


RESEARCH ARTICLE

Distinct brain structural-functional network topological coupling explains different outcomes in tinnitus patients treated with sound therapy

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Funding information

This work was supported by Grant No. 61931013, 62171297 and 82171886 from the National Natural Science Foundation of China, No. [2015] 160 from Beijing Scholars Program

Abstract

Topological properties, which serve as the core of the neural network, and their couplings can reflect different therapeutic effects in tinnitus patients. We hypothesized that tinnitus patients with different outcomes after sound therapy (narrowband noise) would have distinct brain network topological alterations. Diffusion tensor imaging and resting-state functional magnetic resonance imaging (fMRI) were prospectively performed in 60 patients with idiopathic tinnitus and 57 healthy controls (HCs). Graph-theoretical network analyses of structural connectivity (SC), functional connectivity (FC), and SC and FC coupling were performed. Associations between clinical performance and graph-theoretical features were also analyzed. Treatment was effective (effective group; EG) in 28 patients and ineffective (ineffective group; IG) in 32 patients. For FC, the patients in the EG showed higher local efficiency than patients in the IG. For SC, patients in both the EG and IG displayed lower normalized characteristic path length, characteristic path length, and global efficiency than the HCs. More importantly, patients in the IG had higher coupling than the HCs, whereas there was no difference in coupling between patients in the EG and HCs. Additionally, there were significant associations between the SC features and clinical performance in patients in the EG. Our findings demonstrate that tinnitus patients exhibited significant brain network topological alterations, especially in the structural brain network. More importantly, patients who demonstrated different curative effects showed distinct SC-FC topological coupling properties. SC-FC coupling could be an indicator that could be used to predict prognoses in patients with idiopathic tinnitus before sound therapy.

KEYWORDS

functional connectivity, sound therapy, structural connectivity, structural-functional coupling, tinnitus, topological analysis

Abbreviations: CSF, cerebrospinal fluid; EG, effective group; EPI, echo-planar imaging; FA, flip angle; FC, functional connectivity; HC, healthy control; HL, hearing loss; IG, ineffective group; MNI, Montreal Neurological Institute; SAS, self-rating anxiety scale; SC, structural connectivity; SDS, self-rating depression scale; TE, echo time; THI, tinnitus handicap inventory; TR, repetition time; VAS, visual analog scale.

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1 | INTRODUCTION

Tinnitus is usually considered an auditory hallucination perceived in the ear without any external stimulation. It seriously affects patients' lives and is associated with various problems, such as difficulty concentrating and listening, anxiety and depression, and even has a substantial impact on patients' family, job performance, and society (Lewis, Chowdhury, Stockdale, & Kennedy, 2020). Therefore, new effective and even individualized treatments are most urgently needed.

Currently, there are many therapeutic interventions that have been applied to patients with idiopathic tinnitus, such as tinnitus counseling, pharmacological treatments, tinnitus retraining therapy, cognitive-behavioral therapy, sound therapy, hearing aids, retraining therapy, brain stimulation, and even hyperbaric oxygen and acupuncture (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; Zenner et al., 2017). Among these treatment methods, sound therapy, as widely suggested, is considered a cost-effective (Makar, Mukundan, & Gore, 2017) and first-line management for tinnitus (Hoare, Edmondson-Jones, et al., 2014; Hobson, Chisholm, & El, 2012; Sereda, Hoare, Nicholson, Smith, & Hall, 2015; Tutaj, Hoare, & Sereda, 2018) and even listed as an option in clinical practice guidelines (Henry, Schechter, Nagler, & Fausti, 2002; Tunkel et al., 2014). The effect of sound therapy may not completely eliminate the symptoms, but it could help patients become familiar with tinnitus and offer relief from tinnitus-related distress, subsequently improving the quality of patients' lives (Aytac et al., 2017; Hoare, Searchfield, et al., 2014; Hobson et al., 2012; Mahboubi, Haidar, Kiumehr, Ziai, & Djalilian, 2017; Newman & Sandridge, 2012).

To date, a series of studies have focused on the effect of sound therapy in patients with idiopathic tinnitus, but they have reported disparate results (Chen et al., 2021b, 2021c; Han et al., 2019; Lv et al., 2020; Moffat et al., 2009; Oishi et al., 2013; Parazzini, Del Bo, Jastreboff, Tognola, & Ravazzani, 2011; Wei et al., 2021). Among them, using functional neuroimaging methods, some studies have shown that sound therapy plays a significant role in improving the symptoms of tinnitus patients by normalizing the abnormal structural and functional changes in the brain related to tinnitus; this normalizing effect may represent less involvement of the noise-canceling system (Chen, Lv, et al., 2021c; Han et al., 2019; Lv et al., 2020; Wei et al., 2021). However, other studies did not find any measurable improvements in patients' symptoms after tinnitus treatment using sound therapy (Moffat et al., 2009; Oishi et al., 2013; Parazzini et al., 2011); these studies suggest that the lack of improvement may be due to the low quality of methodology and insufficient effect size in statistical analysis. Our recent study focused on tinnitus patients with different outcomes after sound therapy and found that there were significant differences in brain structural reorganization among these patients (Chen, Lv, et al., 2021b). Moreover, one recent study (Chen et al., 2021a) even showed that the network connectivity among these patients was significantly different. These differences are closely related to patients' clinical performance. However, these studies only selected a single mode of imaging data to investigate the possible

differences in brain structure or brain function in patients with different prognoses after treatment.

Analysis employing a combination of structural connectivity (SC) and functional connectivity (FC) networks has been proposed in recent years (Honey, Thivierge, & Sporns, 2010). This measurement, known as SC-FC coupling, has been applied to investigate changes in SC-FC network relationships in numerous neurologic disorders (Chen et al., 2021; Huang & Ding, 2016; Suo et al., 2021; Zhang, Shao, et al., 2019). For instance, Chen, Geng, et al. (2021) found differences in SC-FC coupling in patients with different types of subcortical stroke, which was closely correlated to their clinical performance. However, to the best of our knowledge, there have been no studies thus far that have explored the alterations in SC-FC network couplings in patients with idiopathic tinnitus who had different outcomes after sound therapy.

