Schizophrenia

ARTICLE OPEN

Common and unique white matter fractional anisotropy patterns in patients with schizophrenia with medication-resistant auditory verbal hallucinations: a retrospective tract-based spatial statistics study

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Auditory verbal hallucinations (AVHs) are experienced by the majority of patients with schizophrenia and are often resistant to treatment with antipsychotic agents. White matter (WM) tract abnormalities are associated with AVH treatment efficacy. Using a retrospective design, 115 patients with schizophrenia with AVHs, 48 with medication-resistant AVHs and 67 with treatable AVHs, and 70 healthy controls (HCs) were selected from the database of our cohort study for 5-year follow-up assessment. WM tract integrity was measured using tract-based spatial statistics (TBSS) at baseline and after 5 years of antipsychotic agent treatment. The fractional anisotropy (FA) value was used to demonstrate WM tract alterations in patients with schizophrenia with medication-resistant AVHs, in patients with schizophrenia with treatable AVHs, and in HCs. Our data demonstrated that medication-resistant patients showed significantly greater FA values in the corpus callosum (CC) fasciculus at baseline and in the corticospinal tract post-treatment compared to HCs, but the baseline difference in the CC fasciculus was no longer significant after 5 years of antipsychotic agent treatment. The medication-resistant AVH group exhibited greater FA values in the superior longitudinal fasciculus after 5 years of antipsychotic agent treatment. Compared to the HC group, the treatable AVH group exhibited significantly greater FA values in the visual radiation and CC after 5 years of antipsychotic agent treatment. In the medication-resistant and treatable groups, common WM tract abnormalities were noted, as greater FA values were observed in the CC group at baseline compared to the HC group. At the same time, distinct abnormalities were noted, as greater FA values were observed in the superior longitudinal fasciculus, which may contribute to medication-resistant AVHs, whereas abnormalities in the CC fasciculus may contribute to both treatable and medication-resistant AVHs. In the HCs, a decrease in FA values in the posterior CC was observed after 5 years of observation compared to baseline. In summary, patients with treatment-resistant AVHs with schizophrenia and patients with treatable AVHs with schizophrenia have common and distinct abnormalities in the WM tract.

Schizophrenia (2025)11:46 ; https://doi.org/10.1038/s41537-025-00597-y

INTRODUCTION

Auditory verbal hallucinations (AVHs) are reported by 70–80% of patients with schizophrenia[1], and approximately 20–40% of these patients demonstrate an unfavorable response to available antipsychotic medications[2,3]. These medication-resistant AVHs markedly interfere with normal social function and degrade quality of life[4,5]. As a treatment, these AVHs are frequently addressed by increasing the dose of antipsychotic medication, which in turn can exacerbate drug side effects. Numerous studies have investigated the pathological features of medication-resistant AVHs to identify risk factors[6–10] and alternative treatment methods[11–14]; however, the underlying neuropathology remains obscure[5–18]. Numerous studies have been conducted into white matter (WM) pathological features in patients with schizophrenia over the last two decades. These studies have provided numerous constructive findings for further exploring the brain features of patients with schizophrenia and information for precise treatment and establishment of strategies[9,19–49]. Studies into schizophrenia have reported numerous gray matter features specific to schizophrenic symptoms, such as AVHs[50–55], rather than WM features, due to the difficulty of investigating the brain features of patients with AVHs[56–61]. However, with advances in magnetic resonance imaging (MRI) for the assessment of WM tract abnormalities, a growing number of studies have focused on investigating the relationship between WM tract alterations and AVHs[62–66]. The majority of these studies have indicated that WM abnormalities in the corpus callosum (CC) area, uncinate fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, postcentral and superior parietal lobule, arcuate fasciculus, interhemispheric fasciculi, and interhemispheric auditory pathway (IAP), as well as in tracts connecting the language, auditory, and memory/limbic networks and cingulum bundle and rich-club reorganization of WM structural network, are the pivotal brain pathological features of patients with schizophrenia with AVHs. As such, these studies have provided evidence that

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Published in partnership with the Schizophrenia International Research Society

structures associated with WM abnormalities and neuronal activity are associated with treatment response[54,55,62–66].

Numerous studies have confirmed that medication-resistant AVHs are highly prevalent in patients with schizophrenia. AVHs are reported by 70 to 80% of patients with schizophrenia[67], approximately 20 to 40% of whom demonstrate an unfavorable response to antipsychotic medications[1,2]. Although all of these studies acknowledge that WM abnormalities play a pivotal role in the pathological mechanisms of AVHs[62–70], and some have reported that WM abnormalities are associated with the treatment response to AVHs, limited studies have reported that WM abnormalities are associated with the effects of therapeutic strategies for treating AVHs[5,63,71]. Against this background, exploring the pathological brain features of patients with medication-resistant AVHs can provide useful information for developing effective treatment strategies for treatment-resistant AVHs.

Although a growing number of studies have investigated the pathological features of WM tract alterations in patients with schizophrenia who have AVHs, to the best of our knowledge, limited studies have investigated WM alterations in patients with schizophrenia with medication-resistant AVHs[62]. In fact, WM tract abnormalities play a pivotal role in patients with schizophrenia with medication-resistant AVHs from the perspective of brain informatics[5,63–72]. Indeed, prior studies have reported that the AVH treatment response is related to WM tract abnormalities[5,71,72]. A prior study that examined the ability of repetitive transcranial magnetic stimulation (r-TMS) to induce reorganizational changes within the WM rich-club structural network in schizophrenia shed light on the potential mechanisms through which r-TMS may alleviate AVHs[72]. Another study reported that local alterations of WM integrity abnormalities in the left arcuate fasciculus and in the language pathway in patients with schizophrenia with AVHs are related to medication resistance[71]. Leroux et al. reported that decreased fractional anisotropy (FA) in the interhemispheric auditory pathway (IAP) was observed in patients with schizophrenia who had lifelong AVHs[5]. These and other studies on the relationship between medication resistance and treatment of AVHs and WM abnormalities in patients with schizophrenia[5,62–72] indicate that WM plays a pivotal role in AVH treatment response in patients with schizophrenia[5,71,72]. Hence, investigating WM abnormalities utilizing MRI techniques can help identify the means of treating medication-resistant AVHs in patients with schizophrenia.

Several recent neuroimaging studies have observed WM abnormalities in patients with schizophrenia, although both the direction of change and regional distribution are inconsistent[5,12,63,73–75]. WM abnormalities are usually demonstrated by the following four parameters: 1) average functional anisotropy (FA); 2) average mean diffusivity (MD); 3) average axial diffusivity (AD); and 4) average radial diffusivity (RD)[52,76–84]. The FA value is expressed in the range of 0 to 1, and it is the ratio of the anisotropic component of water molecules to the entire diffusion tensor. The smaller the value, the more unrestricted the dispersion, and the larger the value, the more regular and directional the organization, with the nerve conduction function also strengthened accordingly. Thus, it is possible to infer the arrangement of cellular structures and the integrity of tissue structures within the WM fiber bundles of the brain through FA values. Further, the MD value reflects the total water content of an organism and expresses the total diffusion activity and molecular displacement of water molecules. The maximum value displayed in the tensor is represented by the direction where the diffusion and motion of water molecules are least hindered as described by the AD value in the parallel axis position. The AD value is more sensitive to the integrity and degeneration of axons. The vertical axis position is described by the RD value, which depends on the average value calculated from two relatively low tensor values. The RD value can express the integrity of myelin[52,76–84].

