Pretreatment intranetwork connectivity can predict the outcomes in idiopathic tinnitus patients treated with sound therapy

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Abstract
Previous studies demonstrated that brain morphological differences and distinct patterns of neural activation exist in tinnitus patients with different prognoses after sound therapy. This study aimed to explore possible differences in intrinsic network-level functional connectivity (FC) in patients with different outcomes after sound therapy (narrow band noise). We examined intrinsic FC using resting-state functional magnetic resonance imaging in 78 idiopathic tinnitus patients (including 35 effectively treated and 43 ineffectively treated) and 52 healthy controls (HCs) via independent component analysis. We also investigated the associations between the differences in FC and clinical variables. Analyses revealed significantly altered intranetwork connectivity in the auditory network (AUN) and some nonauditory-related networks in the EG/IG patients compared to HCs; compared with EG patients, IG patients showed decreased intranetwork connectivity in the anterior default mode network (aDMN) and AUN. Meanwhile, robust differences were also evident in internetwork connectivity between some nonauditory-related networks (salience network and executive control network; posterior default mode network and dorsal attention network) in the EG relative to IG patients. We combined intranetwork connectivity in the aDMN and AUN as an imaging indicator to evaluate patient outcomes and screen patients before treatment; this approach reached a sensitivity of 94.3% and a specificity of 76.7%. Our study suggests that tinnitus patients with different outcomes show distinct network-level functional reorganization patterns. Intranetwork connectivity in the aDMN and AUN may be indicators that can be used to predict prognoses in patients with idiopathic tinnitus and screen patients before sound therapy.

KEYWORDS
clinical improvement, idiopathic tinnitus, internetwork connectivity, intranetwork connectivity, sound therapy

Abbreviations: ACC, anterior cingulate cortex; CSF, cerebrospinal fluid; EG, effective group; EPI, echo-planar imaging; FA, flip angle; FC, functional connectivity; GMV, gray matter volume; HC, healthy control; IFG, inferior frontal gyrus; IG, ineffective group; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MOG, middle occipital gyrus; mPFC, medial prefrontal cortex; ROC, Receiver operating characteristic; STG, superior temporal gyrus; TE, echo time; THI, tinnitus handicap inventory; TR, repetition time.
Tinnitus is a sort of phantom sound perception in the absence of any external acoustic stimulation, which is bothersome or debilitating for patients and is a major health issue in society worldwide (Baguley, McFerran, & Hall, 2013; Conlon et al., 2020; McCormack, Edmondson-Jones, Somerset, & Hall, 2016). Tinnitus and its related or secondary complications, such as anxiety, depression, insomnia, and hyperacusis, seriously affect patients’ lives (Bhatt, Lin, & Bhattacharyya, 2016; Sereda, Xia, El Refaie, Hall, & Hoare, 2018). A growing number of studies have provided evidence that tinnitus, as an abnormality in the central nervous system, can result in significant brain structural and functional alterations that are closely associated with patients’ clinical features and may even be the main factors responsible for tinnitus generation (Chen et al., 2015; Chen et al., 2020, 2021a; Han, Yawen, et al., 2019; Han, Na, et al., 2019; Lv et al., 2020; Ryu, Park, Byun, Jahng, & Park, 2016). However, due to limitations of the current research methods, it is still unclear which exact brain region(s) or neural pathway(s) play a major role in tinnitus (Schaette & McAlpine, 2011; Vanneste, Aalsalm, & De Ridder, 2019). This may also be the reason why the current therapeutic interventions cannot achieve satisfactory results for all patients with tinnitus (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013). Thus, effective precise treatments that target the mechanisms of tinnitus (such as certain brain regions or neural pathways) are still urgently needed.

Currently, many therapeutic approaches have been applied in the process of idiopathic tinnitus treatment, such as counseling and psychoeducation, pharmacological treatments, sound therapy, hearing aids, tinnitus retraining therapy, cochlear implants, brain stimulation, hyperbaric oxygen, and acupuncture (Langguth et al., 2013; Zenner et al., 2017). Among these therapeutic measures, sound therapy, such as frequency unmodulated noise generators involving the use of recorded noise, special tinnitus noisers, or tinnitus masker devices (Jastreboff, 1999; Oishi et al., 2013; Zenner et al., 2017), has been widely used in the treatment of idiopathic tinnitus in many studies (Han et al., 2020; Jastreboff, 1999; Lv et al., 2020; Oishi et al., 2013; Wei et al., 2020). Furthermore, it has been listed as an option in clinical practice guidelines (Henry, Schechter, Nagler, & Fausti, 2002; Tunkel et al., 2014) and even used as a first-line means for treating tinnitus patients when combined with other measures, such as hearing aids and information and counseling (Hoare, Edmondson-Jones, Sereda, Akeroyd, & Hall, 2014; Hobson, Chisholm, & El, 2012; Sereda, Hoare, Nicholson, Smith, & Hall, 2015; Tutaj, Hoare, & Sereda, 2018). Moreover, a recent large randomized clinical study found that when combined with electrical stimulation, sound therapy can significantly improve tinnitus symptoms (Conlon et al., 2020).