Therefore, to address these issues, in the present study, we first investigated the prognosis of idiopathic tinnitus patients after 6 months of sound therapy. Moreover, we explored the structural and functional brain network topological patterns in tinnitus patients with different outcomes and analyzed the relationships between these outcomes and prognoses. According to the follow-up Tinnitus Handicap Inventory (THI) scores, patients were divided into an effective group (EG) and an ineffective group (IG). Comparing the differences in brain SC-FC network couplings between the two groups after sound therapy, we aimed to reveal the possible different mechanisms of tinnitus in patients who experienced different therapeutic outcomes and to guide the selection of optimal treatment methods for patients before treatment.

The hypothesis is that tinnitus patients (treated with sound therapy) in the EG and IG would have distinct brain network topological and structural-functional coupling alterations.

2 | MATERIALS AND METHODS

2.1 | Subjects and clinical data

This study was approved by the ethics committees of our research institution (Beijing Friendship Hospital, Capital Medical University, 2017-P2-134-01). Written informed consent was obtained from each subject before the study in accordance with the Declaration of Helsinki. The registration number on [ClinicalTrials.gov](https://www.clinicaltrials.gov) is NCT03764826.

Sixty-one tinnitus patients and 59 healthy controls (HCs) were enrolled in this prospective observational study. Three participants (including 1 patient and 2 HCs) were excluded due to excessive head motion (>2.5 mm). Thus, the data of 60 patients with idiopathic tinnitus and 57 HCs were included in the final analysis. All patients had persistent tinnitus for more than 6 months and less than 48 months. Most of the patients did not suffer from hearing loss (HL) (defined as tinnitus without HL, which was defined as more than 25 dB HL at frequencies ranging from 0.25 to 8 kHz, based on pure-tone audiometry examination audiogram results), while a portion of patients had different degrees of tinnitus-related HL. None of the patients had any

history of associated brain diseases based on conventional magnetic resonance imaging (MRI) results, pre-existing mental or cognitive disorders, or MRI contradictions. Patients with pulsatile tinnitus, sudden deafness, Meniere's disease, hyperacusis, otosclerosis, and other neurological diseases were excluded. We used the THI scores (Newman, Jacobson, & Spitzer, 1996) and a visual analog scale (VAS) to assess the severity of the disease prior to sound therapy. We also evaluated patients' severity of anxiety and depression at the time of assessment using the self-rating anxiety scale (SAS) (Zung, 1971) and self-rating depression scale (SDS) (Zung, 1965). Moreover, we assessed the hearing of the HCs; all of them had normal hearing. Other exclusion criteria used to select the tinnitus patients were also applied to HCs.

2.2 | Sound therapy intervention and clinical evaluation

For the sound intervention, we applied a special tinnitus therapeutic instrument, eMasker[®] (Micro-DSP Technology Co., Ltd), which is a customized personal sound therapy device based on test results on tinnitus characteristics. As an individualized method, we first assessed the tinnitus features of each patient, including examinations of minimum masking levels, tinnitus pitch matching patterns, loudness matching patterns, and residual inhibition. Specifically, we set patients' perceived loudness of tinnitus as the initial volume of the noise for treatment. For the frequency of the intervention sound, we first determined the tinnitus frequency according to the results of a tinnitus pitch-matching assessment and then set narrowband noise according to the tinnitus frequency (1 kHz narrowband, that is, tinnitus frequency \pm 0.5 kHz). We administered therapeutic noise to patients for 20 min three times per day for 6 months. Consistent with the daily treatment time in a previous study (Conlon et al., 2020), we defined the minimum treatment compliance as device usage of at least 72 hr over during this time. The sound was delivered to the patients through headphones. Patients were advised to be awake and use it in a quiet environment to achieve the best therapeutic effect. During the treatment, we adjusted the loudness and frequency according to the actual condition (considering reports of tinnitus sensations and examination results) of each patient every 2 weeks. Adjustments were only conducted by the audiologists on our team, and patients were not allowed to make such changes. Feedback about the treatment was collected about the application of sound therapy every 2 weeks. Patients who did not follow the instructions would have been excluded from the study, but none of the patients had to be excluded due to this criterion. All the patients were asked to complete the THI again after the treatment. Pertinently, the primary outcome of the current study was the changes in THI score (Δ THI score). Consistent with prior studies, we defined the treatment as effective if tinnitus patients had a reduction of 17 points or more in THI scores or the score was reduced to 16 points (Chen, Lv, et al., 2021b, 2021c; Zeman et al., 2011); in contrast, treatment was defined as ineffective if patients did not meet either of these two conditions. Accordingly, patients in this study

were divided into two groups: 28 patients were classified into an EG, and 32 patients were classified into an IG. We did not administer any type of sound intervention to the HCs throughout the entire research process. We calculated the Δ THI score and the %improvement of the THI scores of the patients, which were defined as follows: Δ THI score = THI baseline – THI treated, % improvement of the THI score = (THI score at 6 months follow-up-THI score on admission) \div THI score on admission \times 100%.

2.3 | MRI data acquisition

The diffusion tensor imaging (DTI) and functional imaging data were obtained from each tinnitus patient before the treatment and from HCs using a 3.0 T MRI system (Prisma, Siemens, Erlangen, Germany) with a 64-channel phase-array head coil. Before these two sequences, we used a conventional brain axial T2 sequence to exclude individuals with any visible brain abnormalities. DTI scanning was performed using a single-shot gradient-echo echo-planar imaging (EPI) sequence, and the parameters were as follows: repetition time (TR) = 8,500 ms, echo time (TE) = 63 ms, matrix = 128 \times 128, acquisition voxel size 2 \times 2 \times 2 mm³, field of view (FOV) = 224 \times 224 mm², nonzero b value = 1,000 s/mm², gradient directions = 64, slice thickness = 2 mm, and bandwidth = 2,232 Hz/Px. A total of 74 contiguous slices parallel to the anterior commissure-posterior commissure line were acquired, and the total scan time was 10.56 min. For the resting-state functional images, we used an EPI sequence with the following parameters: 33 axial slices with a slice thickness = 3.5 mm and interslice gap = 1 mm, TR = 2,000 ms, TE = 30 ms, flip angle = 90°, bandwidth = 2,368 Hz/Px, FOV = 224 \times 224 mm², and matrix = 64 \times 64. The latter parameters resulted in an isotropic voxel size of 3.5 \times 3.5 \times 3.5 mm³. The total number of volumes acquired was 240, and the total scan time was 8.06 min. During the scanning process, we used suitable foam padding to minimize head motion and earplugs to reduce scanner noise. All the participants were asked to stay awake, close their eyes, breathe evenly, and try to avoid thinking any specific thoughts.

