Treatment of auditory verbal hallucinations with atypical antipsychotics in healthy individuals: an artificially controlled post-treatment report

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Abstract

Objective: This study was performed to investigate the effects and associated global functional connectivity density (gFCD) alterations associated with the use of atypical antipsychotics in healthy individuals with auditory verbal hallucinations (Hi-AVHs) using gFCD mapping techniques.

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Methods: A magnetic resonance imaging database of 38 Hi-AVHs with chronic or severe AVH symptoms was generated. The Hi-AVHs were administered an atypical antipsychotic (risperidone) for 24 weeks and monitored for a treatment response. All patients underwent functional magnetic resonance imaging pre- and post-treatment.

Results: gFCD alterations were found in the auditory-memory-language and visual circuit regions pre- and post-treatment. However, gFCD alterations differed between patients with strong and weak treatment responses.

Conclusion: This is the first report to show that atypical antipsychotics can improve the symptoms of AVHs and that the treatment effects are associated with gFCD alterations in the auditory-memory-language circuit. These findings provide a foundation for future exploration of new treatment strategies for Hi-AVHs.

Introduction

Auditory verbal hallucinations (AVHs) are defined as the experience of hearing spoken words or sounds in the absence of an actual speaker. This phenomenon is often associated with mental disorders such as schizophrenia, bipolar disorder, borderline personality disorder, major depressive disorder, and post-traumatic stress disorder. While rare, there have also been reports of AVHs in healthy individuals who show no other signs of psychiatric illness or history of mental illness. These healthy individuals with AVHs (Hi-AVHs) have been termed non-clinical AVH subjects. AVHs are often harmful because they can negatively impact patients' social functioning and mental health, which may lead to self-harm and suicide in extreme cases. Although the prevalence of Hi-AVHs in the healthy population has been debated, the estimated prevalence ranges from 0.7% (based on the strictest diagnostic criteria) to 4.0%.[1–3] Serious AVHs can impact multiple neurological functions in Hi-AVHs, which may result in an increased risk of violence, the development of specific disabilities, and potentially death in some individuals.[1–5] Because of the adverse effects that AVHs have on patients' mental health, some clinicians and researchers have expressed an urgent need for treating these patients.

Hence, there is a dire need for researchers to explore the efficacy of current treatment options and the effects of atypical antipsychotics on the associated brain functional alterations in patients with AVHs because this information may be useful in helping physicians optimize future therapies. Several recent studies have proposed the clinical use of atypical antipsychotics for the treatment of patients with post-traumatic stress disorder and borderline personality disorder who experience severe AVHs.[6–8]

While there have been some advances in the treatment of AVHs, advanced magnetic resonance imaging (MRI) techniques have made it possible to observe many of the structural and functional changes that occur in the brain during AVHs. Many studies have shown that AVHs are primarily induced by functional disturbances in

specific brain networks or neural circuits, especially in the regions related to the auditory-memory-language circuit.[8–17]

The global functional connectivity density (gFCD) is an index used to reflect aberrant brain functional connectivity based on connection numbers and can represent the ability to communicate information to some extent.[18–24] The gFCD has been successfully utilized to evaluate functional connectivity alterations in several mental disorders, including schizophrenia, major depressive disorder, borderline personality disorder, and sleep disorders.[25–29] Together, these findings have suggested that FCD mapping may be an effective technique to investigate how atypical antipsychotics affect the associated brain functional activities in Hi-AVHs.

There is currently a need to uncover highly effective therapies for the treatment of AVHs in the general population. In this study, we explored the use of FCD mapping to evaluate the treatment effects and associated gFCD alterations of atypical antipsychotics in healthy individuals with severe AVHs.

