consideration, we also applied education as covariates. All group tests were threshold at $P < 0.01$, corrected with AlphaSim. For each group, the zDC maps were transferred into Z-scores for group comparisons. Next, *post-hoc* pairwise comparisons were performed to reveal the source of ANOVA difference. Thereafter, we performed correlation analyses between PANSS total score, PANSS positive score, PANSS negative score, and DC values in all patients. In patients with AH, we further examined relationship between Hoffman auditory hallucination score and DC values.

Results

Demographics and clinical characteristics

Groups were matched for age and gender, but the NCs showed higher education level than two patient groups. No significant differences were found in age, sex, average antipsychotic dose, illness duration and PANSS score in two patient groups, but P3 (hallucination) score were significant different between APG and NPG ($P < 0.01$). The clinical profile of the participants is given in Table 1.

Degree centrality

The one-way ANOVA showed that the main group effect was observed in the bilateral putamen and the left superior frontal gyrus [Figure 1 and Table 2]. The following *post-hoc* pairwise comparisons showed that (1) both APG and NPG showed decreased DC in the bilateral putamen compared to NC, but APG exhibited decreased DC more than NPG; (2) both APG and NPG showed increased DC in the left superior frontal gyrus compared to NC, but APG exhibited increased DC more than NPG [Table 3].

Correlations analysis

Pearson correlation analyses showed that: (1) PANSS total score, PANSS positive and negative score were negatively correlated with the DC of the bilateral putamen in all patients [Table 4]. (2) Hoffman auditory hallucination score was negatively correlated with the DC of the bilateral putamen, but positively correlated with the DC of the left superior frontal gyrus in patient with AH group [Figure 2].

Table 2: One-way ANOVA comparison on whole-brain DC map among three groups

Cluster location	Peak MNI			Number of voxels	*F*
	X	Y	U		
Putamen-R	30	−12	3	395	5.25
Putamen-L	−25	15	0	362	4.74
Frontal-sup-L	−12	48	39	382	4.37

The main group effect was observed in the bilateral putamen and the left superior frontal gyrus (cluster threshold at $P<0.01$, AlphaSim corrected. DC: Degree centrality; ANOVA: Analysis of variance; MNI: Montreal Neurological Institute.

Table 3: *Post-hoc* pairwise comparisons of DC Z-score in three groups

Cluster location	NC	APG	NPG	*Post-hoc* pairwise comparisons
Putamen-R*	1.05 ± 0.75	0.17 ± 0.62	0.51 ± 0.76	NC > NPG > APG
Putamen-L*	1.32 ± 0.71	0.44 ± 0.85	0.78 ± 0.75	NC > NPG > APG
Frontal-sup-L*	−0.01 ± 0.48	0.43 ± 0.51	0.20 ± 0.51	APG > NPG > NC

*$P<0.01$. DC: Degree centrality; NC: Normal control; APG: Auditory hallucinated patients group; NPG: No hallucinated patients group.

Table 4: Correlation analyses between PANSS scores and DC values in all patients

Brain area	PANSS score		
	Total	Positive	Negative
Putamen-R			
r	−0.309	−0.314	−0.057
P	0.004*	0.004*	0.605
Putamen-L			
r	−0.256	−0.263	0.103
P	0.019*	0.015*	0.353
Frontal-sup-L			
r	0.075	−0.118	0.075
P	0.499	0.264	0.498

*Pearson correlation $P<0.05$, significant relationship is marked in bold type. PANSS: Positive and Negative Syndrome Scale; DC: Degree centrality.

Discussion

This study examined intrinsic dysconnectivity pattern of whole-brain functional networks at voxel level in schizophrenia patients with AH, patients without AH and healthy controls. Our study shows that schizophrenia is characterized by aberrant intrinsic dysconnectivity from a new insight of topological property. The decreased putamen DC value and increased left superior frontal gyrus DC value in all patients and the relationship between symptoms and DC value are the best evidence. Our findings are in line with the previous fMRI study showing dysconnectivity hypothesis in schizophrenia patients with AH.[24,25] And it also extends these previous findings by showing significant abnormalities of DC in schizophrenia patients with AH as compared to those without AH and healthy controls.

