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Targeting auditory verbal hallucinations in schizophrenia: effective connectivity changes induced by low-frequency rTMS

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Low-frequency repetitive transcranial magnetic stimulation (rTMS) has emerged as an effective intervention for alleviating symptoms of psychiatric disorders, particularly schizophrenia characterized by persistent auditory verbal hallucinations (AVH). However, the underlying mechanism of its action remain elusive. This study employed a randomized controlled design to investigate the impact of low-frequency rTMS on the neural connectivity at the stimulate site, specifically left temporoparietal junction (TPJ), in schizophrenia patients with suffering from AVH. Using Dynamic Causal Modeling (DCM), this study assessed changes in directed connectivity patterns and their correlations with clinical symptomatology. The results demonstrated significant improvements in AVH. Notably, significant changes in connectivity were observed, including both abnormal functional connectivity and effective connectivity among multiple brain regions. Particularly, the inhibition effects from the left precentral gyrus and left medial superior frontal gyrus to the left TPJ were closely associated with improvements in AVH. These findings underscore the potential of rTMS to effectively modulate neural pathways implicated in hallucinations in schizophrenia, thereby providing a neurobiological foundation for its therapeutic effects.

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INTRODUCTION

Schizophrenia is a severe and chronic mental disorder characterized by a spectrum of symptoms, including psychotic manifestations such as hallucinations and delusions, as well as cognitive and emotional dysfunctions [1]. Auditory verbal hallucinations (AVH) are most the common core of schizophrenia, affecting approximately 60–80% of individuals with the disorder [2]. These hallucinations often involve hearing voices without external stimuli [3]. Persistent AVH significantly impairs daily functioning, disrupts social interactions, and diminishes quality of life [4]. The chronic and intrusive nature of AVH can lead to heightened anxiety, depression, and somatic complaints [5], further complicating the management of schizophrenia.

Traditionally, antipsychotic medications have been primary treatment for AVH. Although these medications are beneficial, their side effects, including dystonia, parkinsonism, and akathisia, are problematic [6]. Non-pharmacological treatments such as cognitive-behavioral therapy, avatar therapy, and neurofeedback training have also been explored as alternatives or adjuncts to medication [7–9]. However, these approaches have limitations, including the need for extensive patient engagement, long-term commitment, and expensive equipment, which restrict their effectiveness and accessibility, particularly for individuals with severe symptoms. Recent evidence suggests that non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS), may offer an effective alternative for relieving AVH with fewer side effects and relatively safety. rTMS modulates cortical excitability through electromagnetic induction [10]. It is thought to induce longer-lasting changes at the neuronal level, primarily through mechanisms like long-term potentiation or depression [11]. Studies have highlighted its potential, particularly when administered at low-frequency (typically 1 Hz), to alleviate AVH symptoms [11–13], despite some reports of negative findings [14]. This form of rTMS is thought to decrease cortical excitability and restore the neurophysiological balance often disrupted in schizophrenia [15].

Neuroimaging studies have further elucidated the impact of rTMS on brain functional network in schizophrenia with AVH. For instance, Bais and colleagues explored the effects of 10-day 1 Hz rTMS treatment on neural network with an inner speech task [16]. They found that rTMS targeting the left temporoparietal junction (TPJ) decreased the contribution of the left supramarginal gyrus to the bilateral fronto-temporal network, potentially reducing speech intrusions. A seed-based resting state functional connectivity (FC) analysis showed that rTMS on the left TPJ was associated with increased FC between the left TPJ and the right insula [17]. Moreover, our recent study indicated that low-frequency TMS treatment was linked with enhanced static FC of the left TPJ with prefrontal areas and increased dynamic FC with frontoparietal areas in the active group [18]. These findings suggest that low-

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frequency rTMS may affect the connectivity between its stimulation target and associated brain regions.

However, while FC analysis has provided valuable insights, it inherently lacks the capability to determine the directionality of the connections among these areas, thereby limiting a deeper understanding of underlying neural mechanisms of rTMS treatment on AVH. Effective connectivity (EC) analysis based on dynamic causal modelling (DCM), can infer the causal influences from one region to another and depict the signal flow directions within a brain network [19]. This approach has proven particularly insightful in enhancing our understanding of the pathophysiology of neuropsychiatric disorders. For instance, reduced EC from left superior temporal cortex to anterior cingulate cortex has been observed in schizophrenia patients with AVH, and revealing impaired functional integration between self-generated and external speech sources in AVH [20]. Furthermore, a study by Chen and colleagues assessed the EC within the reward network in schizophrenia patients using DCM. Their findings indicated weaker EC from right ventral striatum to ventral segmental area [21], suggesting disrupted neural causal interactions within the reward network associated with AVH.

While it is established that rTMS can modulate brain activity by targeting specific regions like the TPJ, the precise neural circuits involved and the directional influences (inhibitory or excitatory) between these circuits remain unclear. By focusing on regions that are functionally connected to the TPJ, this study aimed to investigate the directionality of these interactions and their relationship with symptom improvements using DCM following low-frequency rTMS in schizophrenia patients with AVH, to enhance our understanding of the underlying neural mechanisms of rTMS treatment on AVH. We assumed that low-frequency rTMS would specifically modulate key neural circuits involved in auditory and language processing, leading to measurable changes in DCM parameters, and that such alternations would associate with clinical improvements in AVH symptoms.

METHODS

Patients

The required sample size for this study was determined using the G*Power software [22]. A statistical power (1-β) of 0.90 was set with an alpha level of 0.05 and a medium effect size (Cohen's $d = 0.5$), indicating that a total sample size of 44 would allow sufficient power to detect group differences in matched pairs. A total of 58 patients were recruited, all of whom were diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Recruitment criteria were based on clinical guidelines and literature [23, 24]. Specifically, the inclusion criteria for patients were as follows: (1) persistent AVH occurring daily despite treatment with at least two antipsychotic medications; (2) a minimum of five AVH episodes per day over the past month. All patients were maintained on a stable dose of antipsychotics throughout the study. Exclusion criteria included: (1) a history of neurological disorders or significant head injury; (2) substance abuse; and (3) contraindications to MRI.

Patients were randomly assigned to receive either rTMS treatment ($n = 32$) or sham rTMS ($n = 26$) at the same site. Randomization was performed using a computer-generated random numbers table and was conducted by an independent researcher to eliminate any potential bias. This process was blinded to both the patients and the clinical raters. Only the rTMS operators were aware of the group assignments, as it was necessary for correctly administering the treatment or sham procedure. The study's workflow is depicted in Fig. 1.