In a prior study, researchers observed the microstructural connectivity of the arcuate fasciculus in adolescents with high-functioning autism[79]. Impairment of WM integrity was observed in patients with Asperger syndrome[80]. Fjell et al. reported that reduced WM integrity is related to cognitive instability[81]. Levitt et al. reported the presence of FA and RD abnormalities in patients with schizophrenia[52]. A recent study used the peak width of skeletonized mean diffusivity (PSMD), a new index, to explore biomarkers of patients on their first episode of schizophrenia. This study reported that the PSMD can be used as an early neuroimaging biomarker for investigating abnormalities in WM microstructural integrity and cognitive functions in schizophrenia[82]. Male et al. reported that lower FA values in the forceps minor and the left inferior fronto-occipital fasciculus are associated with the speed of processing, attention/vigilance, and severity of negative symptoms in patients with schizophrenia[83]. McNabb et al. reported that lower FA values in the superior longitudinal fasciculus, CC, thalamic radiation, corticospinal tract, internal capsule, corona radiata, and fronto-occipital fasciculus were features of medication-resistant schizophrenia[84]. As typical positive symptoms of schizophrenia, AVHs are associated with WM fiber tract abnormalities[85–91], especially in patients with schizophrenia and medication-resistant AVHs[5,92,93].

Although some studies have investigated the association between AVHs and WM abnormalities in patients with schizophrenia, the findings have been highly variable, with some studies reporting increased FA in the arcuate fasciculus of patients with schizophrenia with AVHs[64,94], and others reporting reduced FA in the arcuate fasciculus of these patients[95,96]. Further, reduced FA has been reported in the cingulate gyrus[29], genu and body of the corpus callosum[97,98], internal capsule[99], and inferior occipitofrontal fasciculus[100]. Additionally, increased radial diffusivity has been reported in the anterior corona radiate[101]. A recent review summarized studies reporting increased FA in the interhemispheric fibers of patients with schizophrenia complicated by AVHs[102]. These findings may reflect the well-described symptomatic heterogeneity of schizophrenia and further suggest the need for long-term prospective or retrospective studies of patients with known disease courses and treatment responses.

Prior studies on WM abnormalities in patients with schizophrenia and AVHs have provided more data for further exploration of the specific WM features associated with medication-resistant AVHs. These studies have reported that AVHs in patients with schizophrenia exhibit different responses to antipsychotic therapy. For example, one study reported that the quetiapine and ziprasidone groups exhibited faster decreases in mean hallucination AVH scores than the risperidone group[103,104]. Several studies reported that the response effect of AVH to antipsychotic agents was related to WM abnormalities (WM tract integrity and WM tract region alterations)[4,10,51,53,54,64,71,105–109]. More notably, we previously demonstrated that atypical antipsychotic treatment induced a gradual expansion in WM alterations in patients with persistent AVHs, although the AVHs were alleviated[110]. These studies indicate that WM abnormalities are related both to AVH severity and the treatment effect of AVHs in patients with schizophrenia[5]. Hence, further exploration of WM abnormalities associated with AVHs in patients with schizophrenia can provide more information for further exploration of treatment options for patients with treatment-resistant AVHs, subsequently improving these patients' prognosis[111].

Although approximately one-third of patients with schizophrenia exhibit medication-resistant AVHs[11,57,58,112,113], few studies have attempted to identify neuropathological features unique to this subpopulation. We speculated that such patients may exhibit unique regional WM abnormalities compared to patients with treatable AVHs. We conducted a retrospective study of

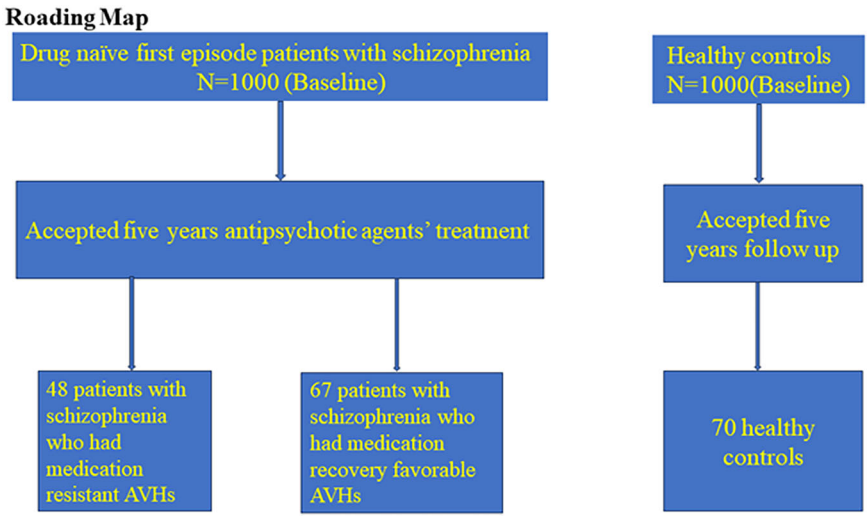

Fig. 1 Flow chart of participant selection.

neuroimaging data from our prior large cohort study in order to test this hypothesis. The current study was designed to test four specific hypotheses: (i) patients with schizophrenia and medication-resistant AVHs will demonstrate regional WM abnormalities compared to matched healthy controls (HCs); (ii) patients with schizophrenia and treatable AVHs will also demonstrate WM abnormalities compared to HCs, but these abnormalities will differ in regional pattern from those of patients with medication-resistant AVHs; (iii) the baseline WM abnormalities (before treatment) will differ between patients with medication-resistant and treatable AVHs; and (iv) the developmental trajectory of WM abnormalities from baseline to post-treatment (after 5 years of drug therapy) will also differ between patients with schizophrenia and medication-resistant and treatable AVHs.

Prior studies have reported that medication-resistant AVHs in patients with schizophrenia are associated with gray matter structural and functional abnormalities. These studies have provided additional data to improve the treatment of AVHs in patients with schizophrenia. Several treatment strategies have been developed for treatment-resistant AVHs based on these findings, including r-TMS, adjunct antipsychotic agents, transcranial direct current stimulation (t-DCS), and adjunct antipsychotic agents; however, there remains no consensus on the most appropriate treatment strategy for AVHs in patients with schizophrenia based on gray matter abnormalities[5,49–72].