The significantly decreased putamen DC value and increased left superior frontal gyrus DC value in APG reveal that schizophrenia with AH has decreased position of the bilateral putamen and increased position of left superior frontal gyrus in the whole-brain networks. It is noteworthy that the DC can reflect the importance of a node or brain regions in complex brain networks from the point of voxel level, which provide new insight to explore further the imaging mechanism.[26]

As far as we know, the putamen was an important part of the lentiform nucleus, which was a main module of the striatum and highly correlated with amygdala and thalamus participating in the regulation of mood and perception.[11] All of these structures belong to striato-pallido-thalamo-cortical circuits.[27,28] An intriguing speculation is that decreased intrinsic FC (i.e., decreased putamen DC) may result in mood and cognitive dysfunction in schizophrenia patients, which may lead to have difficulties to identify one's own voice from an external source.[29,30] The abnormal putamen DC is not surprising; given previous evidence highlight that putamen contains rich dopaminergic neurons, the function of which has been consistently demonstrated to be impaired in schizophrenia.[31] At the molecular level, hallucinations during schizophrenia might result from altered dopaminergic (DAergic) transmission.[32] Several authors have proposed that abnormal DAergic transmission may indirectly contribute to hallucination by inducing

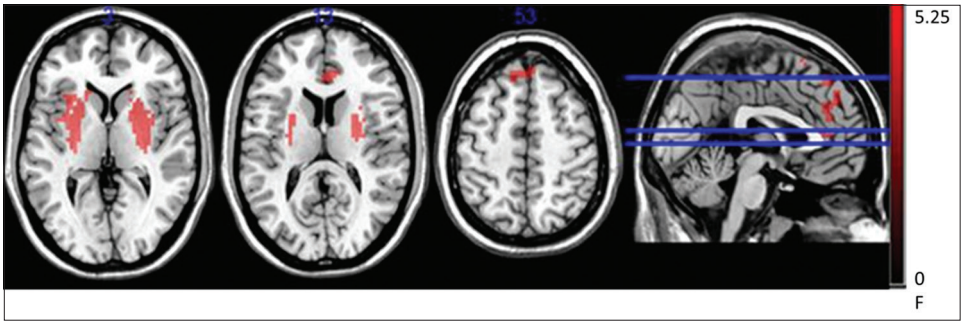

Figure 1: One-way analysis of variance comparison on whole-brain degree centrality map among three groups: The main group effect was observed in the bilateral putamen and the left superior frontal gyrus, and significant abnormal regions are marked in red color (cluster threshold at $P < 0.01$, AlphaSim corrected).

