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Abnormal interhemispheric and intrahemispheric functional connectivity dynamics in drug-naïve first-episode schizophrenia patients with auditory verbal hallucinations

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Abstract

Numerous studies indicate altered static local and long-range functional connectivity of multiple brain regions in schizophrenia patients with auditory verbal hallucinations (AVHs). However, the temporal dynamics of interhemispheric and intrahemispheric functional connectivity patterns remain unknown in schizophrenia patients with AVHs. We analyzed resting-state functional magnetic resonance imaging data for drug-naïve first-episode schizophrenia patients, 50 with AVHs and 50 without AVH (NAVH), and 50 age- and sex-matched healthy controls. Whole-brain functional connectivity was decomposed into ipsilateral and contralateral parts, and sliding-window analysis was used to calculate voxel-wise interhemispheric and intrahemispheric dynamic functional connectivity density (dFCD). Finally, the correlation analysis was performed between abnormal dFCD variance and clinical measures in the AVH and NAVH groups. Compared with the NAVH group and healthy controls, the AVH group showed weaker interhemispheric dFCD variability in the left middle temporal gyrus ($p < .01$; $p < .001$), as well as stronger interhemispheric dFCD variability in the right thalamus ($p < .001$; $p < .001$) and right inferior temporal gyrus ($p < .01$; $p < .001$) and stronger intrahemispheric dFCD variability in the left inferior frontal gyrus ($p < .001$; $p < .01$). Moreover, abnormal contralateral dFCD variability of the left middle temporal gyrus correlated with the severity of AVHs in the AVH group ($r = -.319$, $p = .024$). The findings demonstrate that abnormal temporal variability of interhemispheric and intrahemispheric dFCD in schizophrenia patients with AVHs mainly focus on the temporal and frontal cortices and thalamus that are pivotal components of auditory and language pathways.

KEYWORDS
auditory verbal hallucinations, dynamic functional connectivity, interhemisphere, intrahemisphere, resting-state functional magnetic resonance imaging

1 | INTRODUCTION

Auditory verbal hallucinations (AVHs) are a prominent symptom of schizophrenia and affect approximately 60%–80% of patients (Bauer et al., 2011). AVHs are defined as hearing and perceiving voices in the absence of an external auditory stimulus. Based on the technology of functional magnetic resonance imaging (fMRI), recent findings suggested that AVHs might be traced back to abnormally intrinsic functional organizations involving multiple brain regions and networks (Cui et al., 2017; Hoffman et al., 2007; Kumari et al., 2010; Northoff & Qin, 2011; Scheinost et al., 2019; Silbersweig et al., 1995; Simons et al., 2010; Stripeikyte et al., 2021). Although multiple existing conceptual models of AVHs, such as top-down and bottom-up (Hugdahl, 2009), corollary discharge (Ford et al., 2007), nondominant language intrusion (Sommer et al., 2008; van Lutterveld et al., 2014), and interhemispheric miscommunication (Curcic-Blake et al., 2013; Gavrilescu et al., 2010), were indicated by the previous studies, it is unclear which model is the most relevant for AVHs.

A large number of resting-state fMRI studies indicate abnormal local and long-range connectivity in AVHs (Chang et al., 2017;C. Chen, Wang, et al., 2020; Hare et al., 2021; Mondino et al., 2016; Zhuo et al., 2016). Local functional connectivity was usually estimated using regional homogeneity (ReHo) analysis, and long-range connectivity was usually estimated using resting-state functional connectivity (rsFC) analysis (Hare et al., 2021). On the one hand, the researchers, respectively, explored local and long-range connectivity and found abnormal local and long-range connectivity mainly in the frontal and temporal language-related areas (Chang et al., 2017; Hoffman & Hampson, 2011; Vercammen et al., 2010; Wolf et al., 2021; Zheng et al., 2017; Zhuo et al., 2016). On the other hand, Chen, Wang, et al. (2020), Chen, Cui, et al. (2020), and Cui et al. (2016), respectively, utilized both the two measurements and found that schizophrenia patients with AVHs showed stronger ReHo in the putamen and the dorsolateral prefrontal cortex and weaker rsFC between the putamen and the inferior frontal gyrus (IFG). Moreover, structure functional analysis also indicated stronger interhemispheric auditory connectivity in schizophrenia patients with AVHs (Mulert et al., 2012; Steinmann et al., 2014). Chang et al. (2015) adopted a newly developed index, voxel-mirrored homotopic connectivity (VMHC), to quantitatively describe interhemispheric functional connectivity, and showed aberrant bilateral connectivity of default mode network (DMN), IFG, and cerebellum in the AVH group. These inconsistent findings mean that it is important and necessary to investigate abnormal interhemispheric and intrahemispheric functional connectivity in AVHs across the board using a better approach. The analysis of functional connectivity density (FCD) represents the number of connections between voxels throughout the global or interhemispheric and intrahemispheric brain and is a data-driven graph theory method, which can identify the distribution of highly connected hubs in brain networks (Bullmore & Sporns, 2009; Lee et al., 2016; J. Zhu et al., 2017). To the best of our knowledge, the previous studies adopted FCD to explore altered voxel-wise interhemispheric and intrahemispheric functional connectivity in schizophrenia patients (Agcaoglu et al., 2018; Y. Zhang et al., 2019; F. Zhu et al., 2018; F. Zhu et al., 2019) but not in AVHs. The previous studies only found abnormal ROI-wise interhemispheric connections between auditory and language-related areas (Curcic-Blake et al., 2013; Gavrilescu et al., 2010). The language, auditory, and memory/limbic networks are of particular relevance for AVHs (Ćurčić-Blake et al., 2017). Therefore, voxel-wise interhemispheric and intrahemispheric FCD might be necessary to identify the distribution of highly connected hubs in abnormal brain networks for AVHs.