Materials and methods

Creation of MRI database

We created an MRI database containing the data from 115 Hi-AVHs with chronic or severe AVH symptoms from August 2014 to August 2018. All Hi-AVHs came from Tianjin districts and some adjacent districts of Hebei Province. The diagnostic criteria were based on the work by Johns et al.[30] The inclusion criteria for Hi-AVHs were as follows. 1) The patient had abnormal perception that completely satisfied the criterion for AVHs by answering "yes" to the following question: "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) According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)

Axis-I and Axis-II system, the patient did not completely satisfy any diagnostic criteria for specific mental disorders; the Structured Clinical Interview for DSM-IV (SCID) was conducted by two senior psychiatrists with more than 10 years of experience. 3) The patient had undergone no treatment with antipsychotic agents for 2 weeks before participating in this pilot study. 4) The patient had an intelligence quotient (IQ) of >80 as assessed by the Wechsler Adult Intelligence Scale–Revised for China. The exclusion criteria were as follows. 1) The patient had other psychotic or affective disorders, mental retardation, alcohol dependence, drug dependence, organic brain lesions, or physical or neurological diseases. 2) The patient had a history of >5 minutes of unconsciousness of any cause. 3) The patient had a contraindication to MRI examination. 4) The patient was claustrophobic. 5) The patient had an IQ of <80. All patients were right-handed. The healthy controls were distinguished by a professional psychiatrist using the SCID for Non-Patients (SCID-NP). The healthy controls answered "no" to the question, "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?" None of the subjects included in this study were undergoing antipsychotic treatment for their symptoms. A flow chart of the present study is shown in Figure 1.

This study was approved by the ethics committee of the Tianjin Mental Health Center (7 July 2013, No. TJMH-2013-NC01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.
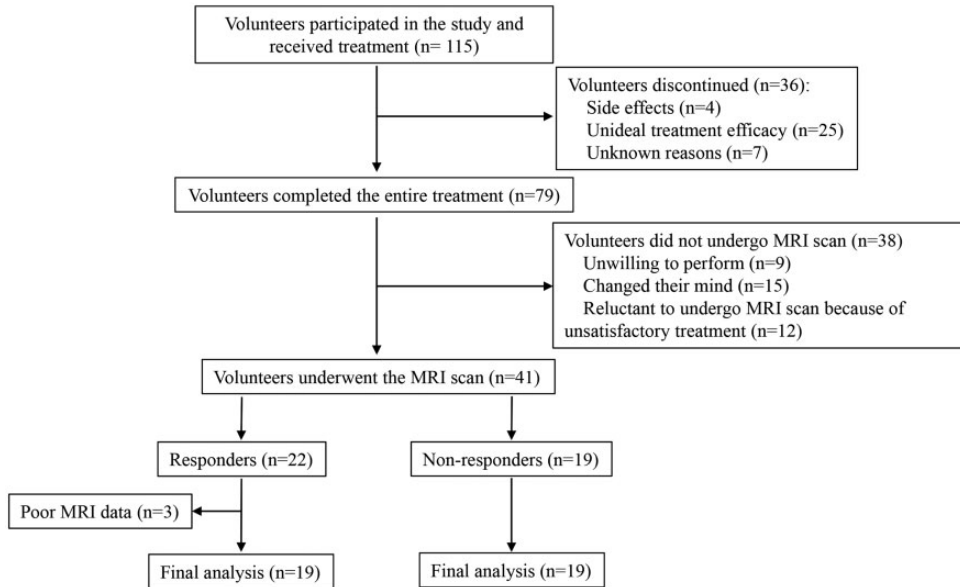
Figure 1. Flow chart of this study. Responders, healthy individuals with auditory verbal hallucinations who experienced obvious improvement after treatment with atypical antipsychotics; non-responders, healthy individuals with auditory verbal hallucinations who did not experience obvious improvement after treatment with atypical antipsychotics; MRI, magnetic resonance imaging.

Table 1. Sociodemographic characteristics and auditory verbal hallucination scores of healthy individuals with auditory verbal hallucinations who experienced obvious improvement after treatment with atypical antipsychotic.