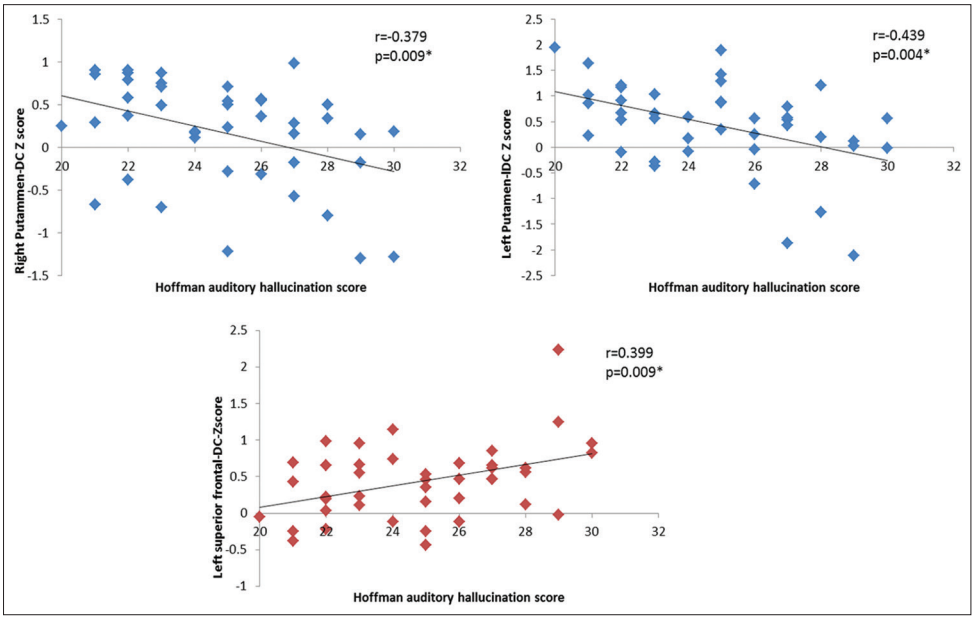

Figure 2: Pearson correlation analyses in patient with auditory hallucination showed that Hoffman auditory hallucination score was negatively correlated with the degree centrality of the right putamen ($r = -0.379$, $^*P < 0.01$; $r = -0.439$, $^*P < 0.01$), but positively correlated with the degree centrality of the left superior frontal gyrus ($r = 0.399$, $^*P < 0.01$).

aberrant salience processes, impairing sensory integration.[33] We summarized that the decreased topological properties of the bilateral putamen within the whole-brain networks might indirectly elicit aberrant DAergic transmission, which involved in the occurrence of the positive symptoms such as AHs. The negative relationship between DC of the bilateral putamen and Hoffman score was the best evidence for this hypothesis. Interestingly, abnormal FC observed in patient with AH mainly included speech-related brain areas such as reduced FC in left superior temporal and anterior cingulate cortex and temporal-parietal cortex.[34,35] However, few FC study reported aberrant FC between putamen and other brain regions in a patient with AH. Based on this current DC study, we highlighted the functional centrality of putamen with the whole-brain network in patient with AH from new insight of topological property, and the decreased topological property of bilateral putamen might be emphasized in occurrence of AH.

Frontal lobe is an indispensable region in the default mode network (DMN).[36] According to reviewing functional connectivity, evidence has revealed that DMN engaged in internally focused tasks such as self-referential processes and autobiographical memory.[37] The frontal lobe, as one of the important network hubs in DMN, has the function of extracting scene memory, integrating emotion and information from external and internal environment, cooperating well with other network hubs of the DMN.[38] The previous fMRI studies have implicated that the frontal region is significantly associated with the spontaneous self-awareness and intrinsic consciousness activity, mediating self-referential, spatial working memory,[39] and self-organized problem solving.[40] The functional connectivity result also revealed that AH was specifically correlated with abnormalities in DMN such as frontal-temporal cortex.[41] It was also noteworthy that APG exhibited increased DC in the left superior frontal gyrus compared with NPG and NC in this study. The result revealed that the left superior frontal gyrus was highly central to the overall connectivity of the network in AH patients as reflected by its elevated DC values. Based on the previous fMRI studies, the left superior frontal gyrus is a significant part of auditory connection cortex, which can receive and integrate all kinds of information from different parts of the brain from inside and outside the body. And, it can also timely organize efferent impulses to ensure the coordination of the central nervous system as a whole.[42,43] A possible explanation for this result was that the increased DC in left superior frontal gyrus might due to feedback inhibition of the over activity in auditory network. In the current study, the positive relationship between DC of the left superior frontal gyrus and Hoffman score also supports this hypothesis.

There are several limitations to this study that warrant further consideration in future research: First, DC technology fails to reflect abnormal FCs vector, such as connection paths and regional interaction. Second, first-episode, drug-naïve schizophrenia patients could be recruited to avoid the impact that antipsychotic medication and other treatment intervention for its possible effects. Meanwhile, DTI Technology can be performed to explore its function connection change in the structure foundation. Also, longitudinal comparative analysis can be used to explore more meaningful research results.

In conclusion, DC as a novel resting-state fMRI parameter in the voxel-wise whole-brain functional networks might provide a new insight to explore further the neuroimaging

mechanism of AHs. The abnormal DC in bilateral putamen and left superior frontal gyrus may be potential biomarker to identify schizophrenia with AH and further to understand the imaging mechanism of AH. Also, this research also provides more evidence of altered brain network properties in all schizophrenia patients.

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Conflicts of interest

There are no conflicts of interest.

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