2.4 | Preprocessing of DTI data

We preprocessed DTI data using the PANDA package (Cui, Zhong, Xu, He, & Gong, 2013), which is based on the FSL software package (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). The main steps were as follows: (1) converting DICOM files into NIfTI format, (2) estimating the brain mask, (3) cropping the raw images, (4) coregistering them to b0 images, (5) correcting for eddy current distortions and head motions, (6) tracking whole-brain fibers, (7) averaging multiple directions, and (8) calculating diffusion tensor metrics. A tensor was fitted to the diffusion profile with each voxel where fractional anisotropy (FA) was calculated. Then, we used fiber assignment by a deterministic fiber tracking algorithm for whole-brain fiber tractography. In this process, consistent with prior studies, we set FA 0.15 or a turning angle >45° as the termination criterion of continuous fiber (Chen, Geng, et al., 2021; Cui et al., 2013).

2.5 | Preprocessing of fMRI data

For the preprocessing of resting-state fMRI (rs-fMRI), we applied the batch-processing tool Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI) (<http://www.rfmri.org/dpabi>) (Yan, Wang, Zuo, & Zang, 2016), which is based on SPM12 (<https://www.fil.ion.ucl.ac.uk/spm>), installed in MATLAB 2016a (Math Works, Natick, MA). The main steps were as follows: (1) we removed the first 10 volumes of each functional time series to allow for steady-state magnetization and stabilization of each participant's data. (2) We conducted slice timing correction on the remaining 230 volumes. Head motion between volumes was evaluated and corrected using rigid-body registration, and we excluded subjects who had a maximum displacement > 2.5 mm, maximum rotation > 2.5°, or mean framewise displacement (FD) > 0.3 (Yan et al., 2013). Thus, three participants (including 1 patient and 2 HCs) were excluded. (3) Based on the standard stereotaxic coordinate system, we spatially normalized the corrected fMRI images to the Montreal Neurological Institute (MNI) template (resampling voxel size = 3 m × 3 m × 3 m). (4) To remove possible variance from the time course of each voxel, 26 nuisance covariates (including white matter and cerebrospinal fluid signals and Friston-24 head motion parameters) were regressed out. (5) Finally, the normalized fMRI data were smoothed with a 6-mm full width at a half-maximum Gaussian kernel.

2.6 | Construction of brain networks

In the present study, we constructed structural networks using DTI tractography of all participants and obtained functional networks from rs-fMRI. The nodes of the structural and functional networks were automatically partitioned into 246 anatomical regions of interest (ROIs; 123 ROIs for each hemisphere) using the automated anatomic labeling algorithm, which was based on the Brainnetome Atlas (Fan et al., 2016). It is important to note that the cerebellum was not

included in this template. We chose to use FA to construct the structural network and extracted the averaged FA of the linking fibers between node weights of the edges of the structural network.

For the functional network, we obtained the mean time series of each ROI by averaging the fMRI time courses over each ROI and took the values of the interregional correlation coefficients as the weights of the edges of the functional network. The structural and functional connection matrix is depicted in Figure 1.

2.7 | Graph theory analysis

We applied the GRETNA toolbox (Wang, Wang, et al., 2015) to calculate the graph-theoretical properties of the structural and functional networks. We applied a threshold of connection sparsity (ranging from 0.05 to 0.5, with an interval of 0.01) for functional matrices and a value of matrix element for structural matrices (the threshold sequence was set as 0). The global network architecture of the structural and functional networks was characterized using seven parameters: normalized clustering coefficient (γ), normalized characteristic path length (λ), small-worldness (σ), clustering coefficient (C_p), characteristic path length (L_p), global efficiency (E_g), and local efficiency (E_{loc}). We calculated the area under the curve (AUC) over the sparsity for between-group comparisons; this approach provided a summarized scale for the topologic characterization of brain networks independent of a single threshold selection.

2.8 | SC-FC coupling analysis

The method used for SC-FC coupling analysis in this research was in line with previous studies (Chen, Geng, et al., 2021; Honey et al., 2009; Suo et al., 2021). The nonzero network edges of the SC matrix were extracted, rescaled to a Gaussian distribution, and then

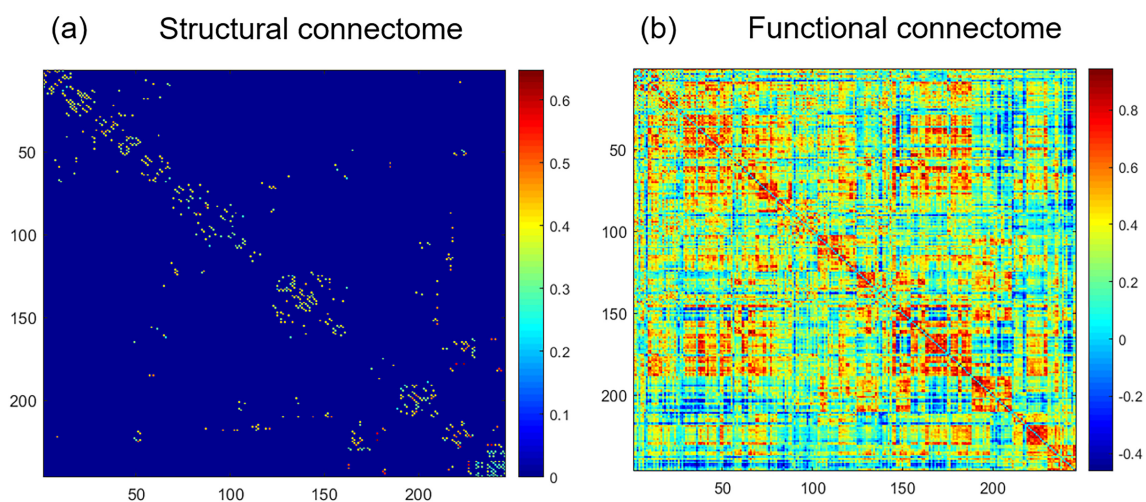


FIGURE 1 Brain connection matrix based on the Brainnetome Atlas. (a) The structural connectome matrix was estimated by Pearson correlation based on the Brainnetome Atlas. (b) The functional connectome matrix was computed by Pearson correlation based on the Brainnetome Atlas

correlated with their functional counterparts. The SC-FC coupling value was calculated for each participant.

