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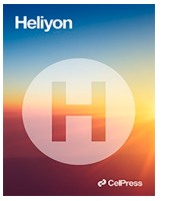

Research article

The efficacy of low frequency repetitive transcial magnetic stimulation for treating auditory verbal hallucinations in schizophrenia: Insights from functional gradient analyses

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ABSTRACT

Background: Auditory Verbal Hallucinations (AVH) constitute a prominent feature of schizophrenia. Although low-frequency repetitive transcranial magnetic stimulation (rTMS) has demonstrated therapeutic benefits in ameliorating AVH, the underlying mechanisms of its efficacy necessitate further elucidation.

Objective: This study investigated the cortical gradient characteristics and their associations with clinical responses in schizophrenia patients with AVH, mediated through 1 Hz rTMS targeting the left temporoparietal junction.

Method: Functional gradient metrics were employed to examine the hierarchy patterns of cortical organization, capturing whole-brain functional connectivity profiles in patients and controls.

Results: The 1 Hz rTMS treatment effectively ameliorated the positive symptoms in patients, specifically targeting AVH. Initial evaluations revealed expanded global gradient distribution patterns and specific principal gradient variations in certain brain regions in patients at baseline compared to a control cohort. Following treatment, these divergent global and local patterns showed signs of normalizing. Furthermore, there was observed a closer alignment in between-network dispersion among various networks after treatment, including the somatomotor, attention, and limbic networks, indicating a potential harmonization of brain functionality.

Conclusion: Low-frequency rTMS induces alternations in principal functional gradient patterns, may serve as imaging markers to elucidate the mechanisms underpinning the therapeutic efficacy of rTMS on AVH in schizophrenia.

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1. Introduction

Schizophrenia is a complex brain disorders characterized by pronounced disturbances in perception, cognition, and behavior [1]. It affects about 1 % population over a lifetime [2], placing a substantial burden on healthcare systems [3]. Auditory verbal hallucinations (AVH) are frequently reported in schizophrenia, denoting the subjective auditory experience while absent an external auditory stimulus [4], experienced by 60–90 % of individuals with the disorder [5]. These hallucinations significantly impair mental health and social functioning [6]. Although numerous studies have probed brain activity during auditory hallucinations or in correlation with a predisposition to towards hallucinatory experiences, the precise neurobiological underpinnings of AVH remain elusive. A prevailing notion posits that the brain regions dedicated to speech and sensory processing are relevant to hallucination experiences [7–9], including the Broca's area, frontal operculum, superior temporal gyrus, inferior parietal lobule. This align with a model that suggests aberrant cortical activations in regions related to speech production (e.g., prefrontal regions) and language perception (e.g., temporoparietal areas) contribute to AVH [10].

Functional connectivity (FC) delineates the statistical interdependence between neurophysiological indices. Specifically in schizophrenia, FC analyses have often focused on the blood oxygen level-dependent (BOLD) signal obtained from functional magnetic resonance imaging (fMRI) data, which revealed the temporal synchronization of neural activity across different brain regions [11]. Schizophrenia is marked by disruptions in FC, notably within key neural networks such as the default mode network, frontoparietal network, and thalamocortical network [12,13]. The alternations are consistently identified among patients with schizophrenia are thought to play a pivotal role in the pathophysiology of the disorder and the manifestation of its myriad symptoms, including cognitive deficits, positive symptoms, and negative symptoms. Studies have shown that schizophrenia is associated with aberrant FC, particularly within regions involved in auditory and language processing such as the auditory cortex, Broca's area, and subcortical regions [14–17]. This aberrant connectivity is linked not only to the occurrent of AVH but also to their severity and frequency [18]. Such findings illuminate the complex interaction of these neural disturbances that define the nature of the disorder.

Recently, gradient-based analysis has become an influential method for examining FC in resting-state fMRI data. This approach differs from traditional voxel- or seed-pairwise characterizations, as it reveals the spatial organization and continuous transitions across functionally distinct cortical regions [19,20]. Brain regions with similar connectivity patterns tend to be located closer along specific gradient axis [21], enabling the illustration of the hierarchical organization of cortex and elucidating the relationship between functional gradient, behavior, and cognition [22,23]. Functional gradients are believed to convey relatively clear physiological implications [22]. The principal gradient, or the first gradient represents a fundamental axis of human cortical organization, charting a hierarchical transitions from primary sensory-motor processing to higher cognitive functions [21].

Functional gradient is increasingly recognized as crucial for comprehending the functional organization of the human brain. Recent studies in psychiatric populations revealed distinct gradient patterns. For instance, patients with major depression disorder (MDD) exhibited a relative compression in the default mode network gradient compared to healthy controls [24]. This compression is also mirrored in the principal gradient with global topographic alterations like a reduced explanation ratio, gradient range, and variation [25]. In schizophrenia, research points to abnormal gradient transitions across cortical regions [26], with prominent compression in the sensorimotor system and a less compression in the frontoparietal regions. This pattern was consistently observed in intracerebellar, cerebellar-cerebral, and cerebral-cerebellar circuits [27], suggesting an broad disruptions in the hierarchical organization of the cortex in schizophrenia.