The study was approved by the Medical Ethics Committee of Xijing Hospital, Fourth Military Medical University, and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the participants. This study was registered in China Clinical Trials (registration number: ChiCTR2100041876; https://www.chictr.org.cn).

Clinical assessments

Schizophrenia symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) to assess positive, negative, and general psychopathology [25]. The Auditory Verbal Hallucinations Rating Scale (AVHRS) [26] measured the frequency, duration, and intensity of AVH. Assessments were conducted by experienced psychiatrists within three days before and after the intervention.

rTMS procedures

rTMS was administered to the left TPJ, identified by the 10-20 EEG system (midpoint between T3 and P3 electrodes: T3-P3), using a Magstim Rapid system equipped an 8-figure coil (YIRUIDE YCD-I, Wuhan, China). The stimulation parameters included a frequency of 1 Hz and intensity set at 110% of the individual's resting motor threshold. The rationale for selecting a 1 Hz frequency is grounded in its inhibitory effects on cortical excitability [27], which is particularly relevant for targeting hyperactivity in the left TPJ [28]. This region is a crucial component of the language circuit, implicated in the pathophysiology of AVH in schizophrenia [3]. The placebo condition involved a sham coil that mimicked the auditory stimulus of rTMS but delivered no magnetic field. Treatments consisted of 600 pulses delivered across 60 trains in daily 15-minute sessions, featuring 10 seconds of stimulation followed by a 5-second interval, for a total of 15 consecutive days.

Image data acquision

All participants underwent MRI scans on a 3.0 T system with an 8-channel head coil (Discovery MR750, GE, USA). Foam padding and earplugs minimized head movement and noise. During scans, participants were instructed to lie still, stay awake, and keep their eyes closed. The resting-state fMRI images were collected using the following parameters: repletion time (TR) = 2000 ms, echo time (TE) = 40 ms, slice thickness = 3.5 mm, slice number = 45 slices, flip angle (FA) = 90, filed of view (FOV) = 260 × 260 mm, and matrix size = 64 × 64. A total of 180 volumes were obtained during 7 min scan. Parameters of T1-weighted structural image included a TR of 9.1 ms, TE of 3.2 ms, FA of 10, FOV of 240 × 240 mm, matrix size of 256 × 256, providing a spatial resolution of 1 mm isotropic voxels. The image data acquisition parameters were selected to effectively capture resting-state blood oxygen level-dependent (BOLD) responses while minimizing susceptibility artifacts, making them suitable for clinical populations and connectivity analysis [29, 30].

Data preprocessing

fMRI data preprocessing was conducted using the DPABI toolkit t (https://rfmri.org/DPABI) based on statistical parametric mapping (SPM 12) (https://www.fil.ion.ucl.ac.uk/spm), integrated with the MATLBA platform (version 2020a; The Math Work, Inc., Natick, MA, USA). The initial 10 images were removed to allow magnetic field stabilization. Slice timing corrections was applied to address temporal differences between slices, followed by realignment procedures to mitigate head motion. Individual T1 image was then coregistered to the functional images and segmented into gray matter, whiter matter, and cerebrospinal fluid. The functional images were normalized to Montreal Neurological Institute (MNI) space using the segmented deformation fields and smoothed using a Gaussian kernel of 6 mm full-width at half maximum. Linear detrending, temporal filtering (0.01–0.01 Hz), and regression of covariates, including head motion parameters, white matter, and cerebrospinal fluid signals, and global mean signal, were employed. Participants with head movements greater than 3 mm or 3^0 in any direction were excluded.

For DCM analyses, data are prepared without spatial smoothing and temporal filtering. Head movement parameters and signals from the white matter and cerebrospinal fluid areas were incorporated into a general linear mode for each individual.

Functional connectivity profiles of the stimulation site

The TPJ was designated as the seed region for FC analysis, based on the previous study [17]. Time series data from the seed (within an 8 mm radius sphere) were extracted. Pearson correlation coefficients were calculated between the mean time series of the seed and those of all other brain voxels. The resulting correlation values were then transformed into *Z*-scores for normalization.

Effective connectivity analysis of the stimulation site with spectral DCM

Following seed-based functional connectivity analysis, regions showing significant connectivity differences with the left TPJ were identified. These