2.9 | Statistical analyses

First, we assessed all the data for normality using the Kolmogorov-Smirnov test. If the data were not normally distributed, nonparametric tests were used. Group differences in demographic data and clinical measures were tested using one-way analysis of variance (ANOVA) among the three groups, followed by a post hoc test (*t*-test for means and χ^2 -test for proportions). The results were reported at the significance level of $p < .05$. SPSS 23.0 (IBM Inc., Armonk, NY, USA) was used for all subsequent statistical analyses. The SC and FC network metrics of the three groups were statistically analyzed separately using analysis of covariance (ANCOVA), followed by a post hoc test ($p < .05$) (we chose the AUCs of all the network metrics for FC statistical analysis). We also applied ANCOVA to compare the SC-FC correlation values among the three groups, followed by a post hoc test ($p < .05$). Partial correlation analyses were performed to identify possible relationships between the brain network features (SC, FC, and SC-FC coupling) and clinical performance in tinnitus patients. The statistical threshold was set at $p < .05$.

3 | RESULTS

3.1 | Demographic and clinical characteristics

The demographic and clinical data of tinnitus patients (28 in the EG and 32 in the IG) and HCs are described in Table 1. Among the three

groups, there were no significant differences in age, sex, handedness, disease duration, or laterality of tinnitus ($p > .05$). We also obtained THI scores at baseline and after sound therapy, changes in THI scores, and the improvement of THI scores. THI score changes were the primary outcome of the current study; pertinently, patients in the EG showed significantly greater improvement in THI scores than patients in the IG (52.30% vs. -15.79%).

3.2 | Structural and functional network analysis

3.2.1 | Small-world properties and network efficiency analysis

In the defined threshold range, the HCs, the EG and the IG all showed small-world topology ($\gamma > 1$, $\lambda \approx 1$, and $\sigma > 1$) (Bassett & Bullmore, 2006) in the brain structural and functional connectomes (Figure 2).

For the structural network, patients in the EG and IG both displayed different λ , L_p , and E_g values compared with the HCs (all $p < .05$, Figure 3a, Table 2). For example, both the EG and IG showed lower λ and L_p values than HCs, but the *p*-value of patients in the EG ($p = .008$) was smaller than that of patients in the IG ($p = .013$). Moreover, patients in both the EG and IG exhibited higher E_g values than HCs, but the *p*-value of the EG ($p = .002$) was larger than that of the IG ($p = .001$). However, there was no significant difference directly between the EG and IG in these graph-theoretical features. Additionally, no significant differences were found among the EG, IG, and HCs in the remaining network indicators.

For the functional network, except for patients in the EG who showed a higher E_{loc} than patients in the IG ($p = .034$, Figure 3b),

TABLE 1 Demographic and clinical characteristics of tinnitus patients (the EG, IG) and healthy volunteers

Demographic	Tinnitus-EG (baseline, $n = 28$)	Tinnitus-EG (treated, $n = 28$)	Tinnitus-IG (baseline, $n = 32$)	Tinnitus-IG (treated, $n = 32$)	Controls ($n = 57$)	<i>p</i> value
Age (year)	46.44 ± 12.11		48.54 ± 12.78		47.44 ± 12.08	.755 ^a
Gender (male/female)	12/16		22/10		31/26	.128 ^b
Handedness (right/left)	28/0		32/0		57/0	>.99 ^a
THI score	68.86 ± 21.74	33.57 ± 20.16	43.13 ± 19.52	47.88 ± 20.24	NA	<.0001 ^c
ΔTHI score	35.29 ± 18.23		-4.75 ± 11.01		NA	<.0001 ^d
% improvement of THI score	52.30 ± 19.34		-15.79 ± 42.26		NA	<.0001 ^d
Duration (month)	≥ 6 & ≤ 48		≥ 6 & ≤ 48		NA	NA
Tinnitus pitch	250 ~ 8,000 Hz		250 ~ 8,000 Hz		NA	NA
Laterality (right/left/bilateral)	12/3/13		8/9/15		NA	.158 ^b
SAS	41.50 ± 10.04		42.41 ± 7.47		NA	.691 ^d
SDS	47.75 ± 11.23		47.66 ± 11.50		NA	.975 ^d

Abbreviations: EG, effective group; IG, ineffective group; NA, not applicable; SAS, self-rating anxiety scale; SDS, self-rating depression scale; THI, Tinnitus Handicap Inventory; ΔTHI score, $THI_{baseline} - THI_{treated}$.

^aOne-Way ANOVA.

^bChi-square test.

^cTwo-Way ANOVA.

^dTwo-sample *t*-test.

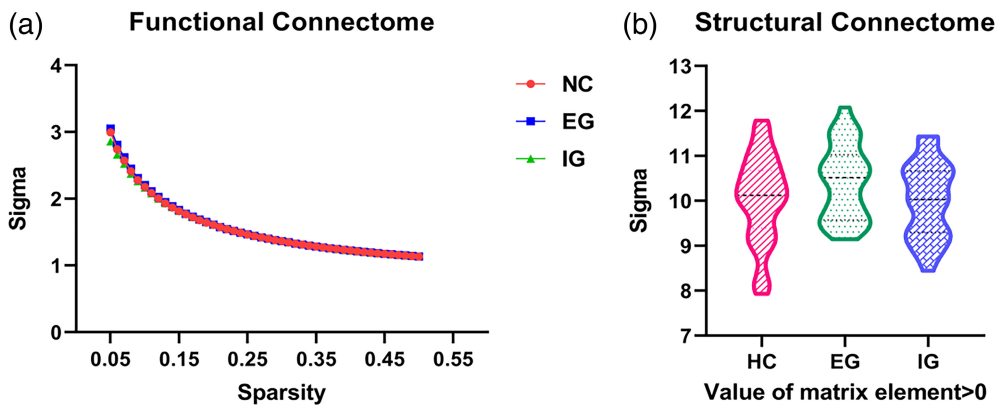


FIGURE 2 The small-worldness of functional and structural network connections. (a) The functional networks of the HC group, EG, and IG exhibited an efficient small-world ($\sigma > 1$) at all sparsities (0.05–0.5). (b) The structural networks of the HC group, EG, and IG exhibited an efficient small-world (a value of matrix element > 0 as threshold)

both the EG and IG demonstrated no changes in the remaining topological properties compared with the HCs. Also, there were no direct differences between the two groups ($p > .05$, Figure 3b).