To date, there have been relatively few noninvasive studies on the effect of sound therapy in the treatment of idiopathic tinnitus, and these studies have had divergent results (Han et al., 2020; Han, Yawen, et al., 2019; Han, Na, 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., 2020). For example, using neuroimaging methods, some studies have indicated that sound therapy (narrowband sound stimulation) may modulate or even have a normalizing effect on abnormal brain activity or functional connectivity (FC) in some tinnitus-related regions, which may reflect less involvement of the noise-canceling system (Han et al., 2020; Han, Yawen, et al., 2019; Han, Na, et al., 2019; Lv et al., 2020). Furthermore, recent studies have even suggested that sound therapy can prevent or normalize atrophic gray matter volume (GMV) and abnormal gray matter-based structural networks (Wei et al., 2020, 2021). These studies suggested that brain structural and functional alterations in patients with idiopathic tinnitus are strongly associated with their clinical symptom improvements (assessed as changes in Tinnitus Handicap Inventory [THI] scores) after treatment. However, some studies also showed that sound therapy has no measurable effect on idiopathic tinnitus (Moffat et al., 2009; Oishi et al., 2013; Parazzini et al., 2011), which may have been due to the low methodological quality (Hoare, Stacey, & Hall, 2010), and the current acoustic therapy measures are generally multimodal (Hobson et al., 2012). Thus, the mechanism by which acoustic therapy is effective or ineffective in tinnitus patients is still unclear, and it cannot be predicted whether the particular method is suitable or not for some patients. Meanwhile, our latest study revealed that significant differences existed in the GMV and white matter microstructure in some areas or fibers between the sound therapy effective group (EG) and ineffective group (IG), which indicated that there may be distinct mechanisms of neural remodelling between these groups of patients (Chen et al., 2021a). Therefore, it is unknown whether such a difference existed in the resting-state network (RSN) FC alterations using independent component analysis (ICA) between the EG and IG, as previous studies have shown functional abnormalities play an important role in tinnitus generation (Chen, Zheng, et al., 2018; Chen, Zhang, et al., 2018; Feng et al., 2018; Han, Yawen, et al., 2019; Han, Na, et al., 2019; Schmidt, Carpenter-Thompson, & Husain, 2017; Zhou et al., 2019).

To address these issues in the present study, we evaluated the long-term (6-month) outcomes of idiopathic tinnitus patients after sound therapy. Moreover, we characterized the intra- and inter-network FC alterations using independent component analysis (ICA) and studied the relationship between brain changes and clinical symptom improvement. Based on the follow-up THI scores, the patients were divided into the EG and IG. Comparing the differences in the RSN FC alterations between the two groups, we aimed to explore the possible different mechanisms in patients showing differential therapeutic efficacy and to guide the selection of optimal methods for patients with idiopathic tinnitus before treatment.

## 2 | METHODS

### 2.1 | Subjects

Data were obtained from 78 untreated persistent idiopathic tinnitus patients (right-handed) and 52 right-handed healthy controls (HCs). In our study, all the patients met the following inclusion criteria: persistent idiopathic tinnitus (persistent for ≥6 months and ≤48 months), no magnetic resonance imaging (MRI) contraindications, no history of...
associated brain diseases confirmed by conventional MRI, and no pre-existing mental illness or cognitive disorder that would affect the brain alteration outcomes. The tinnitus sound of the patients was present as a single high/low-pitched sound and/or 2 high/low-pitched sounds that presented without any rhythm. Based on audiogram results, a proportion of patients did not have significant hearing loss, which was defined as more than 25 dB hearing loss at frequencies ranging from 250 to 8 kHz in pure tone audiometry (PTA) examination, while others had different degrees of tinnitus-related hearing loss. We excluded patients with the following conditions: pulsatile tinnitus, hyperacusis on physical examination, otosclerosis, sudden deafness, Ménière's disease, and other neurological diseases. We asked all the patients to complete the THI (Newman, Jacobson, & Spitzer, 1996) and visual analog scale (VAS) at the time of admission to assess disease severity. We also evaluated the current severity of depression and distress of the patients. The hearing condition of HCs was evaluated by audiologists using a questionnaire, and no HCs reported tinnitus in the last year. Other exclusion criteria for HCs were the same as those for patients described above.