The above abnormal connections in schizophrenia patients with AVHs are static. The traditional functional connectivity, including interhemispheric and intrahemispheric parts, is based on the implicit assumption of spatial and temporal stationary of fMRI data, which is over simple for complex activities of the human brain (Allen et al., 2014). When the mental activity is unconstrained, dynamics are potentially even more prominent under the resting state. Evidence suggested that dynamic functional connectivity supply us new information about abnormal functional connectivity on the brain of patients with various diseases (Chen et al., 2021; Y. Chen, Cui, et al., 2020; Demirtaş et al., 2016; Y. Li et al., 2020; R. Wang, Sun, et al., 2021; J. Zhu et al., 2021). Previous findings showed altered dynamic functional connectivity in the DMN and the language network in schizophrenia patients with AVHs (Geng et al., 2020; Weber et al., 2020; W. Zhang et al., 2018). Moreover, Guo et al. (2020) explored altered temporal variability of interhemispheric and intrahemispheric dynamic FCD (dFCD) using a sliding window approach in autism spectrum disorder, and the interhemispheric and intrahemispheric FCD were discomposed from the whole-brain FCD. Although numerous studies explored the neural mechanism of AVHs, it was unclear whether schizophrenia patients with AVHs exhibited abnormal intrahemispheric and interhemispheric dFCD.

In this study, we explored the temporal variability of voxel-wise contralateral and ipsilateral dFCD, denoting the interhemispheric and intrahemispheric parts, in drug-naïve first-episode schizophrenia (FES) patients with AVHs. The intrahemispheric and interhemispheric of the dFCD were further quantified using the standard deviation of dFCD variance patterns across time. Then, we compared the temporal changes of the intrahemispheric and interhemispheric dFCD between schizophrenia patients with AVHs and without AVH (NAVH) and healthy subjects. Moreover, the correlation analysis was performed between clinical measures with significant results between groups. In this study, we aimed to find abnormal temporal variability of interhemispheric and intrahemispheric dFCD in schizophrenia patients with AVHs and hypothesized that these might be exhibited in the pivotal components of auditory and language pathways.

2 | METHODS

2.1 | Participants

This study randomly recruited 100 drug-naïve FES patients and 50 age- and sex-matched healthy controls (HCs) (Table 1). All patients

TABLE 1 The demographic and clinical data of schizophrenia patients, with and without AVH, and healthy controls

	AVH	NAVH	HC	$F/X^2/t$ values	*p* values
Age (SD, $n = 50$)	21.3 (7.7)	21.9 (7.2)	22.0 (7.7)	0.130	.871
Sex (M/F, $n = 50$)	24/26	25/25	24/26	0.053	.974
AHRS (SD, n = 50)	23.86 (5.99)	-	-	-	-
PANSS (SD) (AVH: $n = 33$; NAVH: $n = 50$)					
PANSS total	83.3 (14.6)	83.0 (14.8)	-	0.098	.922
PANSS positive	20.3 (5.4)	19.2 (6.3)	-	0.774	.441
PANSS negative	20.8 (4.8)	21.1 (5.7)	-	−0.209	.835
PANSS general	42.2 (7.5)	42.6 (7.9)	-	−0.264	.793
PANSS hallucinations	4.1 (1.5)	2.2 (1.5)	-	5.041	.00002

Abbreviations: AHRS, Auditory Hallucination Rating Scale; AVH, auditory verbal hallucination; F, female; HC, healthy control; M, male; NAVH, without auditory verbal hallucination; PANSS, Positive and Negative Syndrome Scale.

did not take any antipsychotic drugs. Schizophrenia diagnosis by a psychiatric specialist was made using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The illness duration of all patients was less than 3 years, and the diapause was less than 6 months. Symptom severity of schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS). Fifty patients reported experiencing AVHs within the past 4 weeks, most within the past week, while the other 50 patients reported no AVH in their lifetime or in the past 4 months. This was based on the PANSS scores at the time of screening, as well as detailed information regarding past symptomatology that was acquired in patient interviews and examination of the patients' medical records. The severity of AVHs was assessed using the Auditory Hallucination Rating Scale (AHRS). Eleven patients reported that the voices appeared at least once a week; the other 39 patients reported hearing these voices at least once a day. Twelve patients reported that the voices continued for several seconds at a time; 26 patients reported voices lasting several minutes; 5 patients reported voices lasting more than an hour; and 7 patients reported that the voices could continue for several hours at a time. We collected PANSS data for 33 of the AVH patients and for all NAVH patients and collected AHRS data for all AVH patients. All participants were right handed. Exclusion criteria for all participants were as follows: (1) contraindications for MRI, (2) alcohol or drug abuse, and (3) severe physical disability or traumatic head injury. HCs had no history of neurological or psychiatric illness. All subjects gave the informed consent, and this study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