Characteristics	Before treatment (n = 19)	After treatment (n = 19)	t	p
Male sex	5 (26.3)	NA	NA	NA
Age, years	32.5 ± 10.2	NA	NA	NA
Education, years	11.4 ± 2.7	NA	NA	NA
Illness duration, years	5.1 ± 2.0	NA	NA	NA
AHRS score	32.0 ± 9.5	13.5 ± 3.7	17.910	<0.001
PANSS score	50.5 ± 10.5	26.1 ± 4.1	24.036	<0.001

Data are presented as n (%) or mean ± standard deviation.
NA, not available; AHRS, Auditory Hallucinations Rating Scale; PANSS, Positive and Negative Syndrome Scale.

Baseline measurements and treatment strategy

For the baseline measurements, two board-certified psychiatrists assessed the severity of the AVHs using the Auditory Hallucinations Rating Scale (AHRS)[31] and the Positive and Negative Syndrome Scale.[32] The psychiatrists used the SCID-NP to exclude the presence of other

mental disorders, and patients with other neurological diseases were excluded prior to enrollment in the study. The recruited patients were then administered the atypical antipsychotic risperidone (Risperdal®; Janssen Pharmaceutica, Beerse, Belgium) for the treatment of AVHs. The dosage was gradually increased to reach a therapeutic level as determined by the leading psychiatrist using a benefit/risk assessment. After 24 weeks of treatment, the Hi-AVHs underwent reassessment of the AVHs and related symptoms along with a post-treatment MRI scan. The mean dose of antipsychotics was 2.2 ± 0.7 mg, and the average treatment time was 24 weeks. For each group analysis, we regressed out these factors to calculate the gFCD. In total, 79 of the 115 Hi-AVHs with chronic or severe AVH symptoms finished all 24 weeks of the treatment and could be included in the final analysis. Treatment was considered to be obviously effective if the patient's AVH score was reduced by 50%.

To investigate the brain alterations associated with the treatment effect, we used Hi-AVHs who showed significant improvement in AVHs after treatment. The post-treatment outcome analysis is a limitation of this study and will be discussed further in a later section. Table 1 shows the sociodemographic characteristics and AVH scores for patients with obvious improvement after treatment, and Table 2 shows those for patients without obvious improvement after treatment.

MRI acquisition and parameters

MRI was performed on a 3 T 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 the supine position and limit their thoughts and head movements during the scan. The imaging parameters were as follows: repetition time, 2000 ms; echo time, 45 ms; slices, 32; thickness, 4 mm; gap, 0.5 mm; 180 volumes; field of view, 220×220; acquisition matrix, 64×64; and flip angle, 90°. All scans were acquired by parallel imaging using the sensitivity encoding technique with a sensitivity encoding factor of 2. Structural images were obtained with a high-resolution three-dimensional turbo-fast echo T1-weighted imaging sequence with the following parameters: repetition time, 8.2 ms; echo time, 3.2 ms; slices, 170;

Table 2. Sociodemographic characteristics and auditory verbal hallucination scores of healthy individuals with auditory verbal hallucinations who did not experience obvious improvement after treatment with atypical antipsychotic.

Characteristics	Before treatment (n = 19)	After treatment (n = 19)	t	p
Male sex	7 (29.2)	NA	NA	NA
Age, years	33.7 ± 7.0	NA	NA	NA
Education, years	12.6 ± 3.3	NA	NA	NA
Illness duration, years	5.6 ± 3.1	NA	NA	NA
AHRS score	33.6 ± 8.1	23.5 ± 3.6	15.481	<0.001
PANSS score	52.0 ± 10.3	38.4 ± 136	20.369	<0.001

Data are presented as n (%) or mean ± standard deviation.
NA, not available; AHRS, Auditory Hallucinations Rating Scale; PANSS, Positive and Negative Syndrome Scale.

thickness, 1 mm; no gap; flip angle, 12°; acquisition matrix, 256×256; and field of view, 256×256.