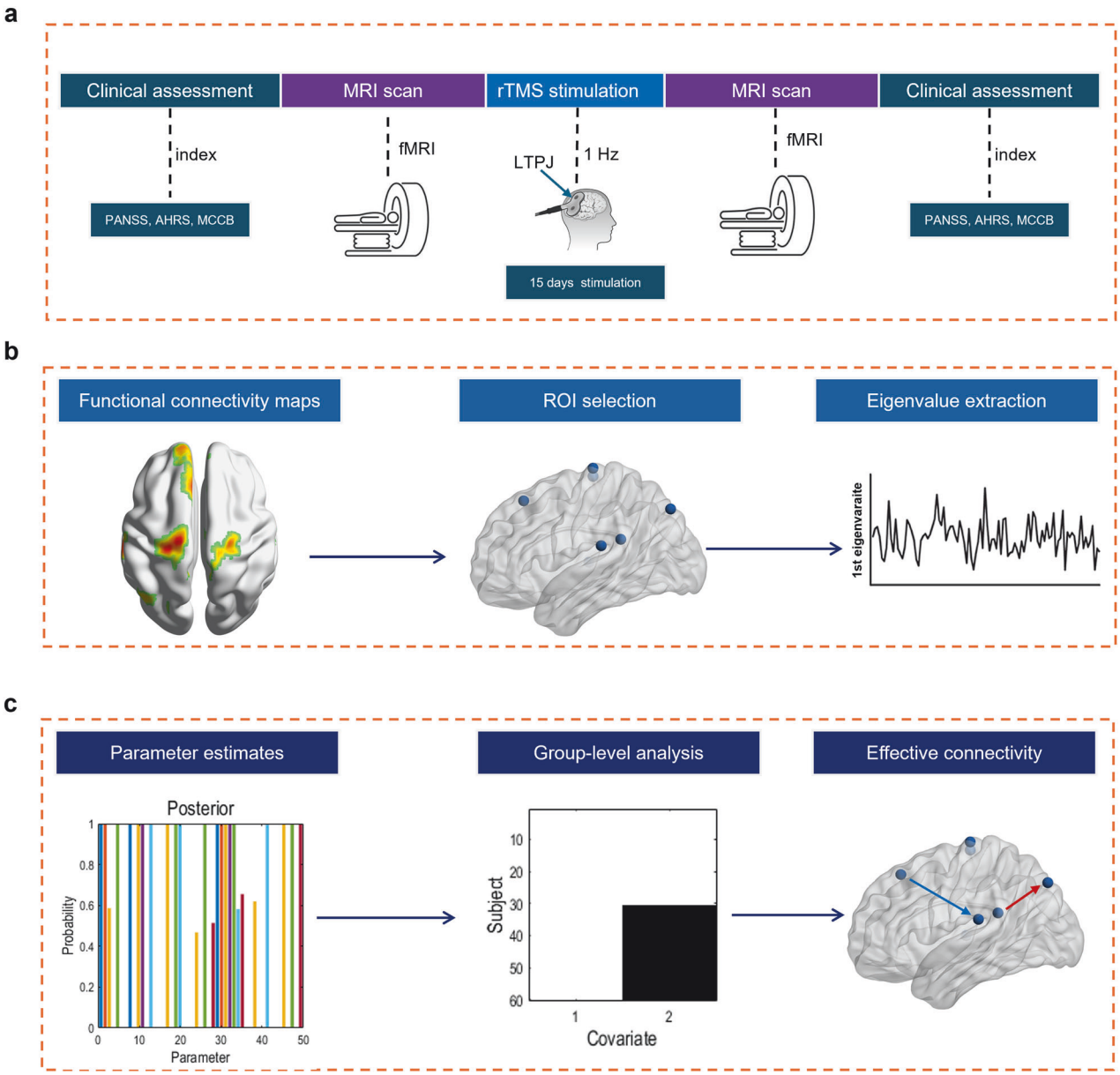

Fig. 1 Study workflow. a flowchart detailing the trial process. **b** analysis of target-based functional connectivity analysis and identification of regions of interest (ROIs). **c** flow diagram illustrating the application of dynamical causal modeling (DCM) for effective connectivity analysis.

regions of interest (ROIs) were defined within an 8 mm radius sphere, and their average time courses were extracted. At the first level, a fully connected EC network among the ROIs was estimated and constructed for each subject using spectral DCM [19]. This model employed a neuronal model that assumes linear coupling between regions, which is suitable for the analysis of spectral data. Priors were set based on standard DCM practices, allowing the model to estimate the strength and direction of connections. At the second level, parametric empirical Bayes (PEB) [31] was used to infer the group mean and group differences in EC for each link. To refine the models, Bayesian Model Reduction (BMR) [32] with a greedy search algorithm was employed to automatically remove redundant connections that did not contribute to model evidence. Finally, Bayesian Model Averaging (BMA) [33] was applied by averaging the final parameters of the selected models, weighting them by their posterior probabilities to ensure a robust representation of the underlying connectivity patterns.

Correlations between connectivity profiles and clinical responses

To determine whether connectivity estimates were associated with clinical responses, Pearson correlation coefficients were calculated to explore the relationship between connectivity measures and changes in clinical scores, particularly regarding AVH. A *p*-value of less than 0.05 was deemed statistically significant.

Statistical analyses

All demographic and clinical data are expressed as means and standard deviations. The distribution of sex was analyzed using the Chi-square test, while other variables were assessed using *t*-tests. Statistical analyses were performed using SPSS 22.0 (IBM SPSS Statistics; IBM, Armonk, NY). Specifically, independent *t*-tests were used to compare baseline scores between groups, and paired *t*-tests were employed to assess changes from pre- to post-treatment within each group. A *p*-value of less than 0.05 was considered statistically significant. Outliers, defined as values exceeding two standard deviations from the mean [34], were identified and excluded from the analysis.

RESULTS

Clinical symptom assessment

Due to excessive head movements, two patients from the active group and one patient from the sham group were excluded from

Table 1. Demographic and clinical characteristics of patients.

	Active group ($n = 30$)	Placebo group ($n = 25$)	t(χ^2)	*p*
Age	30.30 ± 4.46	31.46 ± 6.35	0.644	0.478
Sex	17 (13)	14 (12)	0.045	0.832
Education (years)	13.20 ± 2.67	12.81 ± 2.71	0.458	0.756
Duration of illness (month)	21.36 ± 4.89	20.35 ± 3.38	0.525	0.602
Dosage (CPED, mg/day)	584.8 ± 152.39	573.46 ± 136.88	0.218	0.828
PANSS				
Positive symptom	19.65 ± 4.60	18.65 ± 3.36	0.983	0.330
Negative symptom	19.85 ± 4.53	19.35 ± 3.02	0.178	0.860
General symptom	40.35 ± 6.65	39.50 ± 4.62	0.537	0.593
AHRS	27.45 ± 6.14	25.73 ± 5.08	0.689	0.494

PANSS positive and negative symptoms, *AHRS* auditory hallucination rating scale, *CPED* Chlorpromazine equivalent doses.

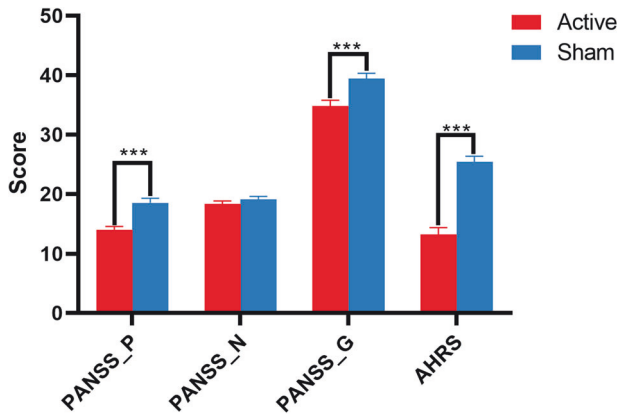

Fig. 2 Changes in symptom scores post-treatment. Significant reductions in positive symptoms (PNASS_P), general symptoms (PANSS_G) measured by the Positive and Negative Syndrome Scale (PANSS), and Auditory Hallucination Rating Scale (AHRS) scores in the active group compared to the sham group. No significant alternations in negative symptoms (PNASS_N) were observed between the two groups.

further analysis. Consequently, the remaining 30 patients in active group and 25 patients in sham group were include. There was no statistically significant difference between the two groups in terms of age ($t = 0.644$, $p = 0.478$), sex ($\chi^2 = 0.045$, $p = 0.832$), or educational levels ($t = 0.458$, $p = 0.756$). At baseline, there were no significant differences in positive symptoms ($t = 0.983$, $p = 0.330$), negative symptoms ($t = 0.178$, $p = 0.860$), general symptoms ($t = 0.537$, $p = 0.593$), or AHRS scores ($t = 0.689$, $p = 0.494$) between the groups (Table 1).