2.2 | Data acquisition

All subjects were scanned using a 3.0 T MRI scanner (Discovery MR750, GE, USA) with an eight-channel receiver array head coil. Head motion and scanner noise were reduced using foam padding and earplugs. All participants were asked to remain alert with their eyes closed. We collected MRI data from all participants. Structural images were acquired using a 3D T1 BRAVO sequence with the following settings: repetition time (TR)/echo time (TE) = 8.2/3.2 ms, slice number = 188, slice thickness = 1 mm, slice gap = 0 mm, flip angle = 12°, field of view (FOV) = 25.6 × 25.6 cm^2, number of averages = 1, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm^3, scan time = 4.33 min. Functional images were acquired transversely with gradient spin echo planar imaging (EPI) sequence with the following settings: TR/TE = 2000/30 ms, slice number = 32, slice thickness = 4 mm, slice gap = 0.5 mm, flip angle = 90°, FOV = 22 × 22 cm^2, number of averages = 1, matrix size = 64 × 64, voxel size = 3.4375 × 3.4375 × 4 mm^3. A total of 180 volumes were collected, resulting in a total scan time of 6 min. The patients in the AVH group reported that they experienced no hallucinations during scanning, and all participants also reported that they were alert in the scanning session.

2.3 | Data preprocessing

Data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF) programs, which are based on Statistical Parametric Mapping (SPM12) and MATLAB (MathWorks). The first five volumes were discarded due to unsteady magnetization. Slice-timing and realignment were performed. We excluded the subjects whose head motion with translational or rotational motion was higher than 3 mm or 3°, and three patients in the NAVH group were excluded. Then, data were spatially normalized to the Montreal Neurological Institute template (resampling voxel size = 3 × 3 × 3 mm^3), detrended, and filtered (0.01–0.08 Hz). Image volumes with framewise displacement (FD) >0.2 mm were scrubbed to reduce the effect of head motion using spline interpolation (He et al., 2018). In this study, we failed to find significant differences in FD between groups ($F = 0.302$, $p = .740$). Nuisance covariates were regressed, including Friston 24 head motion (Friston et al., 1996) parameters and white matter and cerebrospinal fluid signals). The global signal was not regressed out as has been recently suggested (Yang et al., 2017) when processing functional data from patients with schizophrenia.

2.4 | dFCD estimation and temporal variability

Global, contralateral, and ipsilateral dFCD were computed using a sliding-window method. The length of the window we set was 50 TRs (He et al., 2018; R. Li et al., 2018), and this window was used to slide on the time course with a step of 1 TR (2 s). In total, 126 (175–50 + 1) temporal windows were produced, then we calculated FCD for each window. We first calculated the global FCD for each window as the mean number of functional connectivity between one voxel (seed) and other voxels (target voxels) in the whole brain. The global FCD was limited voxels within the gray matter template. Functional connectivity between voxels was calculated using Pearson's correlation, with a correlation coefficient threshold of $p < .05$, uncorrected. Then we discomposed the global FCD into contralateral and ipsilateral FCD based on the relative positions of seed and target voxels. Contralateral (interhemispheric) FCD at each voxel referred to the number of functional connectivity with all voxels in the opposite hemisphere, and ipsilateral (intrahemispheric) FCD at each voxel referred to the number of functional connectivity with all voxels in the same hemisphere. To examine the reproducibility of our findings, we repeated our findings with different window lengths (30 TRs and 80 TRs), correlation thresholds ($p < .01$ and $p < .001$) and shifting step (2 TRs) (Figures S1–S3). We employed one common metric to describe its dynamic characteristics in global, contralateral, and ipsilateral dFCD that was the standard deviation of the dFCD variance patterns over time. After that, *Z*-transformed dFCD variance maps were obtained and spatially smoothed using an isotropic Gaussian kernel (full width at half maximum [FWHM] = 6 mm).

When we set the window length as 175 TRs, global, contralateral, and ipsilateral static FCD (sFCD) was obtained in accordance with FCD analysis for each window. For comparing with dFCD, we also calculated sFCD using Pearson's correlation, with a correlation coefficient threshold of $p < .05$, uncorrected. Finally, *Z*-transformed connectivity maps were also obtained and were spatially smoothed (6 mm).

2.5 | Statistical analysis

One-way analysis of variance (ANOVA), two-sample *t* test, and χ^2 tests were, respectively, used to compare demographic data between groups with SPSS software. One-way ANOVA was also performed to compare the group differences in global, contralateral, and ipsilateral dFCD variances and sFCD between the AVH, NAVH, and HC groups, with age, sex and mean FD as covariates. The statistically significant threshold was set at voxel-wise $p < .001$, cluster-wise $p < .05$, and the minimum cluster size of 19 voxels after Gaussian random field (GRF) correction. We extracted the average dFCD variance or sFCD values of all voxels within each cluster from corrected statistical maps and performed post hoc comparisons using Bonferroni's test. Moreover, the correlation analysis was performed for clinical measures with significant results between groups. Multiple comparisons were corrected using the Bonferroni method ($p < .05/92 = .0005$).

3 | RESULTS

3.1 | Demographic and clinical data

No significant between-group differences in age or sex were found, and no significant between-group differences in PANSS total, positive, negative, or general scores between the AVH and NAVH groups, except for hallucination scores (Table 1).

3.2 | dFCD variance

The mean global, contralateral, and ipsilateral dFCD variance maps for the HC, AVH, and NAVH groups were presented in Figure 1. DFCD variance patterns in the HC group were maximal in the bilateral superior and middle temporal gyri, medial part of bilateral superior frontal gyri, bilateral middle and inferior occipital gyri, bilateral lingual and fusiform gyri, left IFG, whereas minimal in the right inferior parietal lobe, bilateral subcortical regions (thalamus, caudate, and hippocampus).