WM abnormalities have become the focus of schizophrenia research with the development of neuroimaging technology over the past two decades. The relationship between AVHs in patients with schizophrenia and gray matter abnormalities has been studied by numerous scholars using multiple MRI imaging technologies. In contrast, limited studies have investigated the relationship between AVHs in patients with schizophrenia and WM abnormalities[5,9–11], and there have been even fewer follow-up studies to investigate the association between AVHs and WM abnormalities in patients with schizophrenia. More notably, to the best of our knowledge, no prior study has reported an association between the WM modality change trajectory in patients with schizophrenia with AVHs and the treatment effect of AVHs. Hence, we conducted a study using the MRI data from our schizophrenia study database, which was established in 2013, to investigate the relationship between AVHs in patients with schizophrenia and WM trajectory features. We aimed to provide data that scholars can utilize to identify precise therapeutic strategies to treat medication-resistant AVHs in patients with schizophrenia.

The primary goal of this study was to describe the WM abnormality alteration trajectory that accompanies 5 years of antipsychotic agent treatment. As a secondary goal, we sought to describe the unique and common WM abnormalities in patients with schizophrenia who presented with medication-resistant AVHs and patients with treatable AVHs to further explore the pathological WM features of these patients. The treatment strategies developed based on the data presented herein can reduce impairment and improve the prognosis of patients with schizophrenia and medication-resistant AVHs.

METHODS

Study design and participants

A total of 115 patients with schizophrenia were selected from a database of 1000 patients enrolled in our prior cohort study, which monitored first-episode drug-naïve patients for 5 years during antipsychotic drug treatment. Additionally, 70 HCs were selected from our database of 1000 HCs simultaneously enrolled in the same study. The participant selection is schematized in Fig. 1. Schizophrenia was diagnosed according to the second edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[114], while disease severity was assessed at baseline and post-treatment using the Positive and Negative Syndrome Scale (PANSS)[115]. Additionally, AVH severity was graded using the Auditory Hallucinations Rating Scale (AHRS)[116]. Medication-resistant AVH was defined as daily occurrence despite at least 6 months of clozapine treatment at 600 mg/day and at least 6 weeks of treatment at a chlorpromazine equivalent dose of 1000 mg/day[6,7,117–120]. Only medication-resistant patients who declined r-TMS, t-DCS, and electroconvulsive therapy (ECT) were enrolled. Individuals in the HC group were confirmed to be free of psychiatric disorders and history of psychotic episodes in first-degree relatives. The exclusion criteria for all three of the groups were a history of neurological disease, severe medical conditions, head trauma, substance abuse, and other conditions that may influence brain structure and function. Written informed consent was obtained from all of the participants, and the study was approved by the ethics committees of Tianjin Fourth Center Hospital, Tianjin Anning Hospital, Tianjin Kangtai Hospital, Tianjin Jianhua Hospital, and Wenzhou Seventh Peoples Hospital.

Diffusion-weighted image acquisition and processing

Image acquisition. Structural T1 MRI images were acquired on a 3 T Siemens Prisma with a 64-channel head coil using a 3D MPRAGE sequence (0.8 mm isotropic voxels, repetition time/inversion time [TR/TI] = 2400/1000 ms, echo time [TE] = 2.2 ms,

flip angle = 8°, field of view [FOV] = 256 × 240 × 166 mm, matrix size = 320 × 300, 208 sagittal slices, in-plane [iPAT] acceleration factor of 2)[121,122]. T2 volumes were also acquired at the same spatial resolution using the variable-flip-angle turbo-spin-echo 3D SPACE sequence (TR/TE = 3200/564 ms; same FOV, matrix and in-plane acceleration)[123]. The MRI acquisition protocol used was similar to that used in our prior study on the HCP Connectom scanner[124] but with several modifications necessitated by the lower gradient strength of the Prisma scanner (80 mT/m, vs. 100 mT/m for the Connectom scanner). The MRI scans utilized multi-band (MB) sequences from the Center for Magnetic Resonance Research, with 1.25 isotropic voxels, TR = 5000 ms, TE = 104 ms, 6/8 partial Fourier, and MB factor = 4. A full MRI session included six runs (each approximately 8.5 min) representing three different gradient tables, with every table acquired once with anterior-to-posterior and posterior-to-anterior phase encoding polarities. Every gradient table includes approximately 90 diffusion weighting directions plus 6 b = 0 acquisitions interspersed throughout every run. Diffusion weighting consisted of three shells of b = 1000, 2000, and 3000 s/mm^2 interspersed with an approximately equal number of acquisitions for every shell in every run. The diffusion directions matched those used in the HCP, resulting in 69 volumes[125].

Image processing. The diffusion data were preprocessed using the Diffusion Preprocessing stream of the HCP pipelines (v4.3.0)[126,127] utilizing the QuNex container (v0.91.11). This pipeline includes intensity normalization, susceptibility distortion correction (via FSL's "topup" tool)[128], and correction for eddy current distortions and motion via FSL's "eddy" tool[128–130]. The b-vectors were rotated to account for motion[131–135]. Finally, the MRI data were corrected for gradient nonlinearity distortion as part of resampling to the subject's native T1 space from the HCP structural pipeline output while maintaining the same 1.25 mm spatial resolution of the MRI data[136].

TRACULA. After preprocessing, processing continued using FSL's "bedpost" feature[137] to estimate the diffusion orientation distribution. Bedpostx was run outside of TRACULA (TRActs Constrained by UnderLying Anatomy) within the QuNex container (number of fibers per voxel = 3; deconvolution model = 3 [zeppelins]; burnin = 3000; rician noise; gradient nonlinearities accounted for). TRACULA from FreeSurfer v6.0, as an automated method[138] for estimating global probabilistic tractography, utilizes a Bayesian framework for global tractography that determines the connection that best fits two selected endpoints based on the diffusion data. TRACULA also incorporates prior anatomical knowledge based on manually verified tract trajectories in a training set created by Yendiki et al.[138] For each individual, TRACULA reconstructs the probabilistic distributions of 18 major WM tracts. Specifically, TRACULA uses the endpoints established in the training set's tracts and transforms them into every individual's native space. Then, TRACULA establishes probabilistic streamlines constrained by the relative positions of WM pathways to surrounding anatomical structures (obtained from the individual's own Free Surfer segmentation) and uses control points to control the allowed curvature of the tract. It does not presume the exact location or shape of the tract; therefore, the trajectory of the tract is only restricted with respect to the surrounding anatomical structures. This allows for variation across individuals while retaining the same tracts for across-individual comparison.