Following rTMS treatment, statistically significant reductions were observed in the active group in the positive symptoms ($t = 4.900$, $p < 0.001$) and general symptoms ($t = 3.517$, $p < 0.001$), and AHRS scores ($t = 8.010$, $p < 0.001$) compared to sham group (Fig. 2). Based on the reduction rate in AHRS scores (posttest-baseline/baseline) exceeding 50% [35], participants were divided into two subgroups: responders (19/30 = 63.33%) and nonresponders (11/30 = 36.67%).

Stimulation site based on functional connectivity

FC analysis employed a SPM flexible factorial design ANOVA with interaction terms to isolate the specific effects of active versus sham rTMS and the treatment effect over time (pre versus post). Significant changes in FC between the stimulation site and several key brain regions, including the precentral gyrus, superior temporal gyrus, and the medial superior frontal gyrus, were identified (Fig. 3a, b and Table 2). These regions, which exhibited significant FC differences, including the stimulation site (left TPJ) [18], were selected as ROIs for subsequent DCM analyses.

Post-hoc comparative analysis indicated that in the active group, post-rTMS treatment FC at the target site increased with the bilateral precentral gyrus and left superior temporal gyrus, while there was a reduction in FC with the left medial superior frontal gyrus and left inferior parietal gyrus (Fig. 3c). In contrast, the sham group exhibited opposite patterns of connectivity changes post-treatment (Fig. 3d).

The correlation analysis revealed a negative correlation between FC from the left TPJ to the left precentral gyrus and the reduction in AHRS scores ($r = -0.484$, $p = 0.036$) following rTMS treatment (Fig. 3e, f). No significant correlations were found between connectivity and reductions in positive or general symptoms.

Effective connectivity with DCM

The fully connected model was constructed to comprehensively assess the information flow between the stimulation site and the other ROIs. The average DCM connectivity pattern for the active group (at baseline and posttest) revealed inhibitory influences exerted by several nodes, including the bilateral precentral gyrus and the left inferior parietal lobule, on the stimulation target (left TPJ) (Fig. 4a, b). Additionally, Conversely, mean DCM connectivity changes in the sham group indicated excitatory influences from the left TPJ to other nodes, such as the right precentral gyrus (Fig. 4c, d).

Following rTMS treatment, the connection strength from the precentral gyrus to the stimulation site significantly decreased (Fig. 4e, f). Importantly, the reduction in AHRS scores was negatively correlated with the strength of connectivity from the left precentral gyrus to the stimulation site (Fig. 5) ($r = -0.476$, $p = 0.040$).

Comparative analyses showed that, compared to non-responders, responders exhibited decreased connectivity from multiple nodes, including the precentral gyrus and the left medial superior frontal gyrus to the target area (Fig. 6a, b). For responders, the connection strength from the left medial superior frontal gyrus to the target site was negatively correlated with reductions in AHRS scores ($r = -0.609$, $p = 0.006$) (Fig. 6c, d).

DISCUSSION

The present study investigated the EC changes at stimulate site (left TPJ) following low-frequency rTMS on schizophrenia patients with AVH. The main findings were as followed: (i) the active group exhibited significant improvements in the positive symptoms including AVH relative to sham group; (ii) opposing FC pattern