2.2 | Sound intervention

The sound therapy applied is a customized personal sound therapy based on patients’ tinnitus features. For the sound therapy applied in this study, we used the special tinnitus therapeutic instrument: eMasker® (Micro-DSP Technology Co., Ltd), which is a customized personal sound therapy device based on tinnitus characteristics test results. We advise patients to use it in a quiet environment to achieve the best therapeutic effect. First, to prepare individualized therapeutic interventions, we characterized the tinnitus type and evaluated four main factors: tinnitus loudness matching, pitch matching, minimum masking level, and residual inhibition. Then, we applied therapeutic narrowband noise to patients for 20 min three times per day for 6 months. The loudness of the sound used to treat each tinnitus patient was set as the tinnitus loudness plus 5 dB. The frequency was set as a 1-kHz narrowband with the tinnitus frequency as the middle point of the delivered sound (i.e., tinnitus frequency ±0.5 kHz). All the patients were asked to complete the THI to assess tinnitus severity before and after treatment, and the primary outcome of the current study was the changes in THI score. Based on prior studies, we defined tinnitus patients with a reduction of 17 points or more in THI scores or reduced to 16 points as the EG (Chen et al., 2021a; Zeman et al., 2011), while those with a decrease in THI scores that did not meet either of these two conditions were defined as IG. Accordingly, the patients were divided into two groups: 35 patients were classified into an EG, and 43 patients were classified into an IG. We did not apply any type of sound intervention to the HCs throughout the whole research process. We also calculated the △THI score and the %improvement of the THI scores in all the tinnitus patients, which were defined as follows: △THI score = THI baseline - THI treated, % improvement of the THI score = (THI score at 6 months follow-up-THI score on admission) ÷ THI score on admission ×100%.

The present study was approved by the Institutional Review Board (IRB) of Beijing Friendship Hospital, Capital Medical University (Beijing, China). Informed consent was obtained from all study subjects in accordance with the Declaration of Helsinki. The registration number of this study on ClinicalTrials.gov is NCT03764826.

2.3 | MRI protocols

The functional imaging data were obtained from the tinnitus patients at baseline (without any treatment) and HCs using a 3.0T MRI system (Prisma, Siemens, Erlangen, Germany) with a 64-channel phase-array head coil. 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 any specific thoughts. We used a conventional brain axial T2 sequence before the scans to exclude individuals with any visible brain abnormalities. We obtained resting-state functional images of all participants using an echo-planar imaging (EPI) sequence. The scanning parameters were as follows: 33 axial slices with a slice thickness = 3.5 mm and interslice gap = 1 mm; repetition time (TR) = 2,000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; bandwidth = 2,368 Hz/Px; field of view (FOV) = 224 × 224 mm²; and matrix = 64 × 64. The latter parameters resulted in an isotropic voxel size of 3.5 × 3.5 × 3.5 mm³. The total number of volumes acquired was 240, and the total scan time was 8.06 min.

2.4 | Preprocessing of functional data

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) for the preprocessing of resting-state functional MRI (rs-fMRI) data, 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: (a) to allow for steady-state magnetization and stabilization of the subject, we removed the first 10 volumes of each functional time series for all the participants. (b) We conducted slice-timing correction on the remaining 230 volumes. Head motion between volumes was evaluated and corrected using rigid-body registration, and none of the 130 subjects had a maximum displacement >2.5 mm, maximum rotation >2.5° or mean framewise displacement (FD) >0.3 (Yan et al., 2013). (c) Based on the standard stereotaxic coordinate system, we spatially normalized the corrected fMRI images to a Montreal Neurological Institute (MNI) template brain. (d) Each voxel was resampled to isotropic 3 mm × 3 mm × 3 mm. (e) To remove the possible variances from the time course of each voxel, 26 nuisance covariates (including white matter [WM] and cerebrospinal fluid [CSF] signals and Friston-24 head motion parameters) were regressed out. (f) We set a Gaussian
smoothing kernel of $6 \times 6 \times 6 \text{mm}^3$ full-width at half-maximum for the rs-fMRI images.