Initial processing of functional MRI data

SPM8 (http://www.fil.ion.ucl.ac.uk/spm) was used to process the resting-state functional MRI (fMRI) scans. To allow for stabilization of the scanner and acclimation of the patients to the environment, the first 10 volumes of scans were discarded. The remaining volumes were corrected for slice-timing and motion artifacts. The fMRI data were found to be within the allowable motion thresholds with translational and rotational motion parameters of <2 mm or $2°$. Six of the motion parameters and the average blood oxygenation level-dependent signals of the ventricles and white matter were removed. Next, the framewise displacement was calculated, and the data were regressed out of the study if the framewise displacement of a specific volume was >0.5. The datasets were filtered with band-pass frequencies ranging from 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 a 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 the gFCD

The gFCD of each voxel was calculated using an in-house Linux script, as previously reported.[25–29] Functional connectivity between the voxels was evaluated using Pearson's linear correlation with a correlation coefficient threshold of $R > 0.6$.[25–29]

The gFCD calculations were limited to those voxels within the cerebral gray matter mask, and the gFCD at any given voxel (x0) was calculated as the total number of functional connections, denoted as k(x0), between x0 and all other voxels using a growth algorithm, which was repeated for all of the x0 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 $6\text{-} \times 6\text{-} \times 6\text{-mm}^3$ Gaussian kernel to minimize differences in the functional anatomy of the brain among the participants.

Statistical analysis

Paired t-tests were used to analyze the differences in the alternations of the AVHs and gFCD of the Hi-AVHs who showed improvement with the atypical antipsychotic, both pre- and post-treatment. Because the baseline data of the two groups did not match in the pre- and post-treatment assessment, only the paired t-test could be used to analyze the differences in the alterations of the AVHs and gFCD from each group. Multiple linear regression was used to compare the gFCD alterations while controlling for sex, age, AHRS score, education level, illness duration, and dosage. The family-wise error method was used to correct the gFCD alterations in each group ($p < 0.05$).[25–29]

Results

Only 79 individuals in the database volunteered to receive antipsychotic treatment with risperidone. Of these patients who accepted treatment, only 41 underwent MRI twice. Among these 41 patients, 22 were responders; however, the fMRI data from 3 patients were discarded because of head motion artifacts (>2 mm). Hence, only 19 responders were enrolled in the final
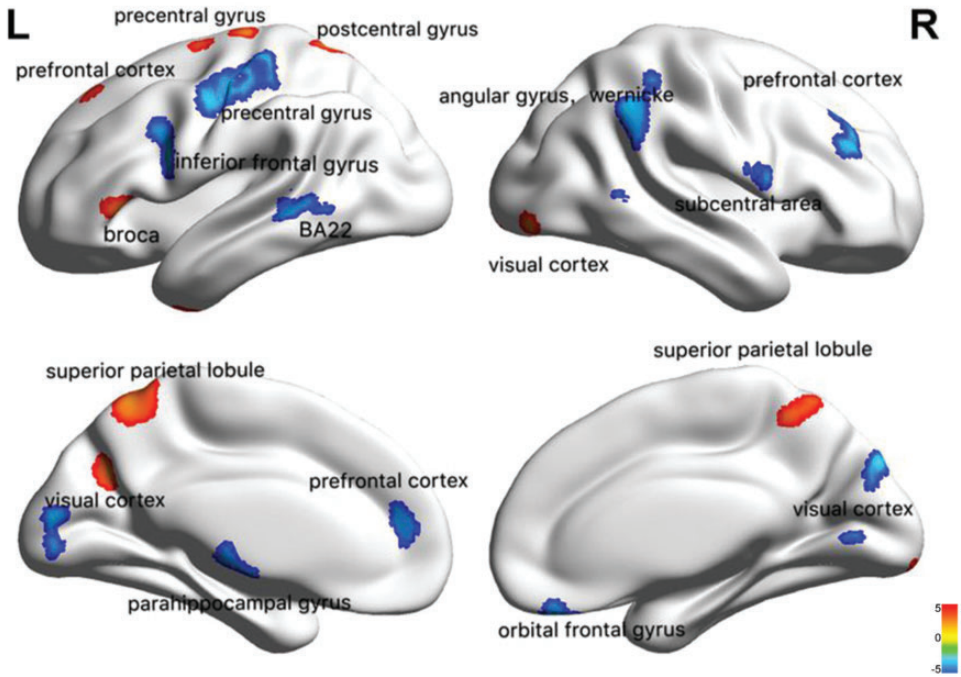
Figure 2. Global functional connectivity density alterations in healthy individuals with auditory verbal hallucinations who experienced obvious improvement after treatment with atypical antipsychotics. L, left; R, right.

analysis. All fMRI data from the 19 non-responders could be used in the final analysis. The demographic parameters, including sex, age, education level, and duration of AVHs, were significantly different between the two groups ($p < 0.05$). Thus, we only compared the brain alterations of each group before and after antipsychotic treatment (n = 19), as shown in Figure 1.