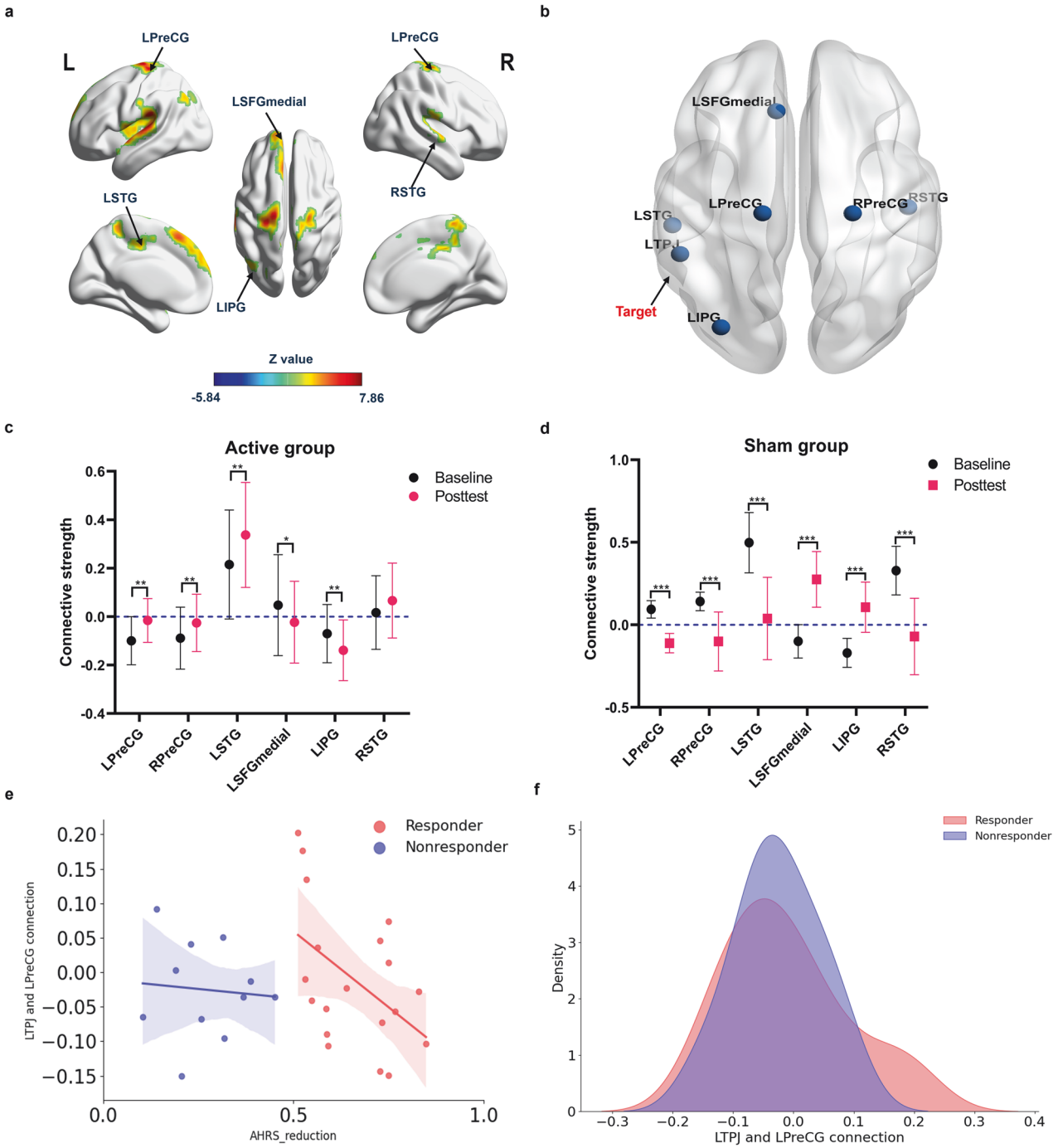

Fig. 3 Target-based functional connectivity analysis and clinical correlations. a Functional connectivity profiles of stimulate target. **b** Regions of interest selected based on functional connectivity analysis. **c** post-hoc comparisons of functional connectivity strength in the identified regions between the baseline and posttest at the active group. **d** post-hoc comparisons for the sham group. **e** Correlations between reductions in Auditory Hallucination Rating Scale (AHRS) score and the functional connectivity of LPreCG in active group post-treatment. **f** correlation distributions of responder and non-responder in active group. Details and abbreviations of regions are listed in Table 2. *$p < 0.05$, **$p < 0.01$,***$p < 0.001$.

changes at the stimulate site with several critical brain regions, including the precentral gyrus (PreCG), superior temporal gyrus (STG), medial superior frontal gyrus(SFGmedial), and inferior parietal gyrus (IPG), were observed between the active group and sham group post-treatment; (iii) inhibitory influences from the key brain regions such as the PreCG and SFGmedial to the stimulate site were noted in the active group; (iv) decreased connectivity from the left PreCG and left SFGmedial to the stimulation site was significantly associated with the reductions in AVH symptoms. The findings suggest that low-frequency rTMS could down-modulate specifical neural circuits, contributing to clinical improvements. The clinical symptom improvements demonstrated the effectiveness of low-frequency rTMS in reducing the severity of auditory hallucinations in schizophrenia patients. The results are consistent with the previous reports [23, 36, 37] and our previous studies [38–40], highlighting the specific therapeutic effects of a low-frequency rTMS treatment on AVH in schizophrenia.

Table 2. Target-based (Left TPJ) functional connectivity profiles.

Connectivity peak	Abbreviation	BA	Size	MNI coordination			z-value
				x	y	z	
Left Precentral Gyrus	LPreCG	4	227	−15	−21	75	7.84
Right Precentral Gyrus	RPreCG	6	68	24	−21	69	6.63
Left Superior Temporal Gyrus	LSTG	42	608	−54	−27	18	7.58
Left Medial Superior Frontal Gyrus	LSFGmedial	8	241	−9	30	51	6.94
Left Inferior Parietal Gyrus	LIPG	7	87	−33	−78	45	6.39
Right Superior Temporal Gyrus	RSTG	48	143	48	−18	6	6.34

TPJ tempoparietal junction, *BA* Brodmann area, *MNI* Montreal Neurological Institute.

Regions connected to stimulation site through rTMS treatment are critical for schizophrenia due to their involvement in critical functional networks governing auditory and language processing. Specifically, the PreCG is located on the lateral surface of the frontal lobe and anterior to the central sulcus, encompasses primary motor cortex (BA4) and premotor cortex (BA6). traditionally known for motor control [41, 42], this area also responds to multimodal stimuli from tactile, visual, and auditory signals [43, 44]. In speed processing, the PreCG supports high-level speech motor processing, akin to the classic Broca's area [45], with selective injuries causing deficits in verbal fluency [46, 47], indicating its role in motor speech production [48]. Volume reduction in the PreCG [49] and its abnormal connectivity [50] in schizophrenia populations imply it may contribute to the mechanisms of schizophrenia with AVH. The STG, positioned at the interface between lower-level auditory structures (primary auditory cortex, BA 41/42) and higher-level association areas (auditory association cortex, BA22) [51], plays a pivotal role in the production, interpretation and self-monitoring of speech [52, 53] and is implicated in the pathophysiology of schizophrenia, particularly language-related psychotic symptoms in schizophrenia such as AVH [54, 55]. Moreover, the superior frontal gyrus is located at the superior part of the prefrontal cortex and is involved in a variety of functions. Particularly, the SFGmedial is anatomically connected with the cingulate cortices and coupled with the IPG, critical nodes of the default mode network (DMN) [56, 57]. The DMN, active during rest and involved in self-referential thoughts and mind wandering [58], has disruptions linked to the pathophysiology of schizophrenia, particularly in symptoms like hallucinations and delusions [59, 60].

Post-hoc analysis of the active group revealed significant changes in target-based FC following the rTMS intervention. The stimulation target showed increased FC with the bilateral PreCG and the left STG. Conversely, there was a decrease in FC between the stimulate site and the left SFGmedial and left IPG. As mentioned above, the role of the PreCG extends into speech production, particularly in linguistic expression and syntactic comprehension, often impaired in schizophrenia [61, 62]. The observed increase in connectivity between the stimulate site and the PreCG following rTMS may reflect enhanced coordination within the motor aspects of speech, relevant in schizophrenia where verb fluency impairment can manifest as the disorganized speech characteristic of formal thought disorder [63]. Additionally, the STG, central to processing auditory information and speech perception [64], showed an increase in connectivity, potentially facilitating more effective auditory and language processing integration [65, 66], thereby reducing the frequency and intensity of AVH by better synchronization of the auditory cortex with regions mediating higher cognitive functions [67, 68]. Furthermore, a significant negative correlation was found between the FC of the stimulate site and the left PreCG with reductions in the AHRS scores, suggesting that enhanced communication between these regions might be crucial in modulating auditory hallucinations in patients with schizophrenia.

