

Brain function differences in drug-naïve first-episode auditory verbal hallucination-schizophrenia patients with versus without insight

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Abstract

Background: Few studies have reported brain function differences in drug-naïve first-episode schizophrenia patients who had auditory verbal hallucinations (AVH) with insight *vs.* those without insight. This study aimed to investigate brain function differences between drug-naïve first-episode AVH-schizophrenia patients with and without insight.

Methods: Forty first-episode drug-naïve AVH-schizophrenia patients with or without insight and 40 healthy controls between December 2016 and December 2018 were recruited in this study. The auditory hallucinations rating scale (AHRS) was used to assess AVH severity, while the insight and treatment attitudes questionnaire was used to distinguish insight. The global functional connectivity density (gFCD) between different groups was compared using a voxel-wise one-way analysis of covariance. The relationship between gFCD and AHRS total scores were analyzed using voxel-wise multiple regression.

Results: Finally, 13 first-episode drug-naïve AVH-schizophrenia patients with insight, 15 AVH-schizophrenia patients without insight, and 20 healthy controls were included for analysis. Except for global assessment of functioning scores, there were no significant differences in sociodemographic information between the AVH-schizophrenia and healthy groups ($P > 0.05$). Compared to the healthy controls, AVH-schizophrenia patients with insight demonstrated a decreased gFCD in the supra-marginal gyrus within the primary auditory cortex, while those without insight demonstrated an increased gFCD in the inferior frontal gyrus and superior temporal gyrus and decreased gFCD in the supplemental motor area. Compared to the AVH-schizophrenia patients with insight, those without insight demonstrated an increased gFCD in the supra-marginal gyrus and posterior superior temporal lobule and a decreased gFCD in the frontal lobe. No significant correlation between gFCD and AVH severity (AHRS total score: $r = 0.23$, $P = 0.590$; and frequency: $r = 0.42$, $P = 0.820$) was found in both AVH-schizophrenia groups.

Conclusions: The gFCD-aberrant brain regions in the AVH-schizophrenia patients without insight were wider compared to those with insight, although the AHRS scores were not significantly different. The AVH-schizophrenia patients without insight had wide functional impairment in the frontal lobule, which may underlie the lack of insight and the abnormal hyperactivity in the inferior frontal gyrus and temporal lobe related to the AVH symptoms.

Keywords: Auditory verbal hallucinations; Schizophrenia; Insight; Global functional connectivity density

Introduction

The prevalence of auditory verbal hallucinations (AVHs) is reported to occur in 70% of patients with schizophrenia.^[1] AVH is a disabling and even fatal symptom of schizophrenia, as it can cause extreme suffering that leads to self-harm and suicidal behavior.^[1,2] Hence, there is an urgent need to understand the mechanisms of AVHs as well as the pathological features and treatment strategies of AVHs in schizophrenia patients.^[3] The International Consortium

on Hallucination Research investigated AVHs from multiple perspectives in 2013.^[4-6] In the last decade, many studies have focused on investigating AVHs in schizophrenia. These studies have reported many important findings and established hypotheses to explain the mechanisms of AVHs from different perspectives. These studies provided pivotal evidence to further investigate AVHs, particularly co-pathological features and other symptoms of AVHs.^[7-10]

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Previous studies of AVHs in patients with schizophrenia found that poor insight could cause AVH deterioration and increase treatment difficulty. More notably, poor insight and reciprocal AVHs deteriorated over time in schizophrenia; however, good insight could help alleviate AVHs in schizophrenia patients.^[11-13] These studies indicated that the relationship between insight and AVHs could influence treatment outcomes of mental disorders.^[14,15] Some studies have reported that insight accompanied by structural and functional brain alterations could influence treatment outcomes.^[16-18] Other studies reported that some brain alterations influenced treatment efficacy of AVHs in patients with schizophrenia.^[19-23] The abovementioned studies suggested that insight and AVHs were both associated with structural and functional brain aberrations and some aberrant brain regions (temporal lobule, frontal lobule, parietal lobule) that were associated with insight and AVH overlap, which might cause poor insight and persistent AVH reciprocal deteriorations, resulting in treatment difficulty. Conversely, good insight might positively affect AVH treatment in patients with schizophrenia and improve treatment outcomes.^[22-25] Therefore, understanding the common and distinct brain pathological features of insight and AVHs in patients with schizophrenia could help us understand brain functional activity associated with AVHs and insight, and develop personalized treatment strategies.