3.2.2 | SC-FC coupling analysis results

Compared with the HCs (-0.212 ± 0.07), IG (-0.16 ± 0.08) showed a significant increase in SC-FC coupling [$p = .024$, ($p < .05$, with Bonferroni correction)] (Figure 4, Table 2). No significant group difference was observed directly between the IG and HCs or between the EG and IG ($p > .05$).

3.3 | Correlations of the clinical variables with the graph-theoretical properties in tinnitus patients

For the structural network, a positive correlation was found between γ and %improvement of THI score of all the patients with tinnitus ($r = .326$, $p = .024$; Figure 5a), and a positive correlation was found between λ and Δ THI score in patients in the EG ($r = .476$, $p = .014$; Figure 5b). We also found negative correlations between the C_p and SAS score ($r = -.481$, $p = .013$; Figure 5c), Eloc and the SAS score ($r = -.511$, $p = .008$; Figure 5d), C_p and SDS ($r = -.518$, $p = .007$; Figure 5e), and Eloc and the SDS score ($r = -.550$, $p = .004$; Figure 5f) in the EG. No significant correlations were found between the clinical variables and remaining graph-theoretical properties in the structural network or between clinical variables and any graph-theoretical properties in the functional network ($p > .05$, uncorrected).

4 | DISCUSSION

In the present study, all tinnitus patients underwent 6 months of individualized sound therapy, and they showed significantly different prognoses when the reduction in the THI score was used as the evaluation criterion. Treatment was effective in 28 patients and ineffective in 32 patients. Patients in the EG showed significant tinnitus symptom relief relative to patients in the IG (52.30% vs. -15.79%). More interestingly, using multimodal neuroimaging methods (a combination of

SC, FC, and SC-FC coupling), we found that except for brain structural changes (Chen, Lv, et al., 2021b) and functional network-level reorganization (Chen, Lv, et al., 2021a), there were significant differences in brain SC network properties and SC-FC couplings between the two groups; these differences were closely related to patient's outcomes. To the best of our knowledge, this is the first study exploring the distinct mechanisms of tinnitus patients with different outcomes after sound therapy from the perspective of functional-structural connectome coalescence, employing combined DTI and rs-fMRI methods. Our findings may provide novel insights into the role of brain structural-functional network topological coupling during recovery in tinnitus patients and may even reveal indicators that can be used in patient screening and prognosis predictions before sound therapy. Notably, we chose the Brainnetome Atlas (Fan et al., 2016) to define the nodes of structure and function networks as it contains information on both anatomical and functional connections and even facilitates investigations into structure–function relationships.

4.1 | Topological property alterations of structural and functional networks

Consistent with the graph-theoretical results from previous tinnitus-related studies (Lin et al., 2020; Mohan, De Ridder, & Vanneste, 2016a, 2016b), a small-world organization of the structural and functional networks was found in both the tinnitus patients and HCs. A small world is an ideal organization in the sense that it permits efficient information segregation and integration (Rubinov & Sporns, 2010), and it even offers a structural substrate for both local and global interactions (Bullmore & Sporns, 2009). Studies have suggested that small-world characteristics exist in brain structural and functional networks and that changes in topological properties are closely related to a variety of neurological or neuropsychiatric disorders, such as Alzheimer's disease (Supekar, Menon, Rubin, Musen, & Greicius, 2008), bipolar disorder (Zhang, Shao, et al., 2019), stroke (Chen, Geng, et al., 2021), and posttraumatic stress disorder (Lei et al., 2015). Thus, represented by the σ value, the generally similar pattern of small-worldness among the three groups may indicate that a generally balanced modulation between integration and segregation was still intact in the whole brain after tinnitus developed. In addition,