Only the TRACULA steps specifically necessary to generate the path distributions were used, given that preprocessing of the diffusion data was implemented using the HCP pipelines to enable the use of more advanced preprocessing features. In particular, the "prep-prior" step was used to estimate the anatomical neighborhood prior for every pathway of interest and the "path" step was used to generate the path distributions using TRACULA. FSL's "dtifit" was applied to perform least-squares tensor estimations, specifically eigenvectors, eigenvalues, and DTI parameters (FA, AD, and RD) using only the b = 0 and b = 1000 s/mm^2 shells, as the tensor model is not valid for high b-values. However, all of the shells were used as input to "bedpost" and thus contributed to the estimation of the path distributions. FA is a commonly used DTI metric that establishes the directional asymmetry of water diffusion at every voxel[139–142]. Tract volumes and average values for FA, RD, and AD within the 20% posterior distribution for every path (tract) of interest were computed as the final step of TRACULA[143].

Statistical analysis

All of the statistical analyses were performed using IBM SPSS Statistics® version 27 (IBM Corp, Armonk, NY, USA). To compare every tract metric (i.e., tract volume, FA, RD, and AD) across groups, multiple analysis of variance was used with the seven tracts as the dependent variables, group as an independent ("class") variable, and age and sex as covariates (i.e., multivariate analysis of covariance [MANCOVA]). Intracranial volume was also included as a covariate for tract volume comparisons. Post hoc pairwise analyses were performed when the MANCOVA results achieved statistical significance ($P < 0.05$) for the diagnostic group effect uncontrolled for multiple comparisons. Z-scores were generated using only the three groups. The relationships between mean FA for every tract, clinical measures, and age were investigated using Spearman's correlations. Associations between various clinicodemographic parameters and imaging metrics were evaluated using correlation analysis[31,144].

RESULTS

Construction of FA maps from HCs and patients with schizophrenia with medication-resistant or treatable AVHs revealed (i) significantly greater whole-brain FA values in patients with medication-resistant AVHs at baseline compared to HCs and patients with treatable AVHs; (ii) significantly greater FA in the corpus callosum (CC) fasciculus of patients with medication-resistant AVHs at baseline compared to HCs; (iii) significantly greater FA in the corticospinal tract of patients with medication-resistant AVHs after treatment (5 years of medication) compared to HCs but no significant group difference in the CC fasciculus post-treatment; (iv) significantly greater FA in the superior longitudinal fasciculus of patients with medication-resistant AVHs after treatment versus baseline; and (v) greater FA in the visual radiations of patients with treatable AVHs at baseline compared to HCs. Aberrant FA in medication-resistant patients did not correlate with PANSS scores, AHRS scores, or accumulated chlorpromazine equivalent dosage. Further, significant differences were observed in baseline or post-treatment regional FA values between the medication-resistant and treatable AVH groups (Tables 1–4, Figs. 2–4).

Our data demonstrated that, when compared to HCs at baseline, the medication-resistant patients with AVHs on their first episode of schizophrenia showed FA of clusters with significant group differences in FA values, AD of clusters with significant group differences in FA values, RD of clusters with significant group differences in FA values, and MD of clusters with significant group differences in FA values. More notably, they showed decreased FA and AD values and increased RD and MD values compared to HCs. Likewise, compared to treatable patients with AVHs on their first episode of schizophrenia, medication-resistant patients with AVHs on their first episode of schizophrenia showed decreased FA and AD values and increased RD and MD values. These indices indicate that the arrangement of cellular structures within the WM fiber bundles and the integrity of tissue

Table 1. Group differences in demographic, clinical, and neuroimaging variables at baseline.

	Patients with medication-resistant AVHs	Patients with treatable AVHs	Healthy controls	*P*
n	*n* = 48	*n* = 67	*n* = 70	0.013[#]
Age (years)	19.18 ± 0.38	26.54 ± 3.00	24.22 ± 3.04	0.013[#]
Sex (male/female)	8/40	25/42	37/78	0.001[#]
Education level (years)	14.60 ± 3.50	16.25 ± 2.59	18.40 ± 1.35	0.039[#]
PANSS total	87.80 ± 10.50	77.00 ± 5.50	-	0.001*
PANSS positive	17.30 ± 4.20	19.00 ± 2.13	-	0.020*
PANSS negative	10.30 ± 1.35	9.15 ± 0.87	-	0.045*
PANSS general	50.20 ± 9.66	48.85 ± 5.0	-	0.047*
AHRS	24.20 ± 1.66	20.25 ± 3.50	-	0.011*
Mean FA of clusters with significant group differences in FA	0.32 ± 0.01	0.50 ± 0.06	0.61 ± 0.04	< 0.001[#]
Mean AD of clusters with significant group differences in FA	0.75 ± 0.01 $^{(10-3)}$	0.83 ± 0.04 $^{(10-3)}$	0.90 ± 0.04$^{(10-3)}$	< 0.001[#]
Mean RD of clusters with significant group differences in FA	0.63 ± 0.03 $^{(10-3)}$	0.40 ± 0.01 $^{(10-3)}$	0.46 ± 0.05$^{(10-3)}$	< 0.001[#]
Mean MD of clusters with significant group differences in FA	0.60 ± 0.04 $^{(10-3)}$	0.45 ± 0.02 $^{(10-3)}$	0.56 ± 0.01$^{(10-3)}$	< 0.001[#]

AHRs Auditory verbal hallucinations, *FA* Fractional anisotropy, *AD* Axial diffusivity, *RD* Radial diffusivity, *MD* Mean diffusivity, *PANSS* Positive and Negative Syndrome Scale. [#]Kruskal–Wallis H-test, [*]Mann–Whitney U-test.

Table 2. Group differences in schizophrenia severity scores, cumulative drug doses, and imaging metrics after the 5-year treatment period.

	Patients with medication-resistant AVHs	Patients with treatable AVHs	Healthy controls	*P*
	n = 48	*n* = 67	*n* = 70	
PANSS positive	10.11 ± 2.92	8.50 ± 0.23	-	0.042[a]
PANSS negative	9.46 ± 3.00	7.95 ± 0.02	-	0.016[a]
PANSS general	27.01 ± 0.31	20.00 ± 2011	-	<0.001[a]
AHRS	18.45 ± 5.33	3.10 ± 1.25	-	<0.001[a]
Accumulated chlorpromazine equivalent (mg)	1817700 ± 126615	1404413 ± 90450	-	<0.001[a]
Mean FA of clusters with significant group differences in FA	0.54 ± 0.02	0.67 ± 0.04	0.48 ± 0.01	<0.001[b]
Mean AD of clusters with significant group differences in FA	0.88 ± 0.02 $^{(10-3)}$	0.92 ± 0.02 $^{(10-3)}$	0.86 ± 0.03 $^{(10-3)}$	<0.001[b]
Mean RD of clusters with significant group differences in FA	0.51 ± 0.05$^{(10-3)}$	0.59 ± 0.05$^{(10-3)}$	0.42 ± 0.01 $^{(10-3)}$	<0.001[b]
Mean MD of clusters with significant group differences in FA	0.63 ± 0.03 $^{(10-3)}$	0.72 ± 0.08 $^{(10-3)}$	0.50 ± 0.07 $^{(10-3)}$	<0.001[b]

[a]Kruskal–Wallis H-test, [b]Mann–Whitney U-test.