As a voxel-wise data-driven method, functional connectivity density (FCD) mapping is widely used to test the density distribution of whole-brain resting-state functional connectivity, especially global FCD (gFCD), which can reflect the brain's ability to communicate to different extents.^[26] Thompson *et al*^[27] reported that gFCD could act as a potential biomarker for quantitative state changes in glucose metabolism. In fact, gFCD is usually used to investigate brain functional connectivity alterations in some mental disorders^[28,29] and provides more information to understand aberrant brain function associated with AVHs in schizophrenia.^[30] Thus, in this study, we adopted gFCD to investigate the common and distinct aberrant brain functional patterns in drug-naïve first-episode AVH-schizophrenia patients with or without insight and analyzed the gFCD differences between the two groups.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of School of Mental Health, Jining University. All participants were given detailed information about the study process and purpose and provided signed informed consent before their enrollment in this study.

Subjects

A total of 40 AVH-schizophrenia patients with or without insight *via* advertising recruitment of our hospitalized patients, outpatients and 40 healthy controls from staffs of hospital between December 2016 and December 2018 were enrolled in the study. The inclusion criteria were as

follows: (1) abnormal perception that completely satisfied the AVH criteria such as “Did you at any time hear voices saying quite a few words or sentences when there was no one around that might account for it?”; (2) completely satisfied the schizophrenia diagnosis criteria of the Diagnostic and Statistical Manual and Mental Disorders, 4th edition (DSM-IV), and the structured clinical interview for DSM-IV (SCI-D) was conducted by two senior psychiatrists with more than 10 years' experience; (3) a first episode not treated with any anti-psychotic agents 2 weeks before participating in this study; and (4) intelligence quotient (IQ) ≥ 80 . The exclusion criteria were as follows: (1) patients with other psychotic or affective disorders, mental retardation, alcohol dependence, drug dependence, organic brain lesions, or physical and neurological diseases; (2) with history of unconsciousness for more than 5 min for any reason; (3) contraindications for magnetic resonance imaging (MRI) examination; (4) claustrophobia; or (5) IQ < 80 . All subjects were right-handed. The healthy controls were distinguished by two professional psychiatrists using the SCI-D non-patient version that no psychological symptoms were observed in the last 6 months according to DSM-IV. All psychiatrists were trained to use SCI-D every 2 weeks, and the mean intra-class correlations were all above 0.85.

Assessment of AVH severity

The auditory hallucinations rating scale (AHRS) was used to assess AVH severity in patients with AVH-schizophrenia.^[31] Regarding psychiatric assessments, all subjects were examined by a trained psychiatrist for affective and other psychotic symptoms using positive and negative symptom scales.^[32] Global functioning was estimated using the global assessment of functioning (GAF) scale.^[33] GAF was scored as the highest level of functioning over the past year defined by the lowest score for social, psychological, or professional functioning. Psychiatric disorders in the participants' family members were quantified using the family interview for genetic studies.^[34] Urine samples were obtained to screen for drug abuse (cannabis, amphetamine, cocaine, methadone, heroine, and other substances). A positive screen for any of these substances led to exclusion. Individuals who had family members with psychiatric disorders were also excluded. Regarding insight, the insight and treatment attitudes questionnaire (ITAQ)^[35] was used to distinguish individuals with AVHs with insight from those without insight. ITAQ scores = 22 were defined as good, while ITAQ scores = 0 were defined as no insight. In this study, we excluded subjects with unclear insight or a positive family history.