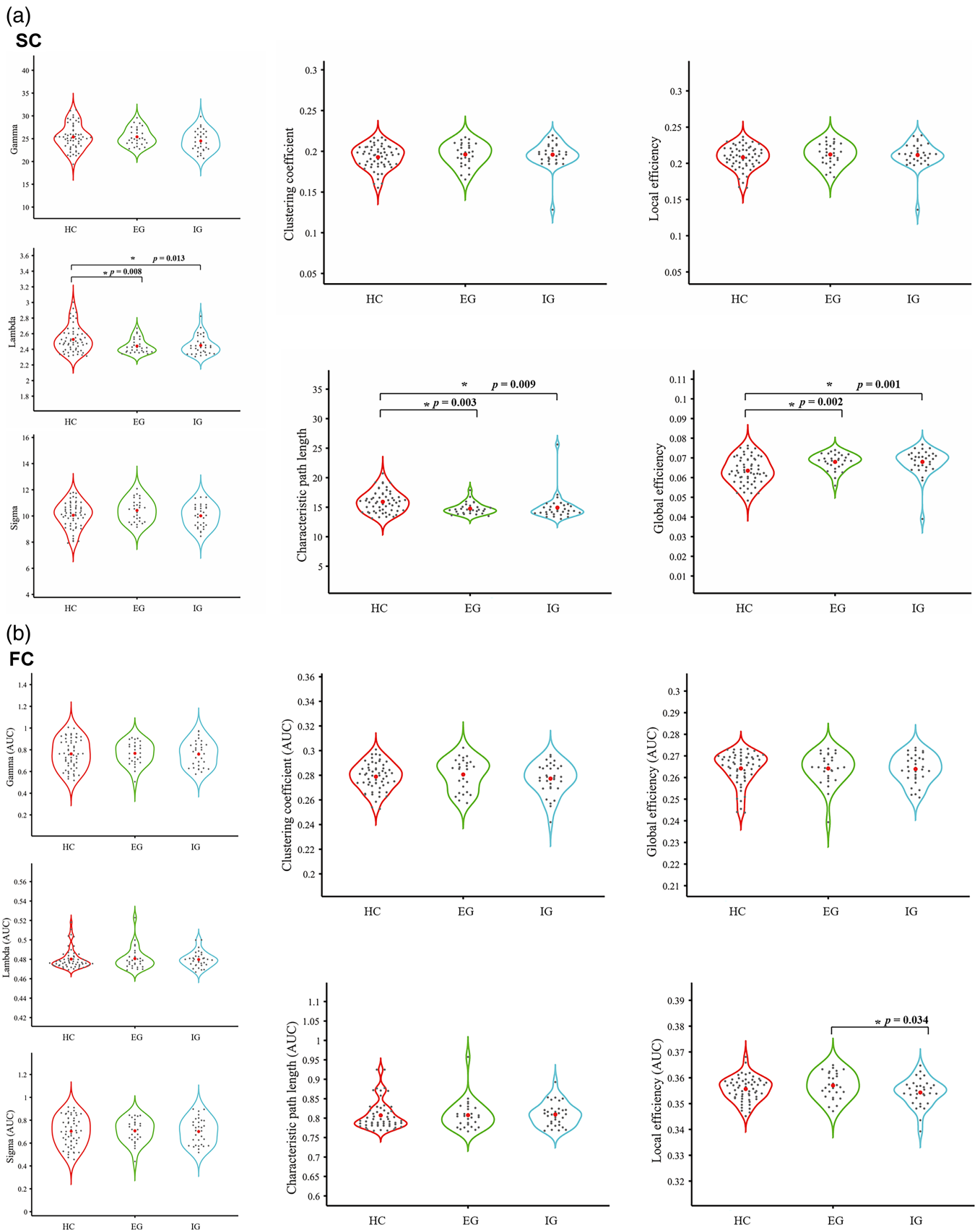


FIGURE 3 The measures of large-scale network properties among the HC group, EG, and IG. (a) The measures of structural network properties among the HC group (red), EG (green), and IG (blue). (b) The measures of functional network properties among the HC group (red), EG (green), and IG (blue). *Significant group differences after post hoc pairwise comparisons. AUC, area under the curve; EG, effective group; HC, healthy control; IG, ineffective group

Graph measures	Tinnitus-EG (n = 28)	Tinnitus-IG (n = 32)	Controls (n = 57)	p value
<i>Structural network</i>				
Gamma (γ)	25.42 ± 1.89	24.51 ± 2.23	25.37 ± 2.72	.219
Lambda (λ)	2.44 ± 0.09	2.45 ± 0.12	2.53 ± 0.16	.008
Sigma (σ)	10.42 ± 0.83	10.01 ± 0.84	10.06 ± 0.97	.144
Cp	0.20 ± 0.01	0.20 ± 0.02	0.19 ± 0.01	.495
Lp	14.76 ± 0.98	14.92 ± 2.17	15.93 ± 1.75	.003
Eg	0.07 ± 0.004	0.07 ± 0.007	0.06 ± 0.007	.001
Eloc	0.21 ± 0.01	0.21 ± 0.02	0.21 ± 0.02	.469
<i>Functional network (AUC)</i>				
Gamma (γ)	0.77 ± 0.14	0.76 ± 0.12	0.76 ± 0.14	.970
Lambda (λ)	0.48 ± 0.01	0.48 ± 0.01	0.48 ± 0.01	.944
Sigma (σ)	0.71 ± 0.10	0.70 ± 0.11	0.70 ± 0.13	.979
Cp	0.28 ± 0.01	0.28 ± 0.01	0.28 ± 0.01	.554
Lp	0.81 ± 0.04	0.81 ± 0.03	0.81 ± 0.04	.967
Eg	0.26 ± 0.007	0.26 ± 0.006	0.26 ± 0.008	.982
Eloc	0.36 ± 0.005	0.35 ± 0.005	0.36 ± 0.005	.104
<i>Coupling</i>	-0.17 ± 0.09	-0.16 ± 0.08	-0.212 ± 0.07	.013

TABLE 2 Brain network graph measures and coupling of structural and functional connectivity in tinnitus patients (EG, IG) and healthy volunteers

Note: Graph measures of functional and structural network area under the curve of the network properties across the full range of sparsity thresholds.

Values in bold indicate $p < .05$

Abbreviations: Cp, clustering coefficient; EG, effective group; Eg, global efficiency; Eloc, local efficiency; IG, ineffective group; Lp, characteristic path length; γ , normalized clustering coefficient; λ , normalized characteristic path length; σ , small-worldness.

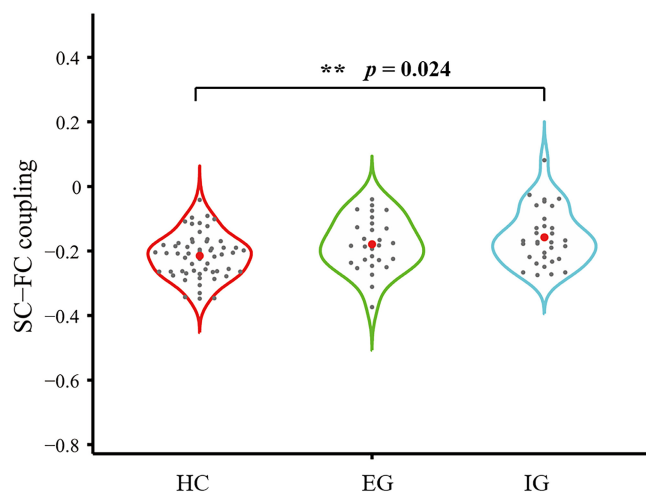


FIGURE 4 The measures of SC-FC coupling among the HC group, EG, and IG. **Significant group differences after post hoc pairwise comparisons with Bonferroni correction, $p < .05$. EG, effective group; FC, functional connectivity; HC, healthy control; IG, ineffective group; SC, functional connectivity

in the present study, we found decreased λ and Lp values in patients in both the EG and IG compared to HCs, but the p -value of patients in the EG was smaller than that of patients in the IG. Small-world characteristics are judged by Cp and Lp, and λ is the normalized form of Lp. Also, Lp is used to reflect the capacity for brain information

transmission (Watts & Strogatz, 1998), and the shortest path between distant brain areas ensures the effective integration and rapid transmission of information (Bullmore & Sporns, 2009). Thus, the decrease of λ and Lp values may indicate that the integration of information and the capacity of neurons to transmit information over long distances were increased in patients with idiopathic tinnitus, revealing a state of overcompensation. The difference in p -values between the two groups means that the enhancement of information integration and transmission is more likely to exist in patients in the EG than in patients in the IG; this enhancement may also be the reason sound therapy works for patients in the EG. Moreover, tinnitus patients showed an increased Eg, but the p -value of patients in the EG was larger than that of patients in the IG. Previous studies demonstrated that the increase of Eg in patients indicated an abnormally increased capacity for information transfer across the entire brain, resulting in less efficient global integration (Sporns, 2011; Zhang, Yu, et al., 2019). In line with the study of Lin et al. (2020), we considered that increased Eg may indicate a more compact global network in tinnitus patients as well; moreover, increased Eg could involve intensified information exchange from distributed regions. The difference in p -values between the two groups means that the enhanced capacity of information transmission was more likely to exist in the IG; this enhanced capacity may also be the reason sound therapy did not work for these patients, we need to expand the sample size in further research on this issue in the future. Therefore, we speculate that these findings may indicate overcompensation in the structural networks of tinnitus