Table 3. Cluster-level differences in FA and related metrics after 5 years of medication compared to baseline for the medication-resistant AVH group.

n	Baseline *n* = 48	Five years later *n* = 48	*P*
Mean FA of clusters with significant group differences in FA	0.32 ± 0.01	0.54 ± 0.02	<0.001[a]
Mean AD of clusters with significant group differences in FA	0.75 ± 0.01 $^{(10-3)}$	0.88 ± 0.02 $^{(10-3)}$	<0.001[a]
Mean RD of clusters with significant group differences in FA	0.63 ± 0.03 $^{(10-3)}$	0.51 ± 0.05$^{(10-3)}$	<0.001[a]
Mean MD of clusters with significant group differences in FA	0.60 ± 0.04 $^{(10-3)}$	0.63 ± 0.03 $^{(10-3)}$	<0.001[a]

[a]Mann–Whitney U-test.

Table 4. Cluster-level differences in FA and related metrics after 5 years of medication treatment compared to baseline for the treatable AVH group.

n	Baseline *n* = 67	Five years later *n* = 67	*P*
Mean FA of clusters with significant group differences in FA	0.50 ± 0.06	0.67 ± 0.04	<0.001[a]
Mean AD of clusters with significant group differences in FA	$0.83 \pm 0.04^{(10-3)}$	$0.92 \pm 0.02^{(10-3)}$	<0.001[a]
Mean RD of clusters with significant group differences in FA	$0.40 \pm 0.01^{(10-3)}$	$0.59 \pm 0.05^{(10-3)}$	<0.001[a]
Mean MD of clusters with significant group differences in FA	$0.45 \pm 0.02^{(10-3)}$	$0.72 \pm 0.08^{(10-3)}$	<0.001[a]

[a]Mann–Whitney U-test.

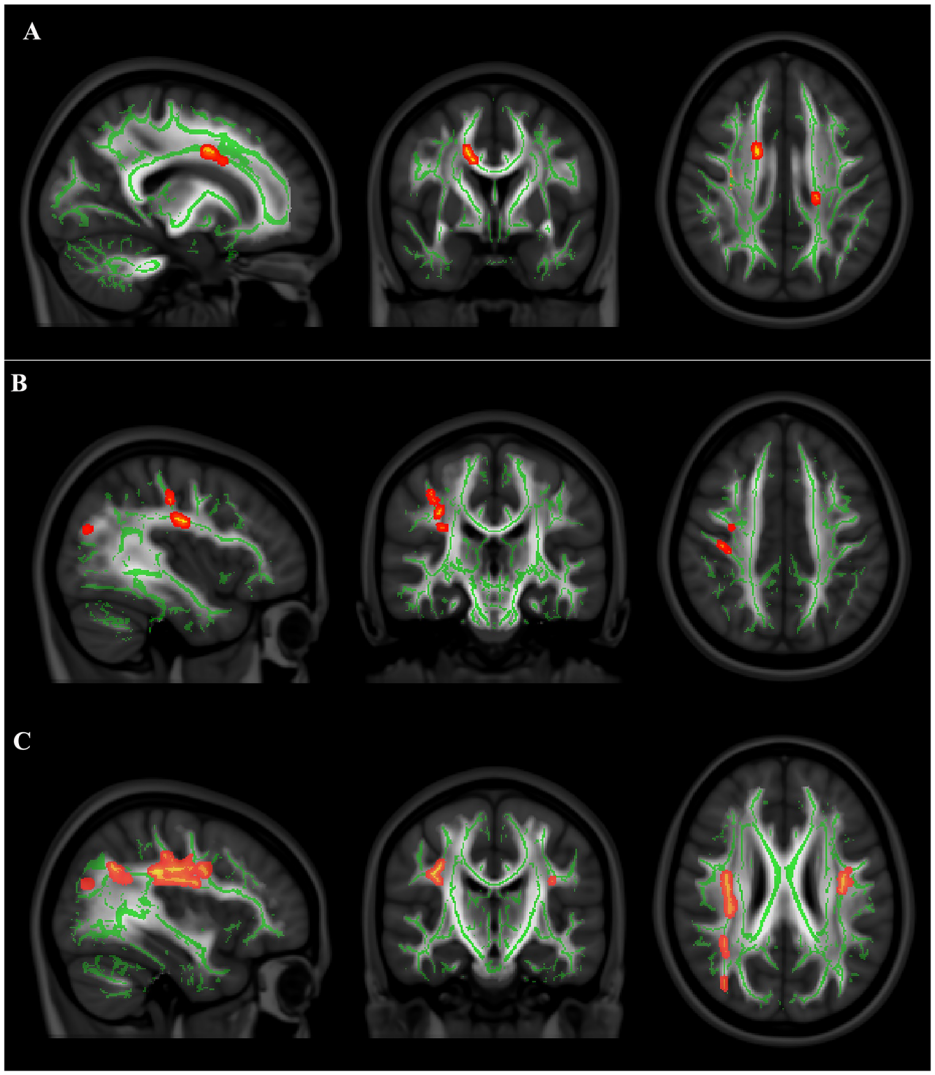

Fig. 2 Fractional isotropy (FA) difference maps overlaid on white matter (WM) tract skeletons illustrating regional changes in WM integrity among patients with schizophrenia and medication-resistant AVHs. Images show FA changes as pseudocolors in the parasagittal plane (left panels), coronal plane (middle panels), and transverse plane (right panels). **A** Patients with medication-resistant AVHs demonstrated significantly greater FA in the corpus callosum fasciculus at baseline compared to healthy controls. **B** Patients with medication-resistant AVHs demonstrated significantly greater FA in the corticospinal tract (but not the corpus callosum fasciculus) after 5 years of antipsychotic drug treatment compared to healthy controls. **C** Patients with medication-resistant AVHs demonstrated significantly greater FA in the superior longitudinal fasciculus post-treatment compared to baseline.

structures, axons, and level of myelin are significantly abnormal in patients with medication-resistant AVHs on their first episode of schizophrenia compared to HCs. Simultaneously, compared to HCs, patients with treatable AVHs on their first episode of schizophrenia showed significantly decreased FA and AD values and significantly increased RD and MD values. These indices indicate that the integrity of tissue structures, axons, and level of myelin were also significantly abnormal in the patients with treatable AVHs on their first episode of schizophrenia compared to HCs. Prior studies support our findings. For example, Ogura et al.