MRI data acquisition

MRI scans were performed using a 3T GE Discovery MR750 scanner (General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil. The participants were instructed to lie down in a supine position and rest without falling asleep during the scan. Whole-brain resting-state fMRI (rs-fMRI) data depicting blood oxygen level-dependent signals were obtained using a gradient-echo-planar imaging sequence with the

following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 45 ms; slices = 32; slice thickness = 4 mm; gap = 0.5 mm; field of view (FOV) = 220 × 220; matrix size = 64 × 64; and flip angle (FA) = 90°. All scans were acquired by parallel imaging using the sensitivity encoding technique with a factor of 2. Structural images were obtained with a high-resolution 3D turbo-fast-echo T1-weighted imaging sequence with the following parameters: 188 slices; TR/TE = 8.2/3.2; slice thickness = 1 mm; no gap; FA = 12°; matrix size = 256 × 256; and FOV = 256 × 256.

Data pre-processing

SPM8 was used to process the rs-fMRI scans (<http://www.fil.ion.ucl.ac.uk/spm>). To allow for imaging unit stabilization and subject familiarization, the first ten volumes of scans were discarded. The remaining volumes were corrected for slice-timing and motion artifacts. Head translation movement for all participants was <2 mm, while rotation was less than 2°. Covariates including head motion, white matter signal, and cerebrospinal fluid signal were regressed out from the time series of every voxel. The Friston 24-parameter model was used to regress out head motion effects. Next, framewise displacement (FD) was calculated and the data were regressed out of the study if the FD of a specific volume was >0.5. The datasets were filtered with band-pass frequencies of 0.01 to 0.08 Hz. Individual structural images were co-registered to the mean functional image, and the transformed structural images were co-registered to the Montreal Neurological Institute (MNI) space using linear registration. The motion-corrected functional volumes were spatially normalized to the MNI space using parameters estimated during the linear co-registration. Finally, the functional images were re-sampled into 3-mm cubic voxels for further analysis.

Calculation of gFCD

The FCD of each voxel was calculated using an in-house Linux script as previously reported.^[36] Functional connectivity between the voxels was evaluated using Pearson's linear correlation with a correlation coefficient threshold of $R > 0.6$.^[26,36] The gFCD calculations were limited to those voxels within the cerebral gray matter mask, and the gFCD at any given voxel (x_0) was calculated as the total number of functional connections, denoted as $k(x_0)$, between x_0 and all other voxels using a growth algorithm, which was repeated for all of the x_0 voxels. Next, gFCD was divided by the mean value of the qualified voxels in the brain to increase the normality of the distribution. The FCD maps were spatially smoothed with a 6 mm × 6 mm × 6 mm Gaussian kernel to minimize inter-subject differences in the functional anatomy of the brain.

Statistical analysis

Statistical analyses were performed using the IBM SPSS software for Macintosh, version 20.0 (IBM Corp., Armonk, NY, USA). The Group differences in gFCD among the three groups were tested using a voxel-wise one-way analysis of covariance (ANCOVA) with age, sex,

education level, and GAF scores as covariates followed by *post hoc* inter-group comparisons. The *post hoc* inter-group comparisons were conducted within a mask showing gFCD differences from the ANCOVA analysis. To investigate the relationship between gFCD and the insight total scores, a voxel-wise multiple regression analysis was conducted in the AVH-schizophrenia with insight group within regions showing significant gFCD differences *vs.* the other two groups. Sex, age, GAF scores, and education level were considered nuisance covariates. Multiple comparisons were also corrected using family-wise error-corrected method.^[37] Differences in demographic measurements among the three groups were examined using the Chi-square test (sex) or one-way analysis of variance (age) in this study. The differences between patients with AVH-schizophrenia with insight *vs.* those without insight were tested using the two-sample *t* test. The level of significance was set at $P < 0.05$