One-way ANOVA revealed significant between-group differences in global dFCD variance in the left middle temporal gyrus (MTG), left IFG and medial dorsal (MD) nuclei of the bilateral thalami, contralateral dFCD variance in the left MTG, anterior nucleus (AN) of the right thalamus and right inferior temporal gyrus (ITG), and ipsilateral dFCD variance in the left MTG and left IFG (Table 2 and Figure 2, left). We extracted global, contralateral, and ipsilateral dFCD variance values for each subject in the above regions that had significant between-group differences and performed one-way ANOVA followed by post hoc comparisons using Bonferroni's test. Compared with the HC group, the AVH and NAVH groups showed weaker global and ipsilateral dFCD variances in the left MTG and stronger global dFCD variance mainly in the MD nuclei of the bilateral thalami (Figure 2, right). Compared with the HC and NAVH groups, the AVH group showed stronger global and ipsilateral dFCD variances in the left IFG, stronger contralateral dFCD variance in the AD of the right thalamus and right ITG and weaker contralateral dFCD variance in the left MTG (Figure 2, right). Moreover, compared with the HC group, the NAVH group showed weaker global and ipsilateral dFCD variances in the left IFG (Figure 2, right).

In the AVH group, the global dFCD variance of the left MTG negatively correlated with PANSS general scores ($r = -.351$, $p = .045$, uncorrected; Figure 3, left), and the contralateral dFCD variance of the left MTG negatively correlated with the AHRS scores ($r = -.319$, $p = .024$, uncorrected; Figure 3, central) and PANSS general scores ($r = -.356$, $p = .042$, uncorrected; Figure 3, right). However, these significances did not remain after Bonferroni correction ($p < .05/92 = .0005$). We did not find any significant correlation between clinical measures and significant results in the NAVH group.

3.3 | Static FCD

One-way ANOVA revealed significant between-group differences in global, contralateral, and ipsilateral sFCD mainly in the MD nuclei of

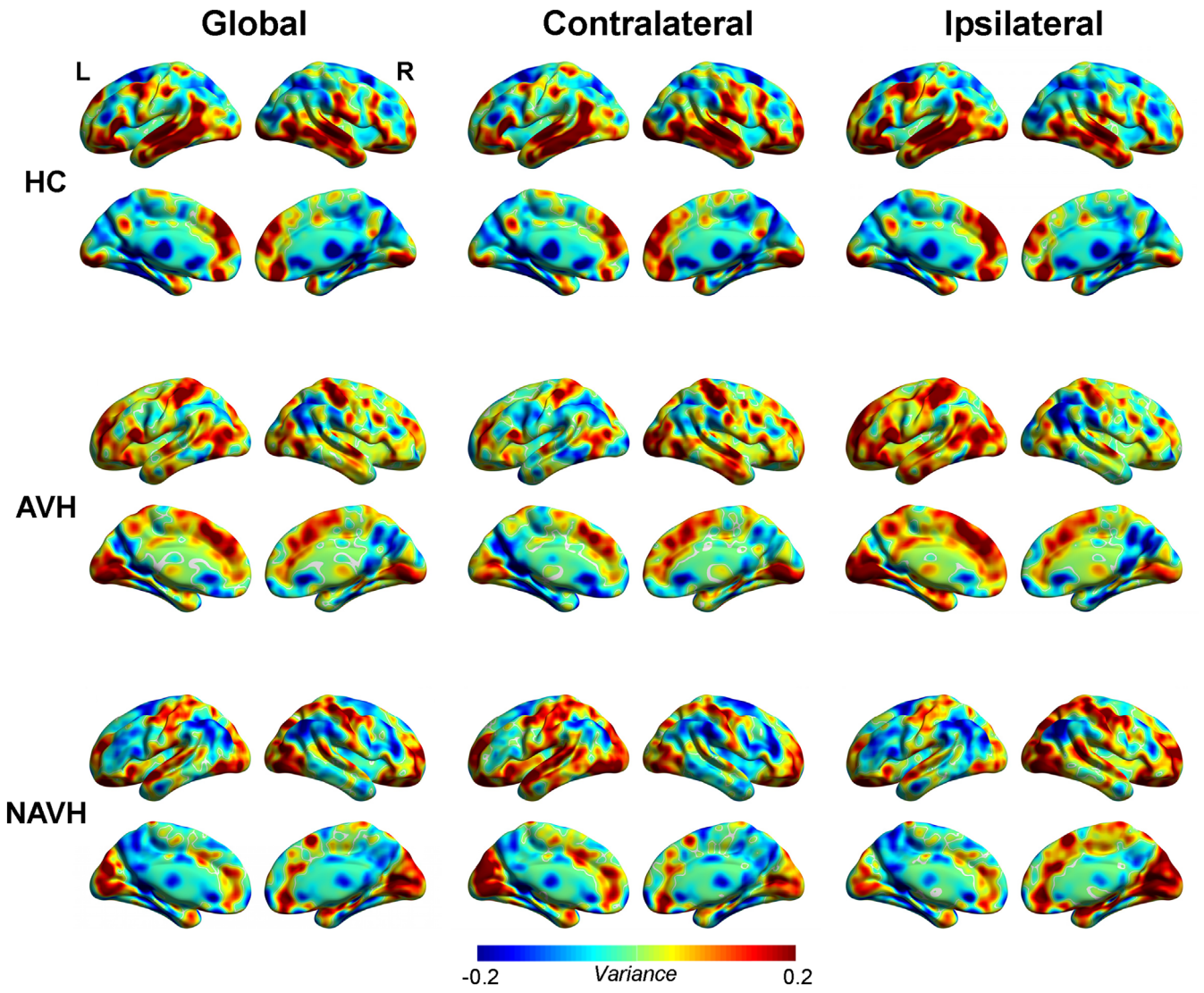

FIGURE 1 Average dynamic functional connectivity density (dFCD) variance for healthy controls (HCs) and schizophrenia patients with auditory verbal hallucinations (AVHs) and without auditory verbal hallucination (NAVH)