The treatment landscape of schizophrenia, primarily pharmacological medications [28], faces challenges due to side effects such as weight gain, extrapyramidal symptoms, and cardiovascular issues [29,30]. Repetitive Transcranial Magnetic Stimulation (rTMS), employing magnetic fields for neural stimulation, emerges as a promising, non-invasive alternations. Its potential efficacy, particularly at low frequency (e.g.,1 Hz), has been scrutinized for treating schizophrenia [31] and specifically AVH [32,33]. fMRI studies have demonstrated that low frequency rTMS can modulate both localized and distributed functional activation and connectivity in schizophrenia patients with AVH [34,35]. Administering 1 Hz rTMS to the left temporoparietal junction (TPJ), for example, modulates activity in language-related regions [36] and influences connectivity patterns with related cortical areas [34]. However, the underlying neural mechanisms by which rTMS alleviates AVH are still need to further clarification.

The present study aimed to explore the characteristics of functional gradients in schizophrenia patients with AVH, utilizing resting-state fMRI data to evaluate the effects of low-frequency rTMS. Based on the existing literature, we hypothesized that rTMS would induce significant alternations in the functional gradients. The changes are expected to be closely associated with a reduction of clinical symptoms, potentially providing deeper insights into the therapeutic mechanisms of rTMS in the treatment of schizophrenia.

2. Materials and methods

2.1. Participants

In this study, 32 individuals diagnosed with schizophrenia, all of whom were experiencing AVH, were recruited. A control group comprising 35 healthy individuals, matched for age, sex, and education background, was also included. The diagnosis of schizophrenia was established based on the criteria delineated in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). The inclusion criteria for patient cohort were as follows: (1) daily persistence of AVH despite undergoing at least two antipsychotic medications, and (2) experiencing a minimum of five AVH episodes daily over the past month. Throughout the study, patients maintained consistent antipsychotic medication dosages. Exclusion criteria, applicable to both patients and controls, involved a history of neurological disorders, substance abuse or dependence, contraindications to MRI, or current use of psychotropic medications.

Clinical evaluations and MRI scans for both schizophrenia patients and healthy controls were conducted within three days of enrollment, with an additional set for schizophrenia patients performed within three days post-rTMS treatment.

Informed consent was obtained from all participants prior to their involvement in the study. The study was approved by the Medical Ethics Committee of Xijing Hospital approved the study (reference number: KY20202055–F-1) and conducted in accordance with the Declaration of Helsinki. Additionally, the study was registered in the Chinese Clinical Trial Register (https://www.chictr.org.cn; registration number: ChiCTR2100041876).

2.2. Clinical measures

The severity of schizophrenia symptoms was assessed utilizing the Positive and Negative Syndrome Scale (PANSS) [37]. To evaluate the severity of AVH, the Auditory Hallucinations Rating Scale (AHRS) was employed [38]. The dosage of antipsychotic medication was documented in chlorpromazine equivalents (CPED), in alignment with clinically equivalent dosing estimates [39].

2.3. rTMS protocol

The rTMS protocol involved administering 1 Hz stimulation to the left TPJ, identified via the international 10–20 EEG channel position system (T3-P3). The treatment was delivered using a YRD CCY-I magnetic stimulator (YIRUIDE Inc., Wuhan, China), whic equipped with a 8-figure coil. Over a 15-day period, patients received daily 15-min stimulation sessions. Each session consisted of one pulse per second for 10 s, followed by a 5-s rest, resulting in a total of 600 pulses over 60 cycles. The rTMS protocol employed in this study was selected based on prior research [40,41], which has demonstrated its effectiveness in the treatment of neuropsychiatric disorders.

2.4. Image acquisition and preprocessing

All participants underwent MRI scans utilizing a 3.0 T scanner (GE MRI 750, Milwaukee, Wisconsin, USA). Resting-state fMRI images were acquired employing a gradient echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle (FA) = 90°, field of view (FOV) = 260 × 260 mm, matrix size = 64 × 64, and slice thickness = 3.5 mm with no gap, accumulating a total of 210 volumes. The T1-weighted images were captured utilizing a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR = 8.1 ms, TE = 3.2 ms, FA = 10°, FOV = 240 × 240 mm, matrix size = 256 × 256, and slice thickness = 1 mm with no gap, covering 176 slices.

Resting-state fMRI data processing was conducted with the DPABI toolbox (http://rfmri.org/dpabi) grouped on Statistical Parametric Mapping (SPM12) software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12), on the MATLAB platform (version 2018b; MathWorks, Inc., Natick, MA, USA). The initial 10 volumes were discarded to ensure signal stabilization. Subsequent volumes were adjusted for slice timing and head realignment. The T1 images were coregistered to the average functional images and segmented into gray matter, white matter, and cerebrospinal fluid. The images were then normalized to the Montreal Neurological Institute (MNI) standard space using the DARTEL algorithm [42]. The functional images were spatially smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. Linear detrending and bandpass temporal filtering (0.01 Hz–0.1 Hz) were executed. Nuisance covariates, including head motion parameters, white matter signals, cerebrospinal fluid signals, and global mean signals, were regressed out. Participants with head movements exceeding 3 mm or 3° in any direction were excluded from further analysis.

2.5. Gradient construction

The Schaefer400 atlas [43] was employed to extract time series from 400 distinctly, spatially contiguous nodes, using pairwise Pearson correlation coefficients. The coefficients were then transformed into z scores via Fisher's z transformation to enhance normality. The connectivity gradients were computed using the BrainsSpace toolbox (http://github.com/MICA-MNI/BrainSpace) [20]. Individual connectivity matrices were thresholded, retaining the top 10 % of connections per row [22], and setting the rest to zero. A positive and symmetric affinity matric was generated using the cosine similarity function, quantifying the similarity of the whole-brain connectivity patterns between each pair of nodes. Principal component analysis (PCA) was performed to decompose the affinity matrices, a method shown to yield more reliable gradients and higher prediction accuracy [19,44]. The gradients, reflecting the variance explained, assigned scores to each cortical parcel, with further emphasis on the first functional gradient (principal gradient), as it elucidated the greatest variance in connectivity patterns in the human brain [45–48]. To ensure consistency across subjects, the individual-level gradients were aligned to the group average gradient template - derived from all patients and controls - via Procrustes rotation.