Results

The MRI data of only 13 AVH-schizophrenia patients with insight and 15 AVH-schizophrenia patients without insight were included in final analysis. MRI data for 20 age, sex, and educational level matched healthy controls were used for comparisons [Figure 1]. Except for GAF scores, there were no significant differences in sociodemographic information between the AVH-schizophrenia and healthy groups ($P > 0.05$) [Table 1].

gFCD analysis

A voxel-wise ANCOVA analysis revealed that the intergroup differences in gFCD were mainly located in the supra-marginal gyrus, primary auditory cortex, inferior frontal gyrus, superior temporal gyrus, and supplementary motor area [Figure 2A and 2B]. Compared to the healthy controls, AVH-schizophrenia patients with insight demonstrated a decreased gFCD in the primary auditory cortex of the supra-marginal gyrus [Figure 2A], while the AVH-schizophrenia patients without insight demonstrated an increased gFCD in the inferior frontal gyrus and superior temporal gyrus and a decreased gFCD in the supplementary motor area [Figure 2B]. Compared to the AVH-schizophrenia patients with insight, the AVH-schizophrenia patients without insight demonstrated an increased gFCD in the supra-marginal gyrus and posterior superior temporal lobe and a decreased gFCD in the frontal lobule [Figure 2C]. Our findings demonstrated that the AVH-schizophrenia patients without insight had wider functional connectivity impairments in most components of the frontal lobule, which might be one reason for the loss of insight.

Another notable finding of this pilot study was that AVH-schizophrenia patients without insight demonstrated an increased gFCD in the inferior frontal gyrus and superior temporal gyrus compared to those with insight. The brain regions of these patients were differently and more widely affected than those patients with AVH-schizophrenia with insight, although the AHRS scores were not significantly different. These findings suggest that AVH-related brain functional alterations in AVH-schizophrenia patients with

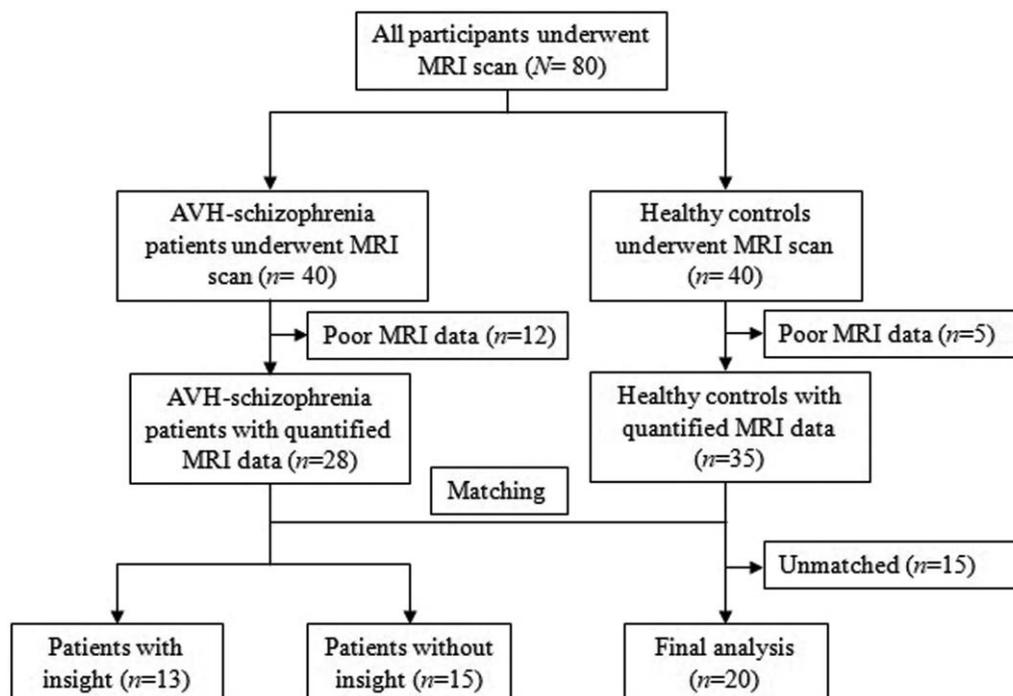


Figure 1: Flow chart of this study. AVH: Auditory verbal hallucination; MRI: Magnetic resonance imaging.