The observed reduction in connectivity between the stimulate site and both the left SFGmedial and IPG post-treatment might indicate a decrease in the hyperconnectivity often associated with the DMN in schizophrenia [69–71]. These changes suggest a potential modulation of overactive self-referential processing and mind wandering, which are characteristic disruptions in the DMN observed in schizophrenia [72–74]. By potentially reducing these disruptions, rTMS may aid in alleviating core symptoms of schizophrenia, particularly by reducing hallucinations and improving cognitive control over internal and external auditory stimuli. This aligns with findings suggesting that modulation of specific neural circuits can lead to symptom mitigation in schizophrenia [75, 76].

The post-hoc analysis results within the sham group reveal distinct changes in FC compared to baseline measurements, indicating intrinsic adjustments in brain connectivity even in the absence of active intervention. The observed decrease in FC between the left TPJ (stimulate site) and the PreCG and the STG in the sham group might reflect a reversion to a more baseline, less stimulated state of neural activity. Since these areas are critically involved in and auditory and speech processing, the reduction could imply a diminished engagement with to simulated treatment protocols, suggesting a decrease in compensatory neural mechanisms that might be more active during actual treatment [77, 78]. Conversely, the increase in FC between the left TPJ and the left SFGmedial and the IPG suggests a reactivation of connectivity within the DMN. This might indicate an increased engagement in internal thought processes or self-referential activities [79, 80]. Such changes could point to a relaxation of task-focused brain networks in favor of a shift towards more introspective networks. The findings highlight the importance of accounting for natural fluctuations in brain connectivity that may occur independently of active therapeutic interventions, underscoring the brain's dynamic nature and its ability to adapt and reorganize, even in the absence of direct therapeutic stimuli.

The post-treatment comparison between the active and sham groups revealed intriguing outcomes. Particularly noteworthy are the numerous inhibitory effects observed among the ROIs following the treatment, especially from the PreCG to the left TPJ. The observed inhibitory effects indicate a specific modulation of neural activity that can be linked to the neurophysiological impact of low-frequency rTMS. This form of stimulation is known for its capacity to decrease cortical excitability [81] and thus may help to normalize the hyperactivity typically observed in the auditory and language processing areas in schizophrenia [82, 83]. The enhanced inhibitory connectivity could be reducing the erroneous sensory interpretations that are hallmark to auditory hallucinations. Furthermore, the significant negative correlation between the inhibitory connectivity and reductions in AHRS score

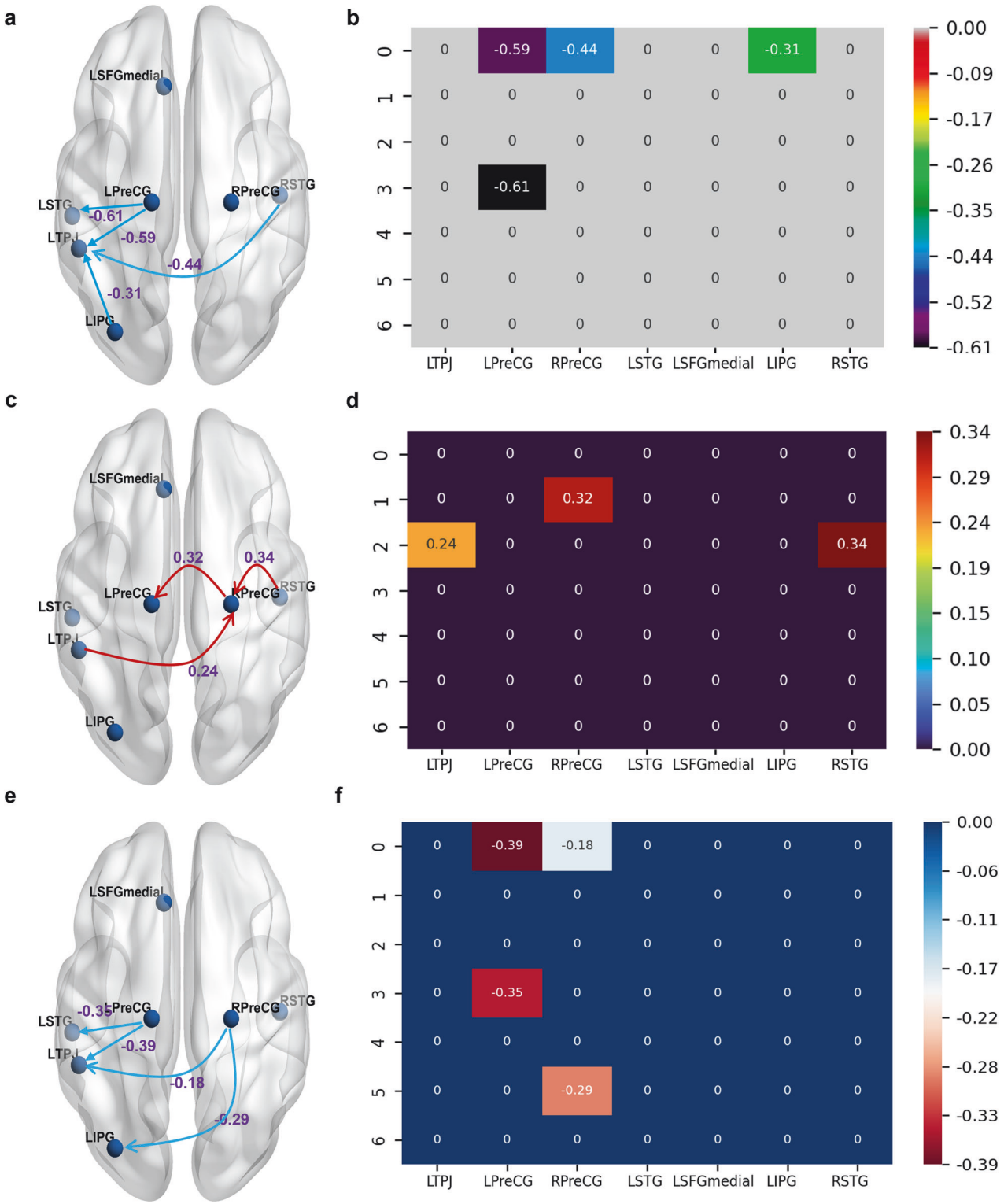

Fig. 4 Effective connectivity dynamics. a, **b** Commodities in the effective connectivity between baseline and posttest in active group. **c**, **d** Commodities in the sham group. **e**, **f** Significant differences in the effective difference between active group and sham group post-treatment, with negative value indicating inhibitory effects, while positive value indicating excitatory influences. Details and abbreviations of regions are listed in Table 2.

suggests that effective modulation of this specific pathway is crucial for the alleviation of AVH [84, 85].