2.6. Network gradient and dispersion

The analysis involved categorizing the individual gradient scores into several principal networks [49], including the visual, sensorimotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks. The network-specific gradient was determined by calculating the average gradient across all nodes within a given network. Within-network dispersion was measured by computing the Euclidean distance between the principal gradient scores of all nodes within a network and the network's centroid, defined as the median score of all nodes. Similarly, between-network dispersion was determined by computing the Euclidean distances

between the centroid of each network and the centroids of all other networks [48]. This approach allowed for a nuanced understanding of network-specific gradient variations and their broader interactions within the brain's functional architecture.

2.7. Statistical analysis

For the analysis of demographic characteristics, appropriate statistical tests were selected based on the data nature. Continuous variables underwent analysis through both independent and paired sample t-tests. In contrast, categorical variables were evaluated using chi-squared tests. Clinical measurements between different groups were compared employing independent samples t-tests. Within the patient group, comparisons before and after the treatment were conducted using paired samples t-tests.

The examination of connectivity gradient changes encompassed global, network, and nodal levels. A two-sample Kolmogorov-Smirnov test (K–S test) was employed to assess the alternations in the global gradient pattern, focusing on the cumulative distribution of the gradient. Network and nodal level analysis incorporated both independent and paired sample t-tests to pinpoint specific networks or nodes that exhibited significant changes in gradient scores between groups.

Spearmen rank correlation analyses were conducted to investigate the relationship between the changes in connectivity gradient patterns and improvements in clinical symptoms among patients, controlling for age, sex, and education. For all these statistical tests, the threshold for statistical significance was set at $p < 0.05$, with adjustments by false discovery rate (FDR) correction or using false positive correction (FPC) ($p < 1/N = 1/400 = 0.0025$) [50], unless explicitly stated otherwise.

3. Results

3.1. Demographic characteristics and clinical outcomes

After excluded two participants from both each of the patient and control groups due to significant head motion artefacts, the study continued with thirty patients and thirty-three controls. The demographic and clinical characteristics are detailed in Table 1. Comparative analysis revealed no statistically significant differences between patient and controls in age ($t = 0.954$, $p = 0.345$), gender ($\chi^2 = 0.101$, $p = 0.751$), or educational background ($t = 1.908$, $p = 0.094$).

Notably, following the rTMS treatment, there was a significant reduction in positive symptoms, general psychopathological symptoms, and especially in the severity a of AVH, as shown in Fig. 1.

3.2. Macroscale gradients between groups

Global-level gradient scores were calculated for each group to characterize cortical organization, with the results visually represented on the cortical surface (Fig. 2). Both groups exhibited a relatively clear transition from a unimodal system to a transmodal system along the principal gradient, aligning with the canonical distribution pattern.

Comparing the principal gradient scores, patients at baseline revealed an expanded distribution compared to controls (K–S stat = 0.064, $p = 2.76e\text{-}21$) (Fig. 3), suggesting an altered cortical organization linked to the pathophysiology of schizophrenia. After rTMS treatment, there was a partial narrowing of the expanded distribution when compared to controls (K–S stat = 0.050, $p = 3.53e\text{-}13$) (Fig. 3), suggesting a normalization process following rTMS treatment.

At a regional level, patients at baseline exhibited increased gradient scores in several clusters, including prefrontal, inferior temporal gyrus, and posterior cingulate regions (FDC correction, $p < 0.0025$) (Table 2 and Fig. 4).

Following rTMS treatment, a reduction in principal gradient scores was observed in regions such as the temporal lobes and prefrontal cortex, compared to baseline (FDC correction, $p < 0.0025$) (Table 3 and Fig. 5).

3.3. Gradient alternation at the network-level

Differences in the principal gradient score between groups at the network level are depicted in Fig. 6. The analysis revealed that only the somatomotor network ($t = 2.334$, $p = 0.023$, FDR $q = 0.085$) and frontoparietal network ($t = 2.456$, $p = 0.017$, FDR $q = 0.085$) had higher principal gradient scores in patents compared to controls, while no significant difference were noted in the principal gradient scores across other networks between the groups.

Significant differences were found in the dispersion of principal gradient scores both within and between network among the groups. Specifically, the within-network dispersion of the principal gradient scores, particularly in the limbic ($t = 5.714$, $p = 0.009$,

Table 1
Demographic and clinical characteristics of participants.