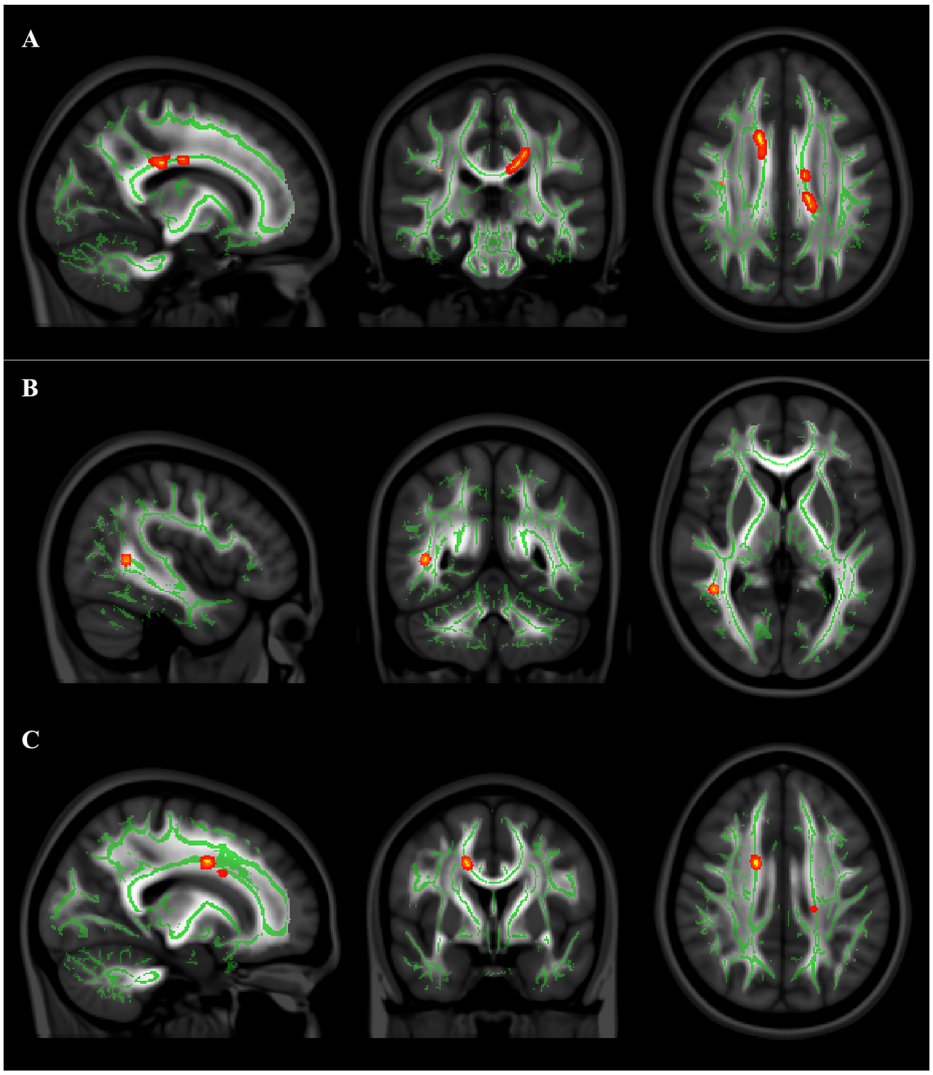

Fig. 3 Fractional isotropy (FA) difference maps overlaid on white matter (WM) tract skeletons illustrating regional changes in WM integrity among patients with schizophrenia and treatable AVHs. Images show FA changes as pseudocolors in the parasagittal plane (left panels), coronal plane (middle panels), and transverse plane (right panels). **A** Patients with treatable AVHs demonstrated significantly greater FA in the corpus callosum fasciculus at baseline compared to healthy controls. **B** Patients with treatable AVHs demonstrated significantly greater FA in the visual radiation post-treatment compared to healthy controls. **C** Patients with treatable AVHs demonstrated significantly greater FA in the corpus callosum fasciculus after 5 years of treatment compared to baseline.

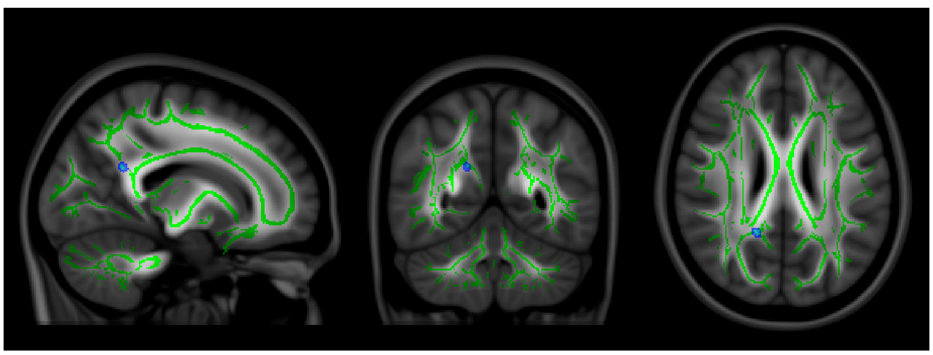

Fig. 4 Healthy controls demonstrated none significantly decreased FA in the posterior corpus callosum fasciculus after 5 years of treatment compared to baseline.

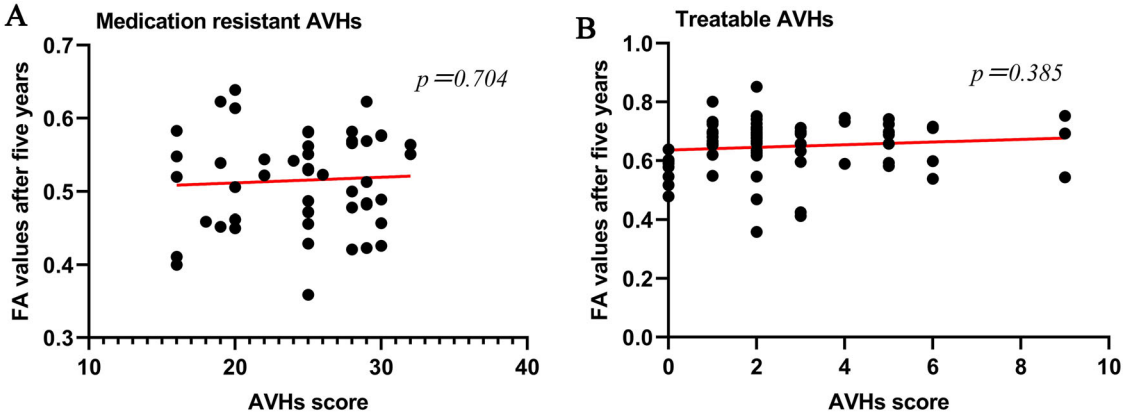

Fig. 5 Scatter plot features of the two patient groups.