TABLE 2 Between-group differences in the global, contralateral, and ipsilateral dFCD variances

dFCD variance	Regions	Hemisphere	Cluster size (voxels)	Peak MNI coordinate			Peak *F* values
				X	Y	Z	
Global	MTG	L	49	−60	−42	−6	12.65
	IFG	L	20	−51	18	15	17.30
	Thalamus	B	19	3	−15	6	11.04
Contralateral	MTG	L	62	−57	−42	−3	14.89
	Thalamus	R	22	15	−6	6	12.51
	ITG	R	50	45	−15	−30	12.46
Ipsilateral	MTG	L	32	−60	−33	−3	11.56
	IFG	L	44	−51	18	15	25.39

Abbreviations: B, bilateral; dFCD, dynamic functional connectivity density; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; MTG, middle temporal gyrus; R, right.

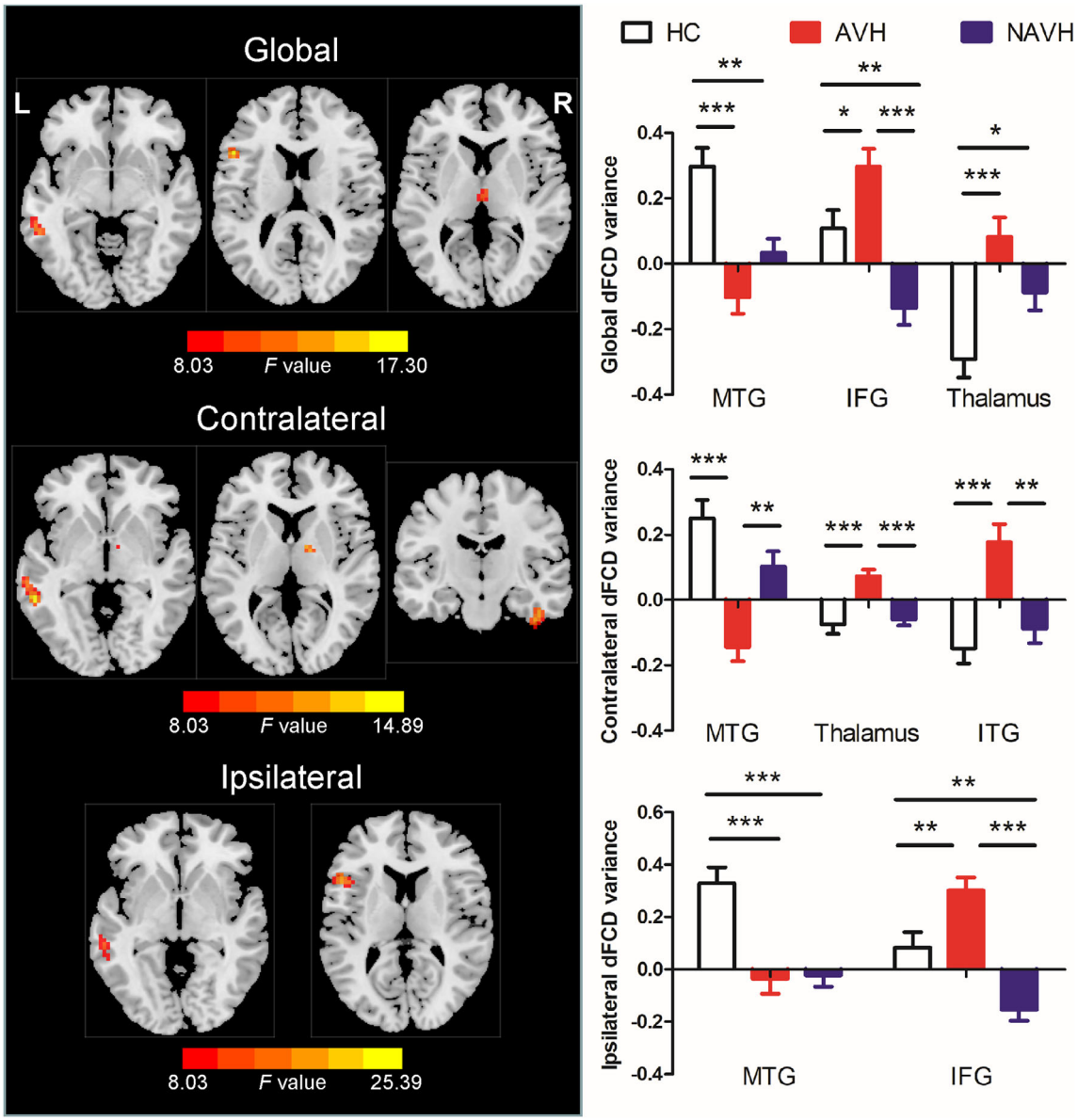

FIGURE 2 Between-group differences for global, contralateral and ipsilateral dFCD variances. AVH, auditory verbal hallucination; HC, healthy control; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; L, left; MTG, middle temporal gyrus; NAVH, without auditory verbal hallucination; R, right. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