Variable	Patients (n = 30)	Controls (n = 33)	t (χ^2)	p
Age (year)	30.30 ± 4.46	32.03 ± 7.31	0.954	0.345
Sex (female/male)	17 (13)	20 (13)	0.101	0.751
Education (year)	13.20 ± 2.67	12.09 ± 2.04	1.708	0.094
Duration of illness (months)	21.36 ± 4.89	–	–	–
CPED (mg/day)	584.8 ± 152.39	–	–	–

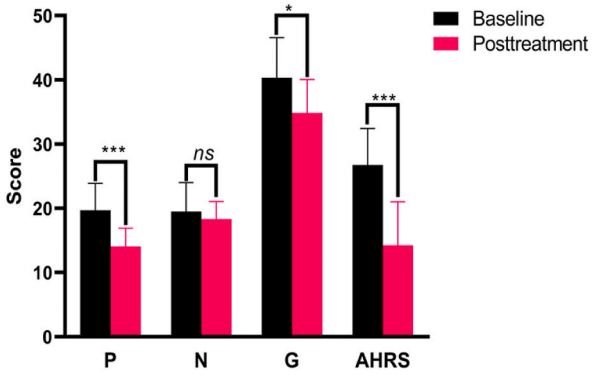

Fig. 1. Clinical symptom changes between patients at baseline and posttreatment. Abbreviations: P, positive symptoms of PANSS; N, negative symptoms of PANSS; G, general symptoms of PANSS; AHRS, auditory hallucination rating scale; ns, non-significance. The error bar indicates the standard deviation; *$p < 0.05$, ***$p < 0.001$.

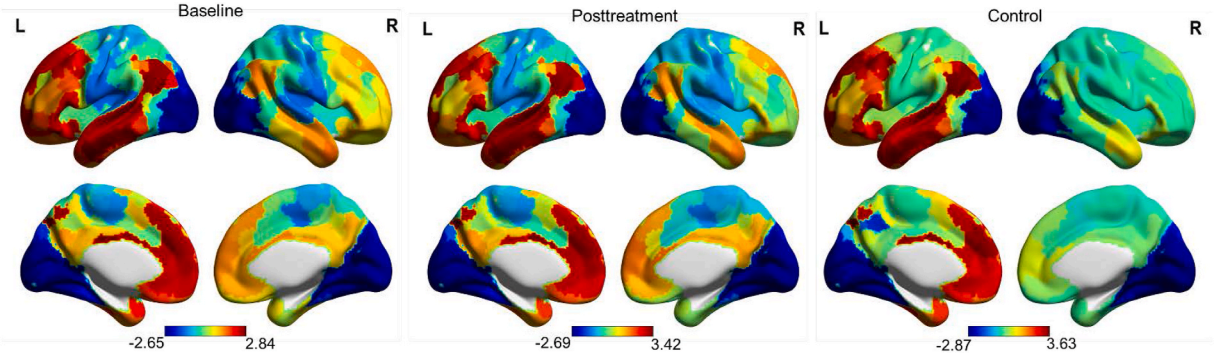

Fig. 2. The group-average principal functional gradient of patients (baseline and posttreatment) and controls. L, left; Right. The color bar indicates gradient score.

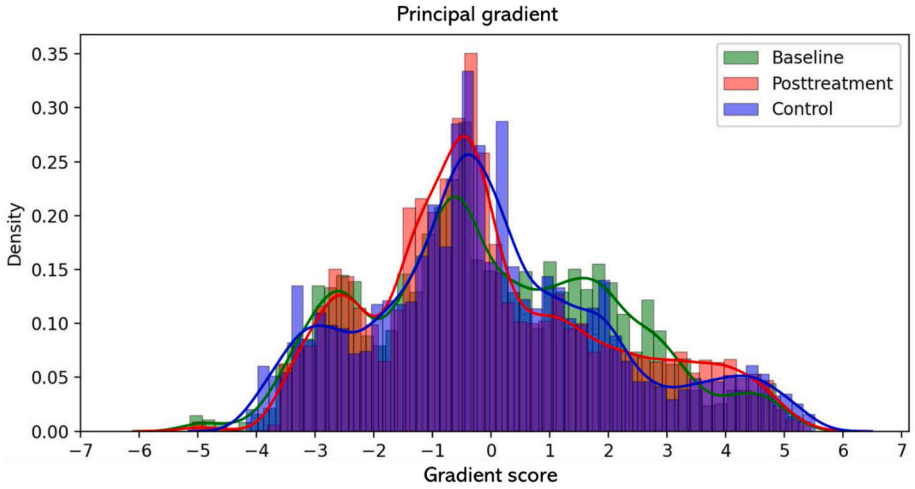

Fig. 3. Global histogram of the principal gradient among patients (baseline and posttreatment) and controls.

FDR $q = 0.012$), frontoparietal (t = 9.702, $p = 0.009$, FDR $q = 0.012$), and default mode networks (t = 12.300, $p < 0.001$, FDR $q = 0.001$), was markedly lower in patients at baseline compared to healthy controls (Fig. 7).

In addition, there was a noticeable reduction in the between-network dispersion of principal gradient scores post-treatment, particularly in the somatomotor network (t = 5.952, $p = 0.014$, FDR $q = 0.018$), dorsal attention network (t = 5.036, $p = 0.003$,

Table 2
The regions showing increase principal gradient scores in patients at baseline compared to healthy controls.

ROI name	Network name	Full component name	t	*p*
LH_Default_pCunPCC_11	Default	PCUN	5.210	2.81e-06
LH_Default_pCunPCC_10	Default	PCUN	4.684	1.83e-05
LH_Default_pCunPCC_9	Default	MCG	3.763	4.04e-4
RH_Cont_PFCl_2	Frontoparietal	MFG	3.647	5.82e-4
RH_Cont_PFCl_3	Frontoparietal	SFG	3.625	6.24e-4
LH_Default_pCunPCC_4	Default	PCC	3.441	1.10e-3
RH_Cont_PFCl_1	Frontoparietal	MFG	3.415	1.19e-3
RH_Cont_Temp_1	Frontoparietal	ITG	3.330	1.54e-3
RH_Default_pCunPCC_8	Default	PCUN	3.184	2.37e-3

Abbreviations: PCUN, precuneus; MCG, middle temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; PCC, posterior cingulate cortex; ITG, inferior temporal gyrus.