In the analysis of DCM following low-frequency rTMS treatment in schizophrenia, significant findings were observed regarding the patterns of inhibitory effects between various ROIs in responders compared to nonresponders. The inhibition effect from the left SFGmedial the left TPJ is particularly notable. This effect exhibited a significant negative correlation with reductions in the AHRS scores. The left SFGmedial, a critical component of the DMN [56], is typically involved in self-referential and reflective activities [86]. In

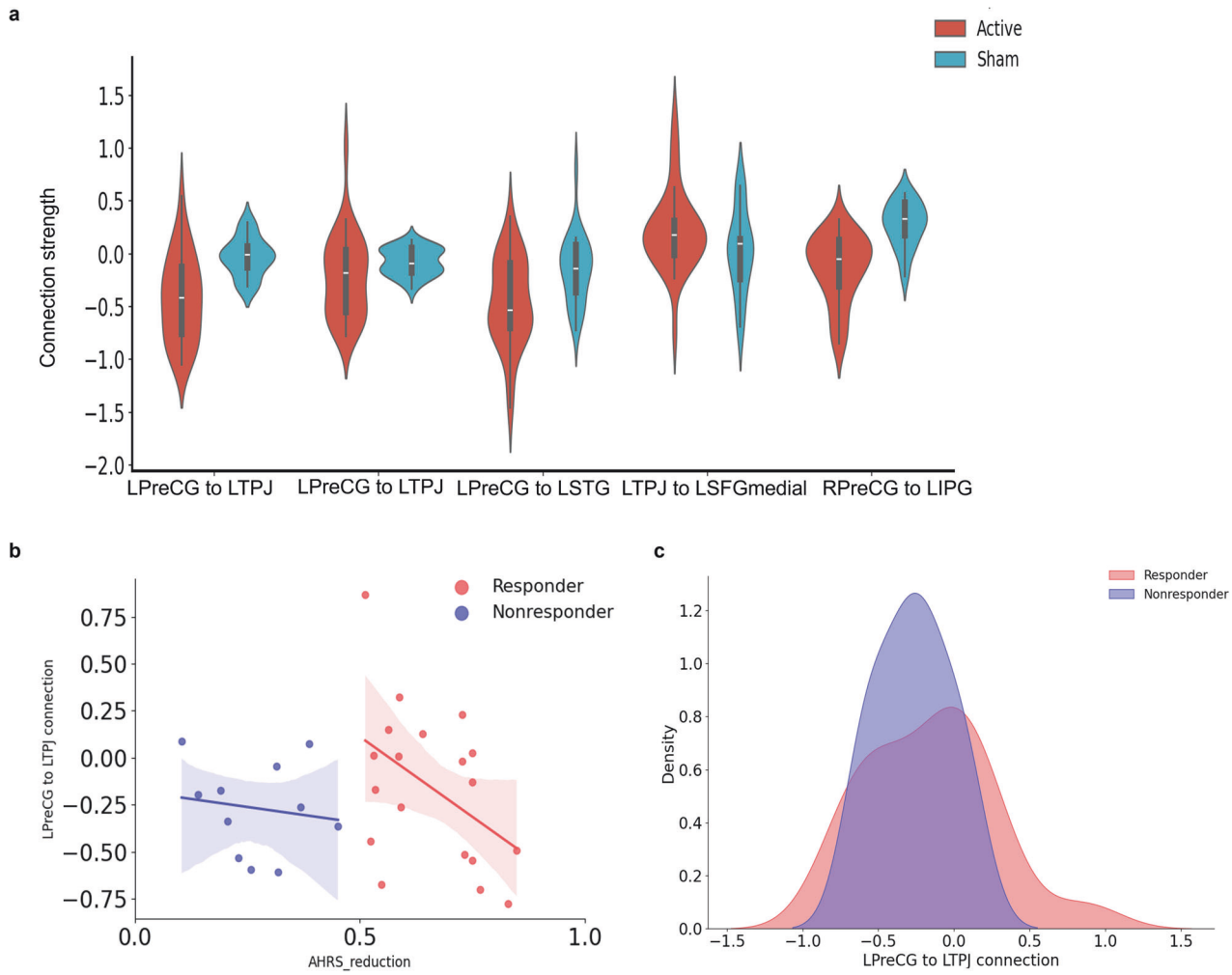

Fig. 5 Differences in effective connectivity and clinical correlations. a differences in effective connectivity strength between active and sham group post-treatment. **b** correlations between reductions in Auditory Hallucination Rating Scale (AHRS) scores and decreased connectivity from left PreCG to Left TPJ. **c** correlation distributions for responders and nonresponders. Details and abbreviations of regions are listed in Table 2.

the context of schizophrenia, aberrant activity in the DMN, especially in this brain region, has been implicated in the dysregulation of internal versus external attention processes [87, 88] and a predisposition to hallucinations [89, 90]. The inhibitory effect on the left TPJ, a region integrated in the perception of auditory stimuli and speech processing [91], suggests a regulatory mechanism that potentially reduces the misinterpretation of internal thoughts as external auditory inputs, a common occurrence in AVH [92, 93]. This aligns with the hypothesis that enhancing DMN control over sensory cortices could mitigate hallucinatory experiences by promoting a more coherent internal narrative and reducing the intrusion of unwarranted sensory input [94–96]. The correlation between enhanced inhibitory connectivity and reductions in AHRS scores emphasizes the clinical relevance of modulating specific DMN components to improve schizophrenia symptoms [97, 98].

Our findings shared similarities with previous report [17] and our earlier study [18], which demonstrated that FC of the stimulation site with sensory and language processing circuits following rTMS treatment, which are implicated in the alleviation of AVH symptoms. However, the present study differs in that it provides more detailed insights into the directionality of information flow within these neural circuits, offering a clearer understanding of the mechanisms underlying AVH improvement. These findings support the optimization of rTMS treatments by focusing on specific neural pathways that directly contribute to the symptomatology of schizophrenia. By identifying and modulating key pathways, such as the inhibitory effects from the left PreCG and left SFGmedial to the stimulation site, rTMS protocols can be tailored to target the unique neural connectivity patterns associated with AVH. This approach not only enhances the precision of the intervention but also significantly improves clinical outcomes, aligning with the broader movement towards personalized medicine.