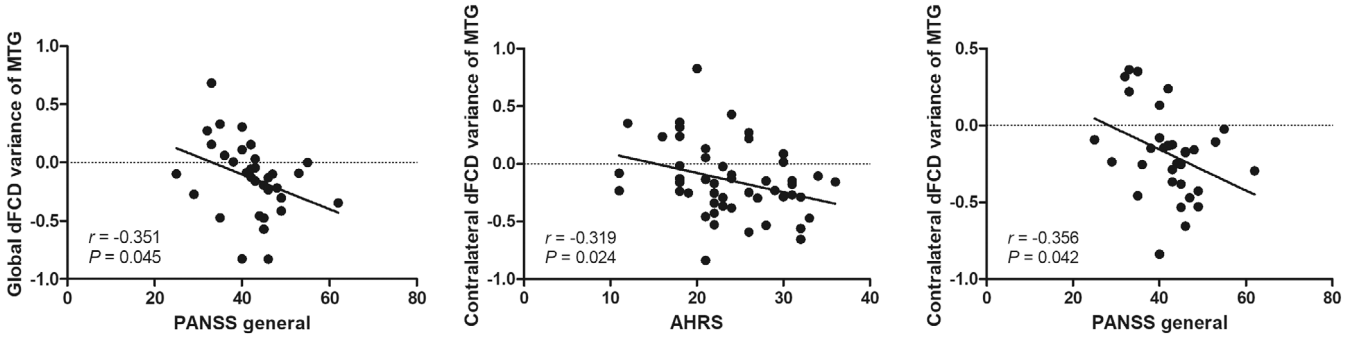

FIGURE 3 Relationships between abnormal global and contralateral dynamic functional connectivity density (dFCD) variances and schizophrenia symptom severity. AHRS, Auditory Hallucination Rating Scale; MTG, middle temporal gyrus; PANSS, Positive and Negative Syndrome Scale

TABLE 3 Between-group differences in the global, contralateral, and ipsilateral sFCD

sFCD	Regions	Hemisphere	Cluster size (voxels)	Peak MNI coordinate			Peak *F* values
				X	Y	Z	
Global	Thalamus	B	112	0	−15	9	13.65
Contralateral	Thalamus	B	97	0	−15	9	13.82
Ipsilateral	Thalamus	B	118	3	−18	9	13.55
	IFG	R	32	27	24	−21	13.77

Abbreviations: B, bilateral; IFG, inferior frontal gyrus; R, right; sFCD, static functional connectivity density.