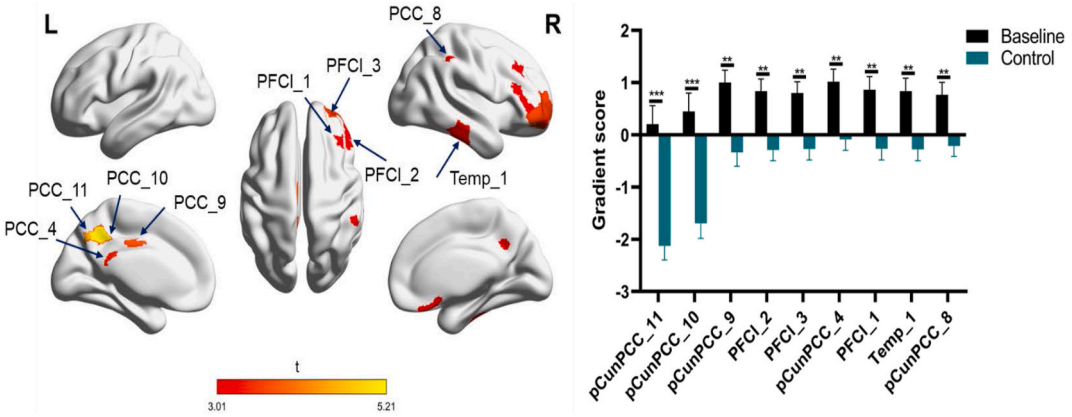

Fig. 4. Regional-parcel principal gradient score comparisons between patients at baseline and healthy controls. Left panel: Cortical surface maps showing regions with significant inter-group differences; Right panel: Bar graph representation of the principal gradient scores for the identified regions. The warm color clusters denote increased regions. The color bar indicates t values. See Table 2 for the specific meaning of the abbreviation of the cluster names. $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 3
The regions showing decreased principal gradient scores in patients after treatments compared to baseline.

ROI name	Network name	Full component name	t	*p*
RH_Cont_PFCl_4	Frontoparietal	IFG_Tri	−3.566	1.28e-3
RH_Cont_Temp_1	Frontoparietal	ITG	−3.509	1.48 e−3
RH_Limbic_TempPole_3	Limbic	Temporal pole	−3.424	1.86 e−3

Abbreviations: IFG_Tri, triangle part of inferior frontal gyrus; ITG, inferior frontal gyrus.

FDR $q = 0.010$), ventral attention network (t = 5.080, $p = 0.022$, FDR $q = 0.018$), and limbic network (t = 5.884, $p = 0.020$, FDR $q = 0.018$), in patients relative to baseline.

3.4. Correlation analysis

Alterations in the principal gradient score in the right inferior temporal gyrus (RH_Cont_Temp_1) demonstrated a positive Spearman correlation with the improvement in AVH symptoms (rho = 0.329, uncorrected $p = 0.038$) (Fig. 8). No correlations between gradient changes in other regions or networks and clinical responses were observed. This finding should be considered exploratory, given the uncorrected nature of the p-value in the context of multiple comparisons, and warrants further investigation to validate the association.

4. Discussion

The present study investigated functional gradient patterns in schizophrenia patients with AVH, following 1 Hz rTMS treatment. A pivotal outcome was the alleviation of clinical symptoms, including positive symptoms and AVH, post-rTMS treatment, aligning with the previous studies [51–53] and underscoring the therapeutic potential of low-frequency rTMS for AVH in schizophrenia.

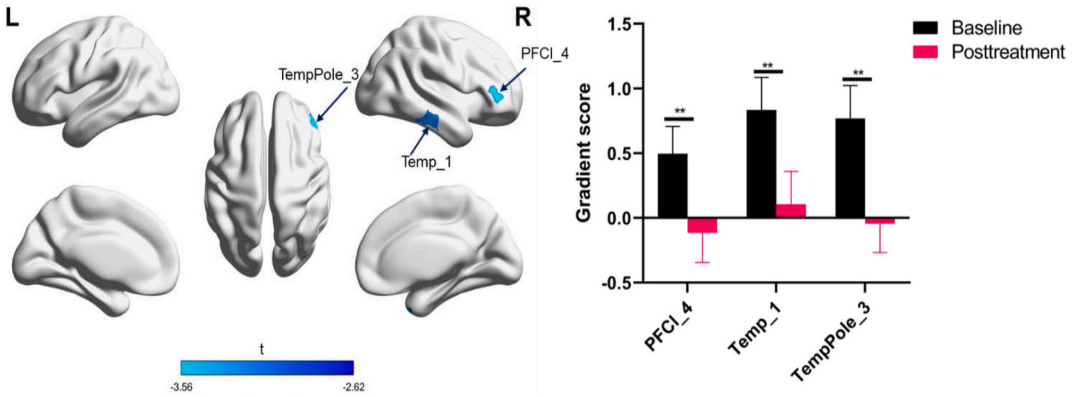

Fig. 5. Regional-parcel principal gradient score comparisons between patients after treatment relative to baseline. Left panel: Cortical surface maps showing regions with significant inter-group differences; right panel: Bar graph representation of the principal gradient scores for the identified regions. The cold clusters denote decrease regions. The color bar indicates t values. See Table 3 for the specific meaning of the abbreviation of the cluster names. $^{**}p < 0.01$.