Responders and non-responders were not matched, and there were significant differences in the demographics between the two groups ($p < 0.05$) (Table 1). Post-treatment alterations in the gFCD were widespread in the Hi-AVHs who showed obvious improvements in their AVH-related symptoms. The aberrant gFCD demonstrated an intricate pattern. As shown in Figure 2 and Table 3, treatment-associated reductions in the gFCD were found in the right prefrontal cortex, right

subcentral region, right Wernicke region, right orbital frontal gyrus, right parahippo-campal gyrus, left precentral gyrus, left inferior frontal gyrus, left visual cortex, and left Brodmann area 22 (BA22). However, the gFCD was increased in the right superior parietal lobule, right visual cortex, left superior parietal lobule, left central gyrus, left prefrontal cortex, and left Broca region.

The gFCD alterations were also measured pre- and post-treatment in the Hi-AVHs who did not show obvious improvement after treatment for the AVHs. The aberrant gFCD in this group also demonstrated a complex pattern. As shown in Figure 3 and Table 4, treatment-associated reductions in the gFCD were detected in the right BA17, thalamus (near the callosum), and left prefrontal cortex. However, the gFCD was increased in the right supramarginal gyrus, right prefrontal

Table 3. Brain regions in which aberrant global functional connectivity density was mainly located (see Figure 1).

AAL regions	Cluster size	MNI space		
Left side (lateral view)				
Left prefrontal cortex	25	−33	55	−7
Left temporal pole	15	−55	11	−15
Left middle frontal gyrus	94	−38	12	47
Left temporo-occipital junction	11	−44	−53	5
Left occipital lobe	22	−33	−87	12
Left side (sagittal view)				
	75	−17	13	−3
	273	−17	−29	0
	509	−11	−48	25
Right side (lateral view)				
Right prefrontal cortex	270	23	57	−7
Right inferior frontal gyrus	196	41	15	−3
Right temporal pole	123	44	9	−32
Right occipital lobe	92	24	−95	−15
Right side (sagittal view)				
	199	−14	16	−2
	306	15	−18	5
Right temporal lobe	86	33	3	−26
Right parietal lobe	420	34	−14	34
Right occipital lobe	33	17	−87	6

MNI, Montreal Neurological Institute; AAL, Automated Anatomical Labeling.

cortex, right temporal pole, and left BA7 and BA31.

We compared the gFCD alterations using multiple linear regression while controlling for sex, age, AHRS score, education level, illness duration, and dosage. The responder group was assigned 0 and the non-responder group was assigned 1. The coefficient of this group was statistically significant ($p < 0.001$), indicating a significant difference in the gFCD between the two groups independent of age, sex, education level, illness duration, and symptom severity.

Discussion

In this post-treatment outcome study, we investigated the treatment-associated gFCD alterations in Hi-AVHs undergoing treatment with an atypical antipsychotic. We found that the atypical antipsychotic could improve the AVH symptoms in Hi-AVHs with a response rate of approximately 50%. Our primary finding showed that gFCD alterations caused by treatment with atypical antipsychotics followed an intricate pattern with both increases and decreases in gFCD throughout the brain. More interestingly, the pattern of gFCD alterations differed between the Hi-AVHs with and without an obvious response to treatment. These findings suggest that atypical antipsychotics can induce gFCD alterations in different brain regions, which may be associated with the effects of treatment on AVH symptoms in Hi-AVHs.