Table 5. Cluster-level differences in FA and related metrics after 5 years of observation for healthy controls compared to baseline performance.

n	Baseline *n* = 70	Five years later *n* = 70	*P*
Mean FA of clusters with significant group differences in FA	0.61 ± 0.04	0.57 ± 0.01	0.130[a]
Mean AD of clusters with significant group differences in FA	0.90 ± 0.04$^{(10-3)}$	0.86 ± 0.03$^{(10-3)}$	0.059[a]
Mean RD of clusters with significant group differences in FA	0.46 ± 0.05$^{(10-3)}$	0.42 ± 0.01$^{(10-3)}$	0.423[a]
Mean MD of clusters with significant group differences in FA	0.56 ± 0.01$^{(10-3)}$	0.50 ± 0.07$^{(10-3)}$	0.544[a]

[a]Mann–Whitney U-test.

reported decreased FA and AD values and increased RD and MD values in patients with schizophrenia compared to HCs[64,145–148].

More notably, compared to the patients with treatable AVHs with schizophrenia, the patients with medication-resistant AVHs also demonstrated significantly decreased FA, AD, RD, and MD values. These indices indicate that the WM fiber tract was significantly abnormal in the patients with medication-resistant AVHs on their first episode of schizophrenia. These data indicate that at baseline, their WM fiber tract abnormalities were more serious than those of the patients with treatable AVHs with schizophrenia. More unexpectedly, no significant correlation was observed between the FA, AD, RD, and MD values and the AVH and PANSS scores in either the medication-resistant or treatable patients. Several prior studies also reported no relationship between AVH severity and FA, AD, RD, and MD values[149–152].

After 5 years of antipsychotic agent treatment, both the medication-resistant and treatable patients with AVHs with schizophrenia had significantly increased FA, AD, RD, and MD values compared to HCs. Compared to the medication-resistant patients, the treatable patients showed significantly increased FA, AD, RD, and MD values. These findings indicate that the WM fiber tract normalized better in the treatable patients than the medication-resistant patients with schizophrenia (Fig. 5).

It is not clear why the WM parameters in both the patients with medication-resistant AVHs and treatable AVHs with schizophrenia demonstrated increased FA, AD, RD, and MD values but the HCs demonstrated decreased FA, AD, RD and MD values. Although this phenomenon is counterintuitive, when we tested our data with another MRI data processor, the results were the same. This phenomenon cannot be explained due to lack a criterion values for FA, AD, RD, and MD for healthy individuals and a lack of values that indicate abnormality. Further studies aiming to establish the criterion values of FA, AD, RD, and MD for healthy individuals and for abnormality are warranted (Table 5).

In the HCs, decreased FA, AD, RD, and MD values were observed after 5 years of observation, indicating that brain aging can be caused by WM fiber tract abnormalities. Prior studies support our findings[105,153–157]. For example, Genc et al. examined diffusion tensor imaging (DTI) metrics (FA, MD, AD, and RD) regarding their relationship to age by performing receiver operating characteristic (ROC) analysis to assess the ability of every metric to classify older and younger participants[158]. However, as aforementioned, standard criterion values for FA, AD, RD, and MD that reflect the healthy WM fiber tract are currently not available. Obtaining these values is urgent to provide reference values for further studies aiming to explore mental disorders from the perspective of WM tract abnormality.

DISCUSSION

The WM tract plays a pivotal role in information processing in the human brain. DTI is highly sensitive to the diffusional information of the WM tract, and numerous factors can influence diffusion anisotropy, including the integrity of axonal membranes, damage to neuronal fiber bundles, and the neural diameter and integrity of the myelin sheath. FA and MD values reflect tissue damage or changes in tract morphology and WM volume at the microstructural level, whereas RD values reflect tissue myelin disturbance. Despite the importance of these values, the majority of the aforementioned studies did not report FA, MD, and RD value alterations in patients with schizophrenia with medication-resistant AVHs and in patients with schizophrenia with treatable AVHs[4,5,10,11,57,58,64,71,159,160].

To the best of our knowledge, our study is the first to retrospectively investigate WM abnormalities in patients with schizophrenia with medication-resistant AVHs and treatable AVHs to examine WM fiber tract alteration trajectories associated with AVH alterations. We observed that patients with medication-resistant AVHs exhibit regional WM abnormalities that are substantially different from those of patients with treatable AVHs, consistent with our primary hypothesis that distinct patterns of WM tract dysfunction may contribute to differences in

antipsychotic drug response. In particular, abnormalities in the superior longitudinal fasciculus were associated with medication-resistant AVHs, suggesting that targeted modulation of this pathway may help alleviate these symptoms. Our results can be summarized as follows: Patients with medication-resistant AVHs exhibited (i) greater whole-brain WM FA after antipsychotic treatment compared to HCs and patients with treatable AVHs; (ii) greater baseline FA in the corpus callosum fasciculus and greater post-treatment FA in the corticospinal tract compared to HCs; and (iii) greater FA in the superior longitudinal fasciculus post-treatment than at baseline. In contrast, patients with treatable AVHs exhibited greater FA in the visual radiation post-treatment compared to HCs. However, these aberrant regional FA values in patients with treatment-resistant AVHs did not correlate significantly with schizophrenia symptom severity, as assessed by PANSS and AHRS scores, or with the cumulative chlorpromazine equivalent dosage. Further, the differences in regional FA between the patient groups at baseline and post-treatment did not reach statistical significance. Nonetheless, these results suggest that specific regional WM tract abnormalities influence the antipsychotic drug response of AVHs independently from other symptoms.

The majority of prior studies on WM alterations in patients with schizophrenia and AVHs found reduced FA, including in the cingulum bundle[161], the genu and body of the corpus callosum, right posterior corona radiata, left superior corona radiata, left external capsule, anterior limb of the internal capsule, right superior occipitofrontal fasciculus[162], interhemispheric auditory pathway, internal capsule and anterior corona radiata, frontotemporal fibers of the left inferior occipitofrontal fasciculus, and arcuate fasciculus[163]. Further, higher MD has been found in the genu of the corpus callosum, left fornix, and stria terminalis[164]. In contrast, only a few studies have reported increased regional FA, including in the left arcuate fasciculus[165], left perisylvian language pathways[166], and corpus callosum[67]. The reasons for these discrepancies are currently unknown but may reflect the clinical heterogeneity of the disease conferred by various demographic, clinical, and genetic factors. However, our neuroimaging studies of WM structure were conducted on drug-naïve first-episode patients, as well as on patients with well-documented 5-year treatment histories segregated into medication-resistant and responsive subgroups. Further, these two groups were relatively well-matched for other clinical parameters such as PANSS scores. Our within-group analysis revealed increased FA in the superior longitudinal fasciculus of patients with medication-resistant AVHs and increased FA in the corpus callosum of patients with treatable AVHs. These findings underscore the potential contribution of unique WM tract abnormalities to the antipsychotic drug response of AVHs.

To the best of our knowledge, no prior study supports the current findings. Compared to baseline values, we found greater FA in the superior longitudinal fasciculus of patients with medication-resistant AVHs, but no such change in patients with treatable AVHs, while FA was greater in the corpus callosum body of patients with treatable AVHs post-treatment but not in patients with medication-resistant AVHs. The superior longitudinal tract connects the temporal and frontal lobes and participates in various advanced cognitive functions, including the perception and processing of language[5,16,62]. Therefore, it is possible that abnormal FA in the superior longitudinal tract allows AVHs to persist despite antipsychotic medication. As the main interhemispheric pathway, the corpus callosum is indispensable for coordinated movement, sensory integration, and language production and comprehension[12,53,54,63,82,88,167–169].