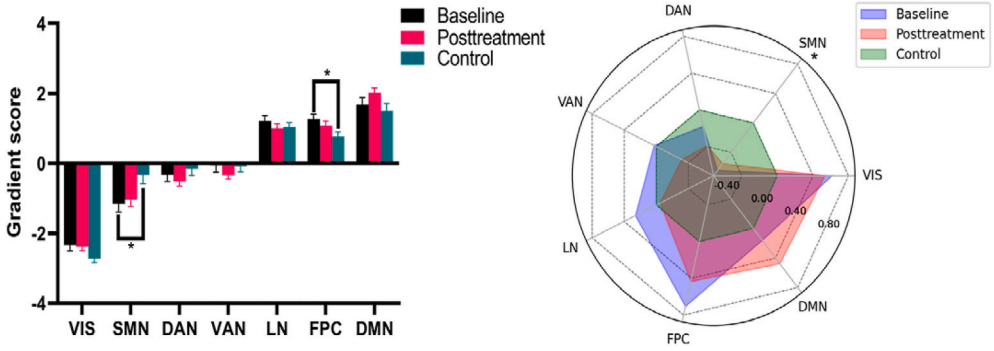

Fig. 6. Network-level comparisons of the principal gradient scores across groups. Left panel: Bar graph representation of the principal gradient scores for subnetworks among the groups; Right panel: The radar chart shows the gradient Z-score (with respect to controls) of subnetworks among the groups. VIS, visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; FPC, frontoparietal network; DMN, default mode network. $^{*}p < 0.05$.

Globally, the principal gradient patterns exhibited a macro topological distribution that was similar across both patients and controls. This distribution reflects a continuum from unimodal sensory cortices to transmodal associated regions, consistent with the established conceptions of principal gradients [54–56]. This hierarchical gradient structure is fundamental to cortical organization [57] and is crucial for transitioning from sensory information processing to higher cognitive functions. The similar macro-topological distribution observed in both groups underscore a preservation of this hierarchical structure. Notably, rTMS treatment elicited a constriction in the wide distribution of global gradient patterns. Compared to controls, the broader distribution of global gradient distribution in patients may signify a baseline state of functional integration disruption, likely due to heightened heterogeneity in cortical circuits [45]. This finding is congruent with the characterization of schizophrenia as a disorder of dysconnectivity [58,59]. Core symptoms of schizophrenia, such as hallucinations, delusions, and thought disorder, are hypothesized to arise from disordered information processing across extensive brain networks [60], potentially manifesting as a broad distribution of functional gradient, reflecting disorganized connectivity patterns.

rTMS, through targeted magnetic pulses delivery, can alter neuronal activity, influencing remotely connected brain areas. In schizophrenia, low-frequency rTMS has been investigated for its potential to modulate cortical connectivity and ameliorate AVH severity [61]. The post-treatment constriction of the principal functional gradient distribution, indicative of a move towards normalization, suggest that rTMS might prompt lasting changes in cortical excitability through mechanisms akin to long-term potentiation (LTP) and long-term depression (LTD) [62,63]. This enduring neural plasticity suggests low-frequency rTMS's potential as a modulatory treatment for cortical dysconnectivity in schizophrenia, especially for AVH.

In gradient analysis, the score of a region along a given gradient represents its relative position based on connectivity pattern [64]. The elevation in the principal gradient scores in schizophrenia patients denotes atypical connectivity profiles within the implicated brain regions compared to controls. For instance, elevated gradient scores in the precuneus, central to self-related mental representations and episodic memory retrieval [65], might reflect disrupted self-referential thinking in schizophrenia [66,67]. Both the middle and posterior cingulate cortices are integral to emotional and cognitive processes [68]. Increased gradient socres in these areas may