Treatment-induced gFCD alterations primarily occurred in specific regions of the brain associated with auditory
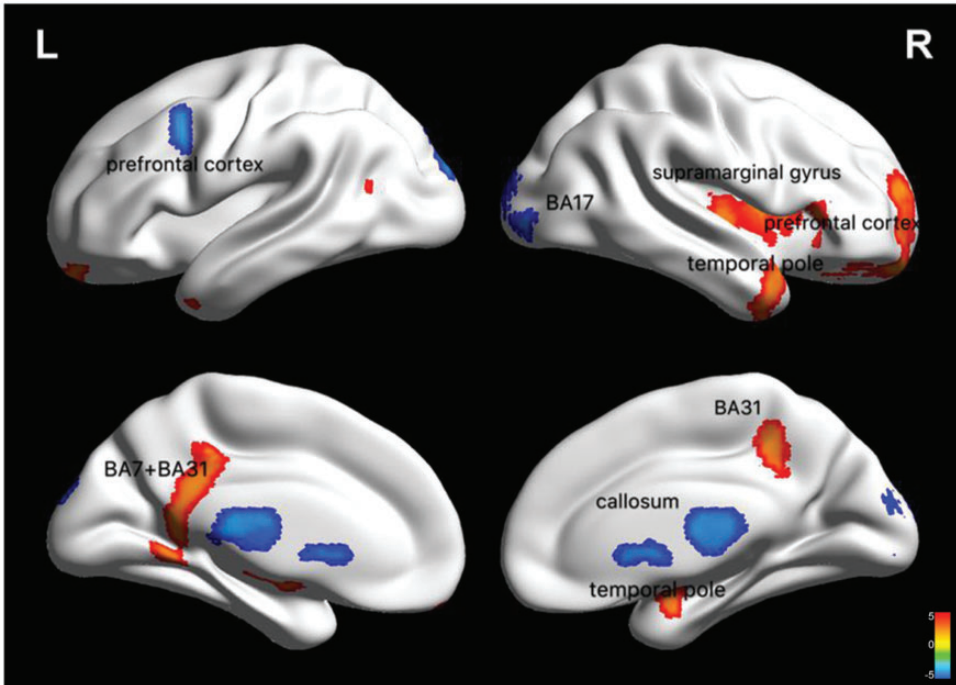
Figure 3. Global functional connectivity density alterations in healthy individuals with auditory verbal hallucinations who did not experience obvious improvement after treatment with atypical antipsychotics. (A black background is used in this figure for differentiation from the individuals with obvious improvement.) L, left; R, right; BA, Brodmann area.

processing (BA22 and the Wernicke region), self-monitoring (superior parietal lobule), processing of visual information (visual cortex), working memory (prefrontal lobe and parahippocampal gyrus), language (supramarginal gyrus, inferior frontal gyrus, and the Broca region), sensory information (thalamus), sensorimotor area (precentral gyrus and postcentral gyrus), and mood states or emotions (orbital frontal gyrus and the temporal pole).[33–35]

The brain regions that exhibited gFCD alterations, as mentioned in the previous paragraph, primarily participated in the sensory, memory, and language processing neural circuits. How atypical antipsychotics can induce these complex alteration patterns (coexistence of increases and reductions) in Hi-AVHs is unclear. Previous studies have shown that AVHs are associated with alterations in many networks, including the auditory, language, and memory networks.[36–40] In agreement with previous studies, our post-treatment outcome comparison also demonstrated alterations in the numbers of functional connections in these networks, providing indirect evidence for the pathological features of AVHs. Our findings also support a previous study showing that AVHs are often associated with disturbances in communication capabilities in patients with schizophrenia.[41]

Our data are partially consistent with a previous study showing that AVHs are associated with brain network alterations in patients with schizophrenia and

Table 4. Brain region in which mainly aberrant gFCD Located (Figure 2).