In the present study, our results demonstrated that increased FA in the CC is associated with a better treatment response to AVHs in patients with schizophrenia. In contrast, numerous studies reported that increased FA in the CC at baseline usually does not correlate with the treatment response to AVHs. Some studies even reported that increased FA in the CC at baseline is associated with poor treatment response to AVHs[25,45,67,76,155]. Hence, further studies are needed to examine the effects of FA changes in the CC on the bilateral neural activity associated with AVHs in medication-resistant and treatable patients[52,77,78,82–86].

As previously mentioned, our findings are inconsistent with prior studies. However, the findings of prior studies are also highly inconsistent. For example, Chawla et al. reported that lower FA values in the left cingulum bundle are associated with AVHs in patients with schizophrenia, indicating that WM pathology underlying AVH involves pathways beyond language and auditory-linked circuits[87]. However, this can be explained by the splenium of the CC carrying fibers to temporal, parietal, and occipital lobes, and thus deficits in this structure could interrupt information flow between regions crucial for delivering and coordinating speech percepts. These notions are in accordance with a more sophisticated view of AVH as emerging from comprised structural connections between multiple extrasensory association and perception areas as opposed to pathways specific to the sensory modality in question[88,89].

Conversely, Bopp et al. reported that the positive symptom of thought disturbance corresponded negatively with FA in the cingulum bundle and that there was no relationship between it and AVHs in patients with schizophrenia[170]. Shergill et al. reported that the propensity to experience AVHs in patients with schizophrenia was significantly associated with an increased rather than a decreased FA in the anterior cingulum[22]. Another study reported a positive correlation between FA values in the cingulum bundle and a positive symptom score, but the authors did not assess the AVH score separately[171]. More notably, Whitford et al. reported that FA abnormality in the cingulum bundle correlated with negative symptoms such as affective flattening and anhedonia/asociality and did not correlate with positive symptoms such as AVHs and delusions[172]. More importantly, unlike other studies regarding WM abnormalities associated with schizophrenia, only one meta-analysis published in 2014 reported that arcuate fasciculus abnormalities are associated with AVHs in patients with schizophrenia[65]. In this meta-analysis, Geoffroy reported that reduced FA in the left arcuate fasciculus is associated with AVHs but did not report the relationship between FA value and AVH score[5,173].

Over the past 10 years, no meta-analysis has been conducted to update the data regarding WM abnormalities associated with AVHs in patients with schizophrenia, and few studies have reported the features of WM abnormalities in medication-resistant patients. Notably, Thomas et al. reported that local FA values in the left arcuate fasciculus correlated with the severity of the attentional salience of AVHs. However, this study also reported that patients with schizophrenia showed higher FA values than healthy controls in the medial portion of the latter transcallosal pathway and the midsagittal section of the interhemispheric auditory pathway[52].

Other studies reported different baseline FA values associated with the response to treatment strategies for alleviating medication-resistant AVHs in patients with schizophrenia. Specifically, the baseline FA difference values in the regions of fasciculi that are involved in the language network, namely, connections between the temporoparietal junction (TPJ) and Broca areas, connections between the so-called arcuate fasciculi on every hemisphere, and transcallosal connections between the TPJ or Broca areas, and those that are part of the default mode network (DMN), namely, connections between the superior parietal cortex and prefrontal areas within every hemisphere and transcallosal connections between the superior parietal cortex or prefrontal areas, can predict the treatment response[75].

In the present study, our results demonstrated that increased FA values in the CC are associated with a better treatment response. However, numerous studies have reported that increased FA values in the CC at baseline do not correlate with treatment response to AVHs in patients with schizophrenia. In fact, some studies have even reported that increased FA values in the corpus callosum at baseline are associated with poor treatment response to AVHs in patients with schizophrenia. Hence, further research is needed to examine the effects of FA changes in the CC on the bilateral neural activity associated with AVHs in medication-resistant and treatable patients.

By analyzing the findings of the studies discussed above, a complex relationship between WM fiber tract abnormalities and AVHs in patients with schizophrenia has emerged. Hence, the identification of a biomarker that can predict treatment response to AVHs based on the common and unique WM features of AVHs in patients with schizophrenia is urgently needed; further studies are needed to achieve this goal despite its difficulty[10,88,174–176].

Limitations

The first limitation of this study is the use of a retrospective cross-sectional study design. Prospective studies with more frequent imaging examinations are needed to characterize the trajectory of WM alterations during treatment and their associations with symptoms and therapeutic responses. Data obtained from such studies could prove invaluable in identifying the most effective therapeutic targets for AVH treatment. The second limitation regards the technical issues that are implicit in any DTI study. Future studies should acquire and process DWI/DTI data using advanced methods to provide more precise information for understanding the relationship between WM abnormalities and AVHs in patients with schizophrenia. DWI can also be combined with other MRI contrasts, such as magnetization transfer imaging (MTI) or myelin water imaging[177]. These methods are sensitive to water in the extracellular space, but with multiple other interpretations. DWI is sensitive to the diffusion of water molecules, have probed for possible WM deficits in the mental disorder; hence, in future studies, DWI should be used to explore the WM abnormalities in AVHs in patients with schizophrenia.

The third limitation is the existence of differences in the average age, sex ratio, and (more modestly) educational level between the two groups. Although this limitation was controlled for by ANOVA, further studies are required to precisely clarify it. The use of a prospective design will allow for better matching between AVH response groups and the control group.

CONCLUSION

To the best of our knowledge, this is the first study to report that medication-resistant auditory verbal hallucinations experienced by patients with schizophrenia are associated with unique WM tract abnormalities compared to treatment-responsive AVHs. Specifically, greater FA in the superior longitudinal tract may contribute to medication-resistant AVHs, whereas increased FA in the CC and visual radiation may be related to recovery. We suggest that interventions targeting the superior longitudinal tract is an effective treatment strategy for AVHs that are unresponsive to conventional antipsychotic drugs.

DATA AVAILABILITY

The data supporting the results of this study are available upon request from the corresponding author.

Received: 12 August 2024; Accepted: 6 March 2025;
Published online: 20 March 2025

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ACKNOWLEDGEMENTS

This work was supported by grants from the National Natural Science Foundation of China (Nos. 81871052 and 81701326) to Chuanjun Zhuo.

AUTHOR CONTRIBUTIONS

C.Z. designed the study. C.L., X.M., R.L., X.C., Y.L., L.Y., Q.Z., and L.W. performed data collection and analyses. C.Z. and C.L. drafted the manuscript. C.Z. revised the manuscript. All of the authors have read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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