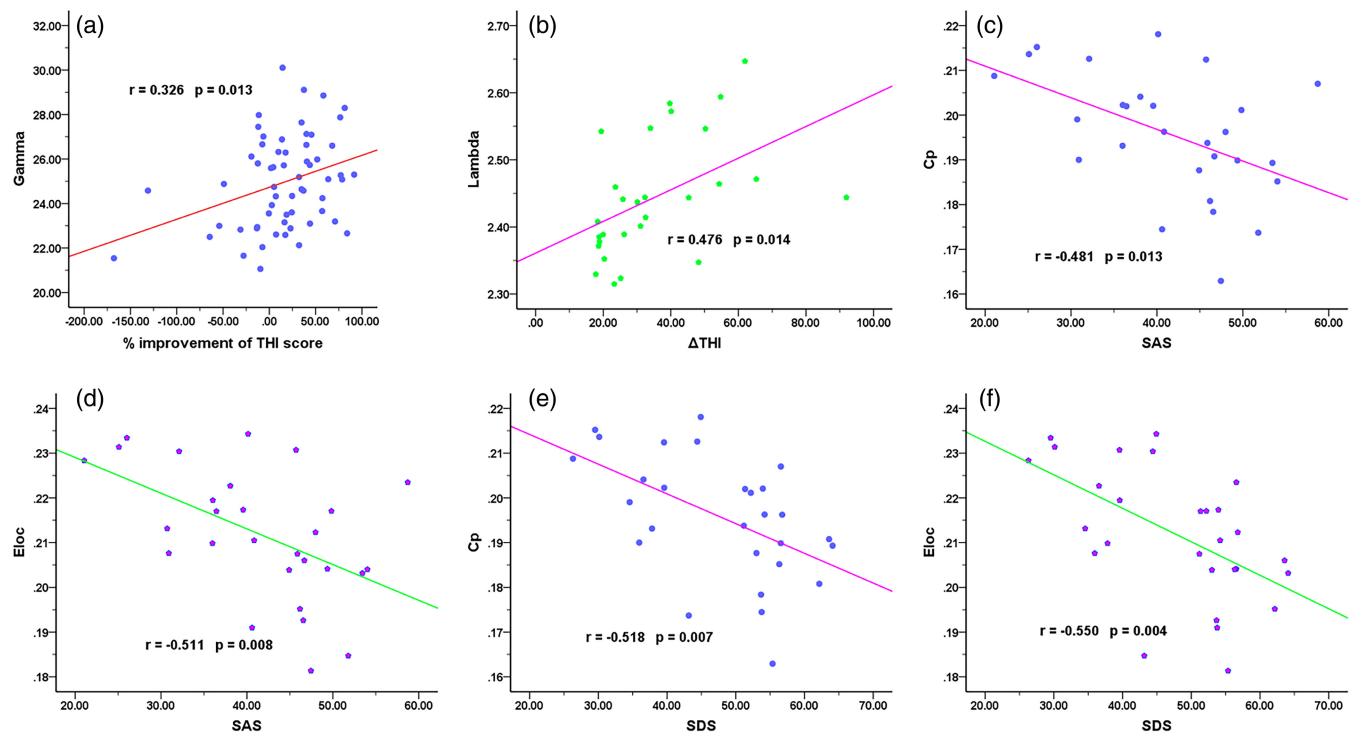


FIGURE 5 Correlations between the structural network properties and clinical variables in tinnitus patients. (a) The Pearson correlation shows a positive association between the gamma value and %improvement of THI scores in total tinnitus patients ($r = .326, p = .013$). (b) The Pearson correlation shows a positive association between the lambda value and Δ THI scores in the EG ($r = .476, p = .014$). The Pearson correlation revealed a negative association between (c) the Cp value and SAS scores ($r = -.481, p = .013$) and a negative association between (e) the Cp value and SDS scores ($r = -.518, p = .007$) in the EG. The Pearson correlation revealed a negative association between (d) the Eloc value and SAS scores ($r = -.511, p = .008$) and a negative association between (f) the Eloc value and SDS scores ($r = -.550, p = .004$) in the EG. Cp, clustering coefficient; EG, effective group; Eloc, local efficiency; SAS, self-rating anxiety scale; SDS, self-rating depression scale; THI, Tinnitus Handicap Inventory

patients, which could contribute to the development of distress, possibly through heightened local synchrony and information integration and transmission over long distances in the brain (Lin et al., 2020).

In this study, we did not find any significant differences in Eloc, γ , or Cp values of the structural network among the three groups. Eloc is mainly associated with short-range connections among neighboring regions to mediate modularized information processing or fault tolerance of a network (Latora & Marchiori, 2001). There was no difference in Eloc among the three groups, which may indicate that although idiopathic tinnitus caused an increase in long-term connections, as mentioned above, it did not result in damage to short-term connections. That is, tinnitus patients still have a normal capacity for information processing and transmission between neighboring brain regions within the large-scale network. As with Lp, Cp also indicates the process of transferring networks from small-world networks to rule networks or random networks. In addition, γ is the normalized form of Cp. A prior study (Lin et al., 2020) demonstrated that increased Lp may indicate a higher level of local connectedness in the neural network of tinnitus patients, which could denote a compensational mechanism for tinnitus-related HL (Langguth et al., 2013; Noreña & Farley, 2013). Thus, our findings regarding Cp and γ may suggest that tinnitus-related HL has not yet led to abnormal changes in local property indices of the brain structural network.

For the topological properties of the FC network, except for the higher Eloc in the EG relative to the IG, we did not find any significant differences in the remaining topological properties among the three groups. As we mentioned above, Eloc is mainly associated with neighboring information processing (Latora & Marchiori, 2001). Patients in the EG showed an increase in Eloc in the functional network analysis but no changes in Eloc in the structural network analysis. We speculate that this result may indicate that patients in the EG have a normal structural connection range and a longer functional connection range. For the remaining functional topological properties, consistent with some prior studies (Chen, Lv, et al., 2021a; Lin et al., 2020), we speculate that structural injury emerges immediately after or in the early stage after tinnitus through the whole brain, while the functional network remains relatively intact in the same phase (Chen, Lv, et al., 2021a; Straathof et al., 2019). The exact mechanism of this inconsistency needs to be further studied in the future.