Several limitations should be considered in this study. First, the relatively small sample size may limit the generalizability of our findings. A larger sample size in future studies would provide more robust statistical power and help confirm the observed effects. Second, the patients were on concurrent medication during the rTMS treatment, which may have influenced neural connectivity and potentially confounded the results. Controlling for medication effects or studying medication-free patients could be valuable in future research. Third, while resting-state DCM is a powerful tool for modeling directional connectivity, it relies on spontaneous brain activity, which might not fully capture dynamic changes in connectivity. Future studies could explore the use of deep brain stimulation as a complementary approach to investigate more direct causal connections,

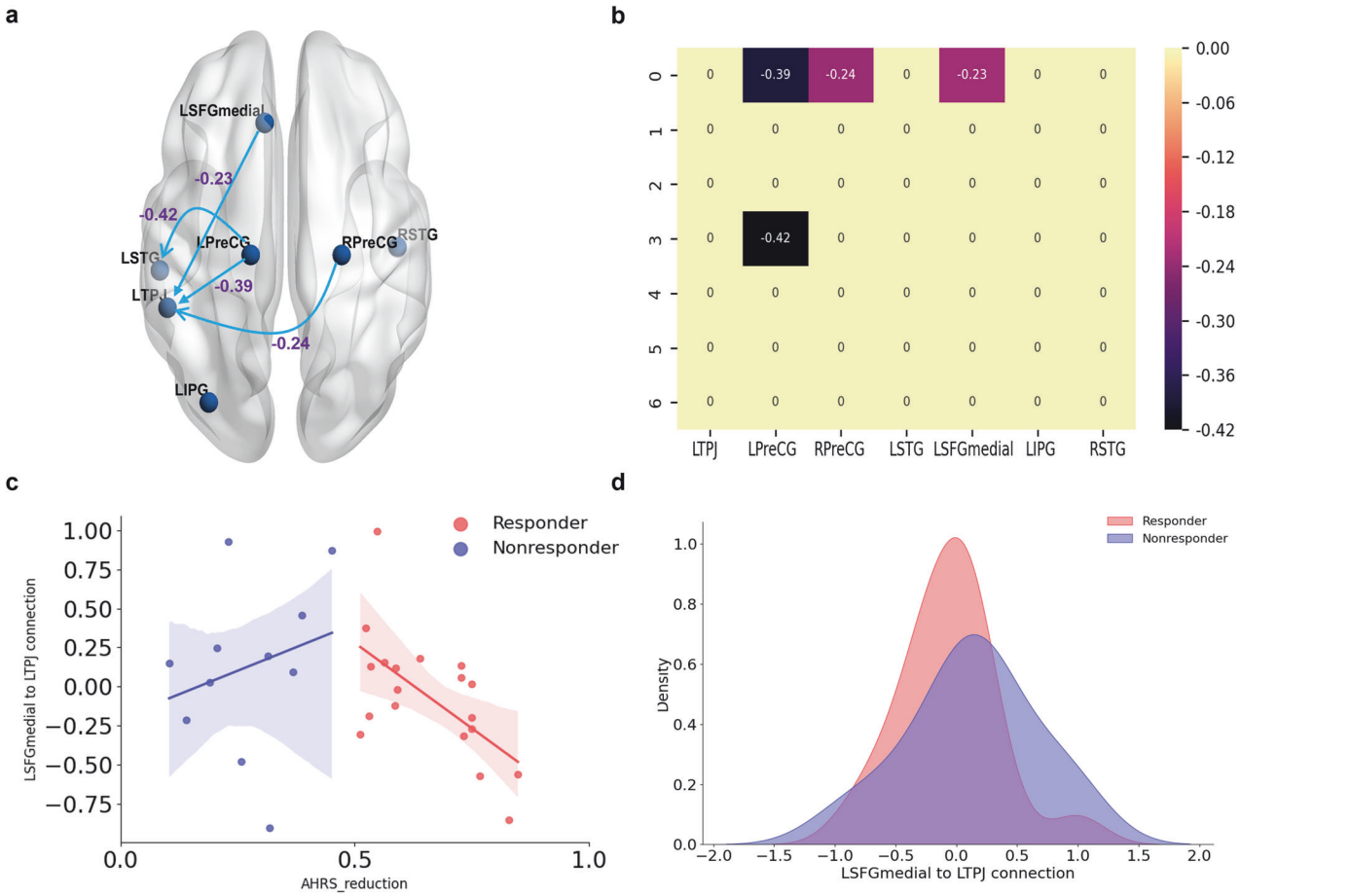

Fig. 6 Effective connectivity changes between responders and nonresponders and clinical correlations. a, **b** differences in effective connectivity between responders and nonresponders. **c** correlations between reductions in Auditory Hallucination Rating Scale (AHRS) scores and inhibitory effect from Left SFGmedial to Left TPJ. **d** correlation distributions for responders and nonresponders. Details and abbreviations of regions are listed in Table 2.

potentially providing clearer insights into the specific neural pathways modulated by rTMS. Additionally, future research should prioritize the integration of MRI-guided rTMS to optimize personalized treatment protocols, ensuring that stimulation targets are meticulously calibrated to each patient's unique neural connectivity profile.

CONCLUSION

By utilizing DCM to illustrate the influence of rTMS on neural connectivity, the present study provides substantial insights into how neural circuits are modulated to reduce AVH. Notably, the observed inhibition effects from the left PreCG and left SFGmedial to the stimulated site, along with their significant correlation with reductions in AHRS scores, underscore the therapeutic potential of targeted neuromodulation. These findings highlight the efficacy of rTMS in enhancing inhibitory connectivity, positioning it as a non-invasive approach to alleviate core symptoms of schizophrenia. Furthermore, the variability in treatment response underscores the need for further exploration into precision and personalized medical approaches, potentially leading to more effective and tailored therapeutic interventions.

DATA AVAILABILITY

The original data is available from corresponding author upon request.

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AUTHOR CONTRIBUTIONS

Yuanjun Xie, Guzhen Guan: Conceptualization, Methodology, Software, Formal analysis, Writing – Original draft preparation, Writing – Review and Editing. Tian Zhang, Chaozong Ma, Lingling Wang, Xinxin Lin, Chenxi Li, Zhongheng Wang, and Zhujing Ma: Investigation, Data curation, Statistical analysis. Huaning Wang, Peng Fang: Supervision, Project administration, Funding acquisition; all authors have read and approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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