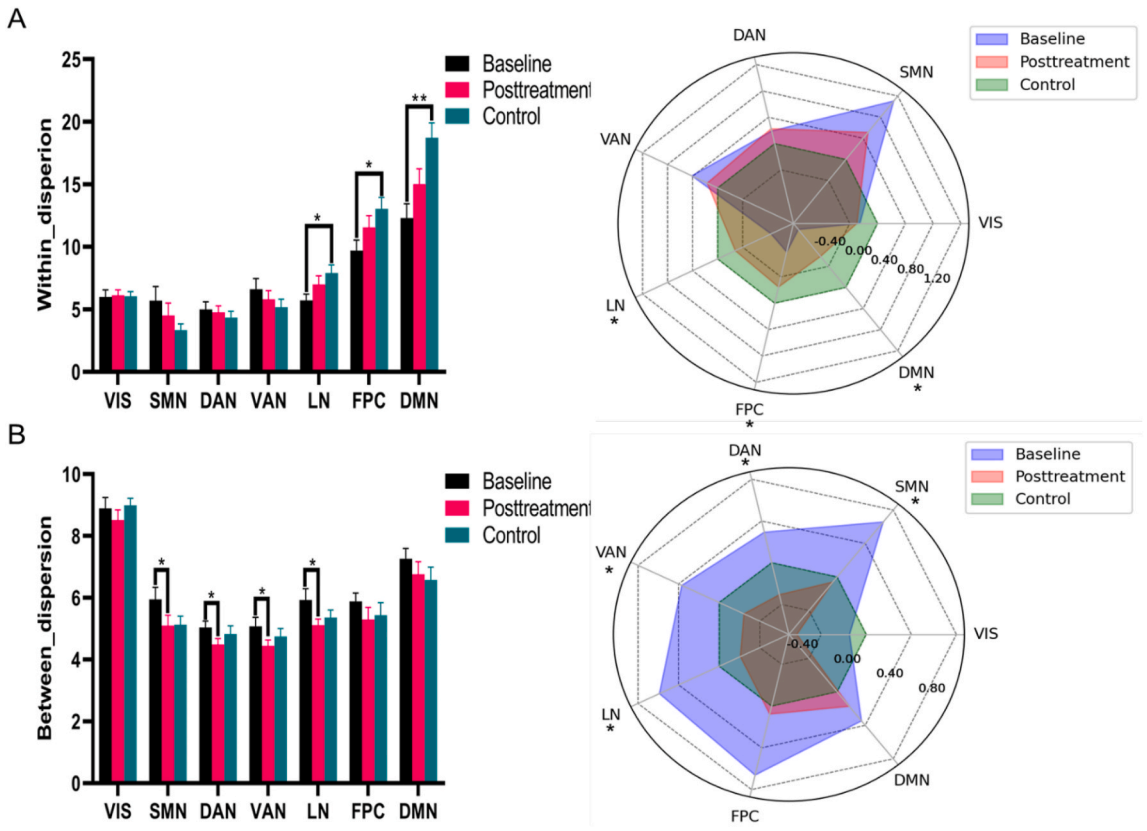

Fig. 7. Subnetwork dispersion comparison of principal gradient scores among the groups. A, Within-network comparison of principal gradient scores and their gradient Z-score (with respect to controls) among the groups; B, Between-network dispersion comparison and their gradient Z-score (with respect to controls) among the groups. Abbreviations: VIS, visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; FPC, frontoparietal network; DMN, default mode network. *$p < 0.05$.

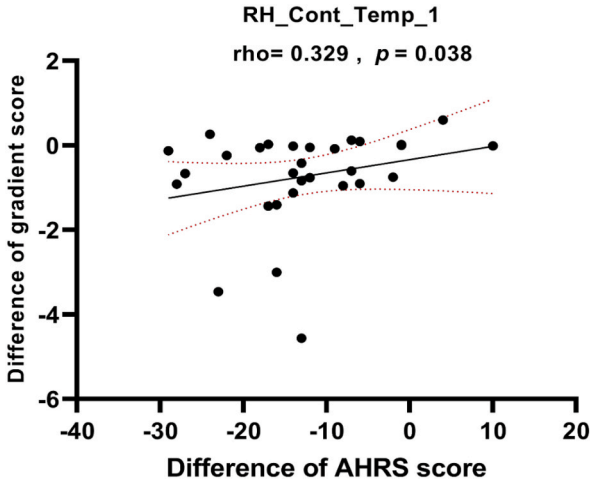

Fig. 8. Spearman rank correlation between the changed principal gradient scores in the temporal lobe and improved clinical symptoms. Abbreviations: AHRS, auditory hallucinations rating scale.

denote disturbances in self-referential thinking and emotional blunting. Additionally, gradient changes in the right middle frontal gyrus and right superior frontal gyrus, pivotal in high-order cognitive functions (e.g., executive control, decision-making, and working memory) [69–72], could be related the disorganized thinking, impaired decision-making, and working memory deficits observed in schizophrenia [73–75]. Similarly, increased gradient scores in the right inferior temporal gyrus, key to semantic processing [76,77]

and sensory integration [78], might indicate a broader sensory processing abnormalities.

Post-treatment, a decrease in principal gradient scores in these regions, including the right inferior frontal gyrus (triangle part), right inferior temporal, and right temporal role, suggests that 1 Hz rTMS might normalize the aberrant connectivity patterns in schizophrenia by its inhibitory effects on cortical activity [79]. The right inferior frontal gyrus (triangle part), essential in inhibition control [80], emotional regulation [81], and language processing [34], may exhibit modulated connectivity post-rTMS., potentially alleviating the cognitive and language impairments of schizophrenia [82–84].

As previously delineated, the right inferior temporal gyrus plays a multifaced role in visual, auditory, and semantic processing. The decrease in gradient scores within this region followint rTMS treatment may indicate a shift towards normalization of sensory processing, which in turn could contribute to a reduction in hallucinatory experiences. This alteration in principal gradient scores in the right inferior temporal gyrus was found to correlate with treatment responses in schizophrenia patients, particularly in the improvement of AVH. However, it's important to note that this correlation is tentative and requires further investigation for confirmation. Future studies should employe more rigorous methodologies to comprehensively understand the implications of rTMS-induced neural changes on AVH symptoms in schizophrenia. In addition, the right temporal pole, implicated in social and emotional processing [85], has been associated with changes in emotional recognition [86] and social cognition [87] among schizophrenia patients. The observed decline in gradient scores in this region suggests that rTMS may modulate its connectivity patterns, potentially improving socio-emotional processing and thereby enhancing overall patient functionality in daily life. Interesting, the stimulation target (left TPJ) shows intrinsic connectivity with the right temporal lobe [88,89]. Targeting rTMS at the left TPJ has been linked to changes in both metabolism and connectivity within the contralateral cortex [61,90], suggesting that stimulating the left TPJ may indirectly influence the opposite hemisphere such as right inferior temporal gyrus. This indirect modulation may underpin the clinical improvements observed, proposing a therapeutic role for low-frequency rTMS in modulating cortico-cortical coupling in schizophrenia patients [91,92]. It is crucial, however, to consider that this finding as preliminary, warranting further validation. It is also noteworthy that the lack of significant findings in the left inferior temporal gyrus may point to the complex and asymmetrical effect of rTMS on brain dynamics [93,94]. This asymmetrical response to rTMS stimulation highlights the intricate dynamics of brain regions in schizophrenia, particularly concerning AVH. Further research is needed to unravel the lateralized effects and their clinical implications.