Table 1: Sociodemographic information of all participants in this study.

Characteristic	AVH-schizophrenia patients with insight (n = 13)	AVH-schizophrenia patients without insight (n = 15)	Healthy control (n = 20)	Statistics	P
Age (years)	26.7 ± 4.3	27.1 ± 4.5	28.0 ± 2.1	0.917*	0.577
Female/male	7/6	7/8	10/10	0.259†	0.280
Duration of illness (days)	87.5 ± 15.5	90.0 ± 20.0	N/A	0.701‡	0.572
PANSS score	74.3 ± 6.5	80.9 ± 10.7	N/A	0.260‡	0.213
AHRS total score	24.7 ± 1.5	25.5 ± 2.5	N/A	0.999‡	0.689
GAF scores	77.7 ± 9.5	80.7 ± 10.5	100 ± 0.0	9.432‡	<0.001

The data are shown as mean ± standard deviation or *n*. *One-way analysis of variance among the three groups; †Chi-square test was used to test the difference among the three groups; ‡Two-sample *t* test between the two AVH-schizophrenia patients with and without insight. AVH: Auditory verbal hallucination; PANSS: Positive and Negative Symptom Scale; AHRS: Auditory hallucination rating scale; GAF: Global Assessment of Functioning; N/A: Not applicable.

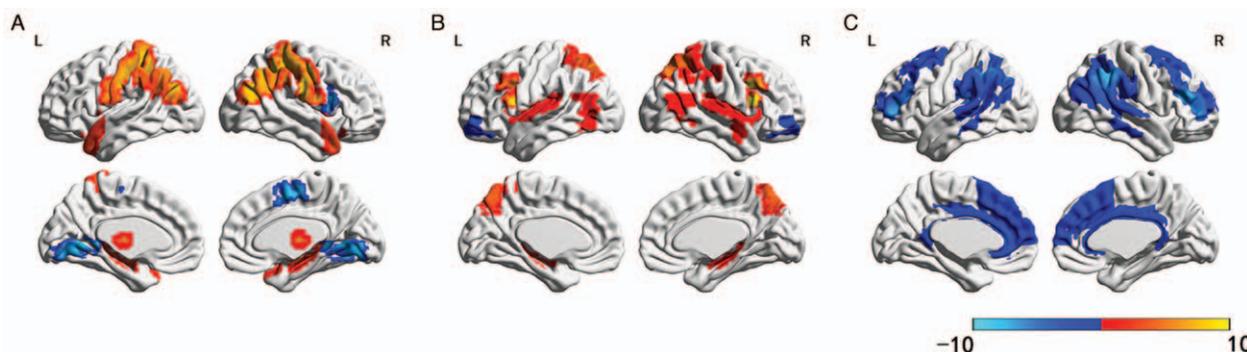


Figure 2: The gFCD alterations in AVH-schizophrenia patients with or without insight, as well as healthy controls. (A) Compared to the healthy controls, AVH-schizophrenia patients with insight demonstrated a decreased gFCD in the primary auditory cortex of the supra-marginal gyrus. (B) Compared to the healthy controls, AVH-schizophrenia patients without insight demonstrated an increased gFCD in the inferior frontal gyrus and superior temporal gyrus and a decreased gFCD in the supplementary motor area. (C) Compared to the AVH-schizophrenia patients with insight, the AVH-schizophrenia patients without insight demonstrated an increased gFCD in the supra-marginal gyrus and posterior superior temporal lobe and a decreased gFCD in the frontal lobule. AVH: Auditory verbal hallucination; gFCD: Global functional connectivity density.

insight *vs.* those without insight might be different. However, because our sample is very small, future studies are needed to validate our findings.