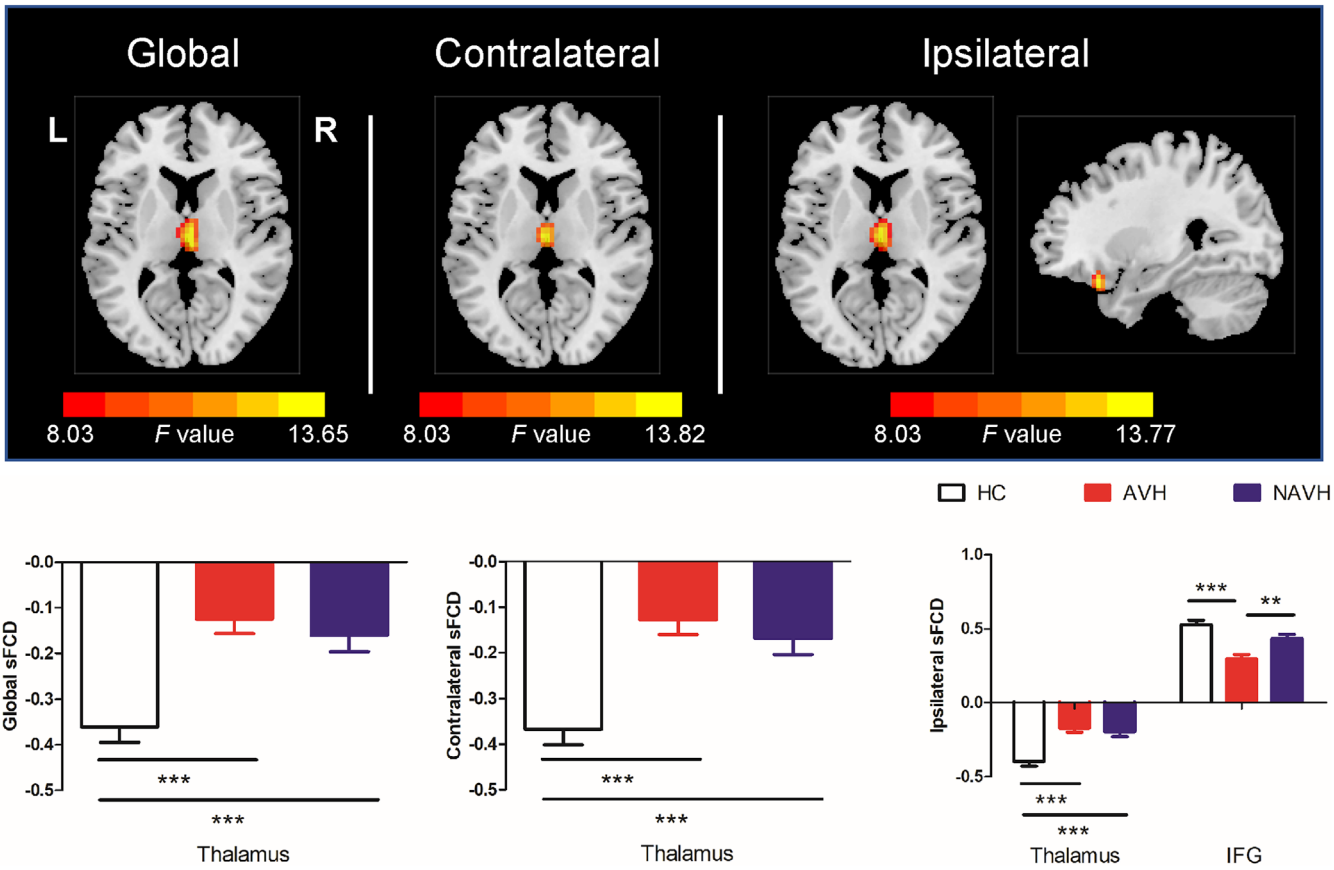

FIGURE 4 Between-group differences for global, contralateral and ipsilateral static functional connectivity density (sFCD). AVH, auditory verbal hallucination; HC, healthy control; IFG, inferior frontal gyrus; L, left; NAVH, without auditory verbal hallucination; R, right.
$^{**}p < .01$, $^{***}p < .001$

the bilateral thalami, and ipsilateral sFCD in the right IFG (Table 3 and Figure 4, upper). We extracted global, contralateral, and ipsilateral sFCD values for each subject in the above regions that had significant between-group differences and performed one-way ANOVA followed by post hoc comparisons using Bonferroni' s test. Compared with the HC group, the AVH and NAVH groups showed higher global, contralateral, and ipsilateral sFCD mainly in the MD nuclei of the bilateral thalami (Figure 4, lower). Moreover, compared with the HC and NAVH groups, the AVH group showed weaker ipsilateral sFCD in the right IFG (Figure 4, lower). No significant correlation was found between abnormal global, contralateral, or ipsilateral sFCD and symptom severity in the AVH or NAVH groups.

4 | DISCUSSION

Using the methods of FCD and sliding-widow analysis, we characterized the temporal variability of interhemispheric and intrahemispheric dFCD in drug-naïve FES patients, with total PANSS-matched AVHs and NAVH, and HCs. Compared with the NAVH and HC groups, the AVH group showed weaker interhemispheric dFCD variability in the left MTG, as well as stronger interhemispheric dFCD variability in the right ITG and the AN of the right thalamus and stronger intrahemispheric dFCD variability in the left IFG. Both the AVH and NAVH groups showed weaker intrahemispheric dFCD variability in the left MTG than the HC group. Moreover, abnormal contralateral dFCD

variance of the left MTG correlated with the severity of auditory hallucinations in the AVH group. These findings help us further understanding the abnormal functional connectivity in AVHs.

Our findings showed some pattern in interhemispheric and intrahemispheric FCD abnormalities in drug-naïve FES patients with AVHs, which further supported the findings of abnormal local and long-range connectivity in the previous studies (Chang et al., 2017; C. Chen, Wang, et al., 2020; Hare et al., 2021; Mondino et al., 2016; Zhuo et al., 2016). It suggests the importance to consider the factors of topological location and anatomical distance in future research investigating abnormal brain network in AVHs. Moreover, we explored voxel-wise interhemispheric and intrahemispheric dFCD variances and sFCD in drug-naïve FES patients with AVHs. In our previous study, we investigated voxel-wise resting-state functional connectivity of the thalamic nucleus in drug-naïve FES patients with AVHs and found that the critical structure in the thalamus underlying AVHs is the PuM nucleus, and the DM nucleus and AN of the thalamus dysconnectivity are specific for schizophrenia, but not AVHs (Wei et al., 2022). Here, we found abnormal interhemispheric dFCD variance of the thalamic AN in AVHs and abnormal dFCD and sFCD of the bilateral thalamic DM nuclei in drug-naïve FES patients. Therefore, dynamic functional connection or a combination of static and dynamic functional connectome approaches may provide more evidence for the neural substrate of AVHs.

Similar to global FCD, contralateral and ipsilateral FCD show interhemispheric and intrahemispheric functional hubs in the neural networks (Guo et al., 2020; Tomasi & Volkow, 2010, 2011). The AVH group showed abnormal interhemispheric and/or intrahemispheric dFCD variability in the left MTG, left IFG, right ITG, and AN of the right thalamus. The upper regions are the pivotal components of auditory and language pathways (Acheson & Hagoort, 2013; Nauchi & Sakai, 2009; Opitz et al., 2002; Wahl et al., 2008) and highly associate with the neural mechanism of AVHs (Shergill et al., 2004; Silbersweig et al., 1995; Vercammen et al., 2011; Wei et al., 2020). Abnormal activations and connectivity in auditory and language pathways have highly linked to schizophrenia patients with AVHs (Benetti et al., 2015; Chang et al., 2017; Lavigne & Woodward, 2018; Steinmann et al., 2019; Xie et al., 2019). Our findings also indicated that interhemispheric dFCD variance could clearly distinguish the AVH group from the NAVH and HC groups. Moreover, the interhemispheric dFCD variance of the MTG correlated with the AHRS scores and PANSS general symptom scores. Our previous findings indicated aberrant cerebello-thalamo-cortical functional and effective connectivity in drug-naïve FES patients with AVHs, and the cortex also included the MTG and IFG (Wei et al., 2022). A significant deficit in the static interhemispheric and intrahemispheric connectivity in the left MTG was revealed in schizophrenia (Y. Zhang et al., 2019), which is similar to our findings. The previous study also indicated that aberrant bilateral static interhemispheric dysconnectivity of the IFG might contribute to the occurrence of AVHs (Chang et al., 2015). The previous studies utilized the parameter of asymmetry (PAS) (static interhemispheric functional connectivity subtracts static intrahemispheric functional connectivity) to describe functional asymmetry, and reduced PAS scores of the MTG was found in schizophrenia patients and unaffected siblings compared with healthy subjects (F. Zhu et al., 2018). Abnormal activations and connectivity in these regions might be the core neurobiological markers of auditory and language impairments in schizophrenia patients with AVHs (Hashimoto et al., 2010; Hoffman & Hampson, 2011; Lavigne & Woodward, 2018). From a dynamic perspective, our present findings supplement evidence for the neural mechanism of AVHs and provide sensitive views of the temporal variability changes of functional connection hubs that may be masked in conventional static studies. The previous and present studies consistently demonstrate the important role of the auditory and language pathways associated with the MTG, IFG, and thalamus in the pathophysiological mechanisms underlying AVHs.