Although the principal gradient scores at the network-level did not exhibit significant alternations post-treatment, the distinct scores observed in the frontoparietal and somatomotor networks in patients at baseline relative to controls are notable. The frontoparietal network, vital for executive functions, attentional control, and working memory [95,96], showed elevated principal gradient scores in patients. This elevation might suggest a hyperconnected state in the frontoparietal network, potentially leading to difficulties in attention, memory, and executive control - common deficits in schizophrenia [97,98]. Conversely, the somatomotor network, which processing sensory and motor information [99], exhibited lower gradient scores, possibly reflect disruptions in integrating sensory input with motor functions. This aligns with previous findings of impaired sensory and motor processing in schizophrenia [100,101]. The lack of significant changes in network-level gradient scores post-rTMS treatment raises the possibility of the resilience of network-level abnormalities to neuromodulatory interventions.

Within-network dispersion of principal gradient scores, including the limbic, frontoparietal, and default mode networks, was comparatively lower in patients at baseline. However, these score did not exhibit significant changes post-treatment. A lower dispersion could indicate more homogenized connectivity pattern within these networks. Specifically, the limbic system, crucial for memory and emotion regulation [102,103], and involving structures like the amygdala, hippocampus, and parahippocampal cortex [104] might exhibit less functional differentiation within the network, possibly contributing to emotional dysregulation in schizophrenia [105].

Similarly, reduced dispersion within the frontoparietal network could indicate less diversity in functional roles among its regions, potentially underpinning cognitive deficits related to AVH [106]. In the default mode network, responsible for self-referential thought and introspection [107], decrease dispersion might reflect a narrower range of introspective thought processes, potentially linked to the internalized experiences of hallucinations [108]. The persistence of these homogenized network configurations post-rTMS suggest that they may be inherent characteristics of schizophrenia, particularly in those experiencing AVH.

Furthermore, a notable decrease in dispersion of principal gradient scores between networks, including the somatomotor, dorsal attention, versal attention, and limbic networks, was observed in patients following rTMS treatment, indicating a tighter integration among these networks. The somatomotor network, a critical role in sensory-motor integration [109], comprising the somatosensory (postcentral gyrus), motor (precentral gyrus) regions, and the supplementary motor areas [110,111], demonstrated closer alignment with other networks following rTMS. This could reflect a 'neural reset' [112] induced by rTMS, fostering closer network alignment and enhanced interaction among sensory motor and cognitive functions. The dorsal and versal attention networks, crucial in attentional processes [113,114], also aligned more closely with other networks post-treatment. this change might signify a recalibration of attentional processes in schizophrenia, potentially alleviating attentional deficits characteristics of the disorder [115]. In addition, a closer alignment of the limbic network with others could hint a normalization in emotional regulation processes often disrupted in schizophrenia. The decrease between-network dispersion in principal gradient scores after 1 Hz rTMS treatment suggests a potential harmonization of neural networks in schizophrenia patients with AVH, underscoring the capacity of rTMS to modulate and realign functional connectivity patterns. This promotes a more coherent and neural architecture, indicative of rTMS's therapeutic potential. Intriguingly, functional gradients, as markers of the hierarchical organization of the brain's networks, provide vital insights into the effects of rTMS across different neuropsychiatry conditions. Future research should focus on understanding how rTMS modulates brain gradients in diverse pathological states, thereby uncovering its underlying mechanisms.

The present study has several limitations warranting consideration. Firstly, the small sample size and the exploratory nature of

some findings may limit the generalizability of our results. Future studies with larger participant pools are needed for validation. Secondly, the absence of a sham control group makes it difficult to clearly differentiate the specific effects of rTMS from placebo effects. Incorporating a sham group in future studies would help establish a more definitive causal link between rTMS and clinical improvements. Lastly, the concurrent use of medication by participants during the rTMS treatment poses a potential confounding factor. Future research should aim to control for medication effects, potentially through participant stratification or selecting medication-free individuals, to more accurately assess the direct impact of rTMS. Additionally, further research with enhanced methodologies is necessary to thoroughly evaluate the effectiveness of rTMS in treating hallucinations in schizophrenia.

5. Conclusion

In summary, the present study investigated the functional gradient characteristic and their associations with clinical responses in schizophrenia patients with AVH, following treatment with 1 Hz rTMS. The findings indicate that low-frequency rTMS can induce significant changes in principal functional gradient patterns, contributing to certain clinical improvement. This study provide valuable insight into the functional gradient of cortical organization in the context of rTMS treatment, potentially shedding light on the underlying mechanisms of rTMS.

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Ethics declarations

The study was approved by the Medical Ethics Committee of Xijing Hospital (reference number: KY20202055–F-1). All participants provided informed consent to participate in the study.

CRediT authorship contribution statement

Yuanjun Xie: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chenxi Li:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Muzhen Guan:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tian Zhang:** Visualization, Software, Methodology, Investigation. **Chaozong Ma:** Visualization, Software, Methodology. **Zhongheng Wang:** Visualization, Methodology, Investigation, Data curation. **Zhujing Ma:** Visualization, Validation, Investigation, Data curation. **Huaning Wang:** Supervision, Resources, Project administration, Funding acquisition. **Peng Fang:** Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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