For SC-FC coupling, previous studies have revealed that SC and FC interact with each other and that SC-FC coupling strength may even be an intrinsic reflection of a person's mental state (Huang & Ding, 2016; Wang, Dai, et al., 2015). SC provides scaffolding for FC, and FC shapes SC through a plasticity mechanism (Dacosta-Aguayo et al., 2014; Honey et al., 2010). Decreased SC-FC coupling may suggest a loss of coherence of functional and structural connectomes

(Zhang, Shao, et al., 2019). Disrupted SC-FC couplings have been reported in many diseases, such as stroke, Alzheimer's disease, epilepsy, and schizophrenia, and SC-FC coupling is correlated with clinical symptoms (Cao et al., 2020; Chen, Geng, et al., 2021; Cui et al., 2019; van den Heuvel et al., 2013; Wang, Dai, et al., 2015). In line with these studies, we found that patients in the IG had a significant increase in SC-FC coupling compared to HCs, while there was no significant difference between the EG and HCs. A prior study on stroke has suggested that the motor recovery of patients may rely not only on the severity of structural damage but may also depend on the functional plasticity of the motor system (Chen, Geng, et al., 2021); that is, this process involves a combination of functional and structural brain reorganization. Moreover, characterized by abnormal increases in brain activity, FC, or even structural indices, current studies have shown that the brains of idiopathic tinnitus patients are in a state of overcompensation or overactivation (Han et al., 2020; Han, Na, et al., 2019; Han, Yawen, et al., 2019; Lin et al., 2020) through Bayesian inference (De Ridder, Joos, & Vanneste, 2014; De Ridder, Vanneste, & Freeman, 2014). Therefore, we speculate that the increased SC-FC coupling in the IG of our study may indicate that these patients experience a more abnormal overcompensation state through the increased brain structural and functional connections. This hypothesis may also explain the ineffectiveness of sound therapy for these patients.

4.2 | Correlations between the clinical variables and graph-theoretical properties in tinnitus patients

To date, some studies have investigated relationships between changes in brain structure and function and clinical manifestations in patients with idiopathic tinnitus with different prognoses after sound therapy (Chen, Lv, et al., 2021a, 2021b; Han, Na, et al., 2019). For instance, previous studies revealed that the differences in brain structural changes (gray matter volume and white matter integrity) of tinnitus patients are closely related to the improvement of clinical performance (Chen, Lv, et al., 2021b), as are the functional changes (Han, Na, et al., 2019). Consistent with prior studies (Chen, Lv, et al., 2021b; Han, Na, et al., 2019), we observed that small-world characteristics (γ and λ) were positively correlated with the changes and %improvement of THI scores. The changes and improvement of THI scores indicated that tinnitus patients' symptoms improved significantly after sound therapy. Thus, in this study, the correlations between small-world characteristics and THI improvement mean that, for all tinnitus patients or the patients with good treatment outcomes, the more obvious alterations in their small-world characteristics were, and the better their prognosis was.

Few studies have explored correlations between the large-scale brain network properties in tinnitus patients and clinical variables (Lin et al., 2020). In Lin et al. (2020), graph-theoretical analysis was applied, and the researchers investigated the possible relationships between the brain structural network properties and clinical characteristics in tinnitus patients; however, the authors failed to find any

correlations, which may be due to the small sample size. Unlike that study, in our study, we found that parameters (C_p and E_{loc}) of the structural network in patients in the EG were negatively correlated with SDS and SAS scores. As the primary evaluation standard of anxiety and depression severity, the correlations between SDS/SAS scores and structural network indices in patients in the EG indicate that, for patients with good prognoses, the more a patient is able to perform neighbor information processing and transmit information in his or her brain, the less likely it is that tinnitus will cause anxiety and depression. The specific mechanism underlying these findings needs further study in the future.

4.3 | Limitations

Our study has several limitations. First, we only obtained the baseline MRI data of patients in the present study. We also need to obtain imaging data of patients after treatment in the future to further analyze the changes in brain network properties of patients with different prognoses before and after treatment. Second, as a therapeutic study, sham treatment may need to be administered to patients and HCs to eliminate the possible placebo effect of sound therapy. Third, a proportion of the patients had different degrees of HL, and the tinnitus lateralization of patients was also heterogeneous. In future studies, we will recruit tinnitus patients with HL, patients without tinnitus-related HL and patients with the same tinnitus sidedness to further understand the possible effects of HL and lateralization on changes in patients' large-scale network properties after sound therapy. Fourth, the Brainnetome Atlas we used in this study did not include the cerebellum. In future research, we will use other templates containing the cerebellum to study the possible role of the cerebellum in diseases.

5 | CONCLUSION

In conclusion, idiopathic tinnitus patients with different outcomes after sound therapy in the present study exhibited both brain structural and functional network topological changes, especially in the structural network. In addition, for patients in the EG, the changes in structural brain network properties were closely related to the improvement of tinnitus symptoms and abnormal emotions. More interestingly, patients in the EG and IG showed distinct brain SC-FC topological coupling patterns; that is, the more increased SC-FC coupling was, the worse the patients' prognosis was after sound therapy. SC-FC coupling may be an indicator that can be applied to predict outcomes in patients with idiopathic tinnitus before sound therapy. Our findings may contribute to a better understanding of the anatomical-functional interaction mechanisms underlying different outcomes among tinnitus patients.

ACKNOWLEDGMENTS

The authors thank the patients and healthy volunteers who participated in this study and gave generously of their time.

CONFLICT OF INTEREST

The authors declare no financial or other conflicts of interest.

AUTHOR CONTRIBUTIONS

Qian Chen and Han Lv contributed to the study concept, design, and imaging data processing. **Qian Chen** performed the statistical analysis, interpretation, and drafting of the article. **Zhaodi Wang, Xuan Wei, Jiao Liu, Fang Liu, Pengfei Zhao, Zhenghan Yang, and Shusheng Gong** provided technical and clinical support and revised the article for intellectual content. **Zhenchang Wang** contributed to study concept, design, revising of the article for the intellectual content and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

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How to cite this article: Chen, Q., Lv, H., Wang, Z., Wei, X., Liu, J., Liu, F., Zhao, P., Yang, Z., Gong, S., & Wang, Z. (2022). Distinct brain structural-functional network topological coupling explains different outcomes in tinnitus patients treated with sound therapy. *Human Brain Mapping*, 43(10), 3245–3256. <https://doi.org/10.1002/hbm.25848>