The findings of interhemispheric and intrahemispheric dFCD for AVHs also support hybrid models of AVH (i.e., top-down and bottom-up, corollary discharge, nondominant language intrusion, and interhemispheric miscommunication) that was overviewed by Ćurčić-Blake et al. (2017). Part of our findings might support one of the above-mentioned models, and another part of our findings might support anther model. First, abnormal interhemispheric and intrahemispheric dFCD of the MTG might correspond to impaired bottom-up sensory processing (perception deficit) and abnormal interhemispheric dFCD of the thalamus and intrahemispheric dFCD of the IFG might correspond to impaired top-down prior expectation (attention deficit), which might also suggest the imbalance in top-down/bottom-up influences (Hugdahl, 2009). Second, abnormal intrahemispheric dFCD of the MTG and IFG might also correspond to impaired corollary discharge. The previous studies showed deficient corollary discharge in schizophrenia patients with AVHs (Ford et al., 2007) and indicated that fronto-temporal transcranial direct current stimulation improved corollary discharge function in schizophrenia (Bose et al., 2019). Third, our findings also showed abnormal interhemispheric dFCD and intrahemispheric sFCD in nondominant language areas, such as the right ITG and IFG, which was similar to the previous studies (Sommer et al., 2008; van Lutterveld et al., 2014). Finally, our findings directly support interhemispheric miscommunication (Curcic-Blake et al., 2013; Gavrilescu et al., 2010). Compared with the NAVH and HC groups, the AVH group showed weaker interhemispheric dFCD variability in the left MTG, as well as stronger interhemispheric dFCD variability in the right thalamus and ITG.

We also investigated abnormal interhemispheric and intrahemispheric sFCD in drug-naïve FES patients with AVHs. The findings showed higher interhemispheric and intrahemispheric sFCD on the DM nuclei of bilateral thalami in drug-naïve FES patients with AVHs and NAVH and weaker intrahemispheric sFCD on the right IFG in patients with AVHs. As an important component of aberrant neural circuitry in schizophrenia, the gray matter volume of the DM nucleus of the thalamus is impaired in schizophrenia (Gilbert et al., 2001; Sui et al., 2015), higher functional connection might be a compensatory response to structural impairments. Moreover, the previous studies found reduced PAS scores of the thalamus and IFG was found in schizophrenia patients and ultra-high risk for psychosis (F. Zhu

et al., 2019). However, we found opposite pattern between the whole-brain and intrahemispheric dFCD variances and sFCD in drug-naïve FES patients with AVHs or NAVH, which is consistent with the findings in the previous study exploring the neural substrates of other neurological diseases, such as bipolar depression and major depressive disorders (Pang et al., 2020), generalized anxiety disorder (Lu et al., 2020), and Parkinson's disease (S. Wang, Cai, et al., 2021). Higher dFCD may reflect the indicative of flexible communication, but it may also be a sign of unstable interactions (S. Wang, Cai, et al., 2021). And weaker sFCD may be the result of unstable interactions.

Several limitations should be noted when interpreting our findings. First, although we designed three groups that included 50 subjects for each group, the sample size is small. The future study should increase the sample size to make the findings more reliable. Second, we showed abnormal interhemispheric and intrahemispheric dFCD in drug-naïve FES patients with AVHs, but how temporal dynamics of interhemispheric and intrahemispheric dFCD develop in other illness stage was unclear. The interhemispheric connectivity between posterior auditory regions may depend on the phase of illness, with increases in nonpsychotic individuals and FES patients and decreases in chronic patients (Ćurčić-Blake et al., 2017). The future study should explore whether the illness stage affect interhemispheric and intrahemispheric dFCD in AVHs. Third, we collected resting-state fMRI data, and it remains unknown whether abnormal interhemispheric and intrahemispheric dFCD in AVHs associated with impaired auditory processing. Future task state fMRI studies are needed to examine the association between interhemispheric and intrahemispheric dFCD variability and auditory cognitive function.

In conclusion, the findings demonstrate that abnormal temporal variability of interhemispheric and intrahemispheric dFCD in drug-naïve FES patients with AVHs mainly focuses on interhemispheric pattern in temporal cortex and thalamus and intrahemispheric pattern in the frontal cortex, and these regions are pivotal components of auditory and language pathways.

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CONFLICT OF INTEREST

All authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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