AAL regions	Cluster size	MNI space		
Left side (lateral view)				
Left superior frontal gyrus	55	−38	33	30
Left central anterior gyrus	58	−30	−24	63
Left parietal lobe	51	−30	−66	52
Left inferior frontal gyrus	54	−58	29	−8
Left middle frontal gyrus	87	−33	12	19
Left central anterior gyrus, posterior gyrus	305	−21	−30	56
Left temporal gyrus	271	−55	−35	−5
Left side (sagittal view)				
Left frontal lobe	198	−12	50	15
Left parietal lobe	89	−9	−11	−10
Left occipital lobe	123	−19	−66	53
Left temporal occipital lobe	77	−18	−75	25
	94	−11	−87	4
Right side (lateral view)				
Right middle frontal gyrus	87	39	28	20
Right inferior frontal gyrus	45	50	4	7
Right angular gyrus	221	43	−52	32
Right occipital lobe	93	39	−78	−6
Right side (sagittal view)				
Right inferior frontal gyrus	52	15	38	−17
Right parietal lobe	89	16	−64	56
Right occipital lobe	75	16	−84	21
Right inferior temporal gyrus	34	29	−82	−9

MNI, Montreal Neurological Institute; AAL, Automated Anatomical Labeling

schizoaffective disorder.[42] The difference in the results may be related to the difference in the sample size between the two studies. The previous study included patients with schizophrenia or schizoaffective disorders, while our participants were Hi-AVHs.

Previous studies have shown that antipsychotics can normalize the abnormal functional connectivity in patients with schizophrenia,[43–45] and some functional connectivity alterations have been correlated with positive symptoms, such as auditory hallucinations, after antipsychotic treatment. Many studies have also revealed that antipsychotics can correct the abnormal metabolism in some brain regions in patients with schizophrenia, leading to an improvement of AVHs. According to the postulation of Hamilton et al.[46] and Thompson et al.,[47] gFCD alternations induced by antipsychotics may normalize the functional connectivity and metabolism in key brain regions. However, this is only a postulation, and further studies are needed to clarify it.

Limitations

This study has several fundamental limitations. First, our definition of Hi-AVHs can be misinterpreted, but we were still inclined to use this definition. Of course, this definition may be temporary and may change over time because of further research findings, similar to the separation of obsessive-compulsive disorder from anxiety spectrum in DSM-V. This condition may be classified differently in the future, such as

"disruptive mood dysregulation disorder" in DSM-V. At present, however, we believe that this optional definition is more effective than other definitions. Simultaneously, according to DSM-IV and International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), the participants of our study may be diagnosed with three codes: (1) DSM-IV Code: 297.3 shared psychotic disorder, detailed in 293.82 (with hallucinations), (2) ICD-10: F99: unspecified mental disorders, or (3) F23.9 acute and transient psychiatric disorders, unspecified. In the present study, we used the term Hi-AVHs to define these subjects, which may be beneficial to the development of this field. Second, the results of our study were obtained from post-outcome analysis, which is considered to be weaker than randomized, double-blind controlled trials. Third, this study did not consider how other factors, such as a family history of mental disorders, may impact the treatment effects in Hi-AVHs. These factors could be confounders and should be evaluated in future studies. Fourth, we did not compare the differences between the two groups (responders vs. non-responders) because the baseline data were not matched. For this reason, we only analyzed the gFCD alterations pre- and post-treatment in each group, which may weaken our findings. Fifth, this study did not focus on structural alterations, which may be more stable than the functional indices. Finally, our study lacked a control group of healthy patients without mental illness or a history of AVHs.

Conclusions

This is the first report to describe the effects of treatment-associated gFCD alterations on AVH symptoms in Hi-AVHs. In this post-outcome analysis, we found that most Hi-AVHs experienced some degree of symptom alleviation by treatment with atypical antipsychotics. More importantly, all of the Hi-AVHs demonstrated post-treatment gFCD alterations, which were primarily located in the auditory-memory-language circuits. These gFCD alterations may reflect specific disturbances in the communication capabilities of these regions. Moreover, the gFCD alterations were more complex in the Hi-AVHs with than without an obvious response to the treatment. Despite the limitations of this study, these findings may provide a baseline for future research focusing on treatment targets or strategies for Hi-AVHs.

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