Correlation analysis

There was no significant correlation between gFCD and AVH severity (AHRS total score: $r = 0.23$, $P = 0.590$; and frequency: $r = 0.42$, $P = 0.820$) in the AVH-schizophrenia groups.

Discussion

This small study described the brain functional connectivity alterations in first-episode drug-naïve AVH-schizophrenia patients with or without insight. We found that AVH-schizophrenia with or without insight had different aberrant gFCD patterns and that patients with insight had wider functional activity and metabolism throughout the frontal lobe. The frontal lobe is the pivotal hub of information processing in the brain, and impairments in functional connectivity can influence memory, judgment, analysis, thinking, and operation processing of the brain, subsequently causing disturbances in each area and reciprocally influencing these functions. The abovementioned disturbances cause cognitive and executive dysfunction in patients with schizophrenia.^[38-42] Our findings indicated that lack of insight might be related to functional impairment of the frontal lobe in AVH-schizophrenia patients. Future studies with large-sample sizes are needed to clarify these findings.

Another significant point of this study was that the aberrant brain regions in the patients without insight were wider than those in the patients with insight. AVH-schizophrenia patients without insight demonstrated an increased gFCD in the inferior frontal gyrus and superior temporal gyrus compared to those with insight. The inferior frontal gyrus, superior temporal gyrus, and supramarginal gyrus participate in AVH processing.^[9,43,44] We postulated that the intergroup differences might be related to the pathological features of insight; a decreased gFCD in the frontal lobe might deteriorate the functional activity in the temporal and inferior frontal gyrus, thus the abnormal activity of these regions could not be inhibited, reflected as an increased gFCD in these regions. This postulation requires further studies to clarify, despite many AVH hypotheses supporting the disinhibit postulation. The brain disinhibit hypothesis was postulated to explain one of the sources of AVH, and this hypothesis has been supported by some previous findings.^[45-49] However, these findings were based on patients with anti-psychotic treatment, which might influence brain activity. Hence, “clear” patients are needed to fully explore the source of AVH. In the present study, drug-naïve patients were enrolled to avoid anti-psychotics influence. Our findings provided new evidence on which to base further study.

The third notable finding of this study was that we did not find a relationship between AHRS score and gFCD alterations. Previous studies have reported that the relationship between psychotic symptom severity (such as AVH and delusions) and brain functional connectivity

number/strength was very complex; some studies reported correlations, whereas others did not.^[50-51] Similarly, we did not find any correlations in the present study. Our findings were based on drug-naïve first-episode patients. Therefore, our findings provided some evidence to support the none-correlations concept, which considered symptom-related aberrant brain activity as one of a trait feature, and not state features.

Although we used gFCD analysis in this study to examine the whole-brain intrinsic functional architecture with a sample of AVH-schizophrenia patients with insight *vs.* those without insight, the present study had some limitations. First, the small sample size might limit the significance of our findings, but still provided a path for further study. Second, this was a cross-sectional study, and thus we could not characterize the dynamic trajectory of the brain functional alterations and AVH alterations accompanying treatment. Hence, a cohort study is needed to clarify the trajectory, investigate the precise treatment target, and provide more useful information for clinical practice.

In conclusion, this study found that the gFCD-aberrant brain regions in AVH-schizophrenia patients without insight differed from and were more widespread than those in AVH-schizophrenia patients with insight, although the AHRS scores were not significantly different. AVH-schizophrenia patients without insight had wide functional impairments throughout the frontal lobe, which might be a reason for lack of insight and abnormal hyperactivity in the inferior frontal gyrus and temporal lobe related to AVH symptoms. Despite its limitations, this study provided some important direction for further studies.

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Conflicts of interest

None.

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