2.5 | ICA analysis

We performed ICA through GIG-ICA using GIFT software (version 3.0b) (http://mialab.mrn.org/software/gift/). This process consisted of three main steps: (a) data reduction, (b) application of the ICA algorithm, and (c) back-reconstruction for each subject. In the current study, we performed group independent component analysis (GICA) 100 times on all the participants using 20 and 30 components separately and found that 30 would be the optimal number of components. During this process, through visual inspection, previous reports, and prior templates, we identified 11 components as meaningful RSNs. We also obtained the individual-level components using back-reconstruction and transformed the subject-specific spatial maps to z scores.

2.6 | Intranetwork FC analysis

In accordance with previous studies (Chen, Zheng, et al., 2018; Chen, Zhang, et al., 2018; Wang et al., 2014), the main process was as follows: to generate a sample-specific spatial map for each component, each ICA component was entered into a random-effect one-sample t-test with a familywise error (FWE)-corrected $p < .05$ and with a cluster size of >100 voxels (Song et al., 2013; Wang et al., 2014). We compared the differences in intranetwork FC among the EG patients, IG patients, and HCs at baseline using a voxel-based, one-way analysis of covariance (ANCOVA) with post hoc t-tests controlling for age and sex (FWE-corrected $p < .05$). Using a general linear model (GLM), we extracted and compared intranetwork FC in each region of interest (ROI) with a significant difference among groups, with age and sex serving as covariates.

2.7 | Internetwork FC analysis

For the process of the internetwork FC analysis, first, before the calculation of the mean time course of each RSN, we averaged the time courses of all voxels within the sample-specific RSN mask of each subject. Then, we calculated Pearson’s correlation coefficients of the mean time courses between all pairs of RSNs for each subject. To improve normality, the correlation coefficients were converted to z-values using Fisher’s r-to-z transformation. For each group, individual z-values were entered into a random-effect one-sample t-test to determine whether the correlation between each pair of RSNs was statistically significant ($p < .05$). Intergroup comparisons were conducted only if the internetwork FC of each group was statistically significant ($p < .05$). We performed a GLM with age and sex as covariates to determine whether the pairs of internetwork FC were significantly different ($p < .05$) among the EG, IG, and HC group using one-way analysis of variance (ANOVA) with post hoc t-tests.

2.8 | Statistical analyses

During the statistical analysis process, we assessed all the data for normality using the Kolmogorov–Smirnov test. If the data were identified as not normally distributed, we applied nonparametric tests. We conducted a partial correlation analysis to explore any potential associations between changes of brain FC and clinical variables (such as duration, THI scores, and VAS scores) in tinnitus patients after controlling for age and sex effects ($p < .05$). The last steps were performed using IBM SPSS Statistics software, version 23.0 (IBM Inc., Armonk, NY). The results of the internetwork/internetwork FC were presented using MRIcron (https://www.nitrc.org/projects/mricron), BrainNet Viewer (http://www.nitrc.org/projects/bnv/), (Xia, Wang, & He, 2013) and xjView (https://www.alivelearn.net/xjview/).

3 | RESULTS

3.1 | Sample characteristics

Table 1 summarizes the group-level sample characteristics. Seventy-eight tinnitus patients with persistent idiopathic tinnitus (35 were classified as EG and 43 as IG based on the therapeutic effect) and 52 healthy volunteers were enrolled in this study. Among the three groups, there were no significant differences in age, sex, handedness, disease duration, or laterality of tinnitus. We also obtained THI scores before and after sound therapy, changes in THI scores, and the improvement of THI scores. As the primary outcome of the current study, the EG showed significantly greater improvement in THI scores than the IG (55.08% vs. –14.18%).

3.2 | Meaningful components of the RSNs

The 11 RSNs identified in the present study were as follows: the auditory network (AUN), the anterior (aDMN) and posterior (pDMN) default mode networks, the left (LFPN) and right (RFPN) frontoparietal networks, the medial (mVN) and lateral (lVN) visual networks, the sensorimotor network (SMN), the dorsal attention network (DAN), the salience network (SN) and the executive control network (ECN; Figure 2a,b). The locations of these RSNs were in line with some prior studies (Du et al., 2015; Ma et al., 2016; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Smith et al., 2009).

3.3 | Altered FC within RSNs among the EG, IG, and HC group

One-way ANOVA showed that significant differences in internetwork FC existed among the three groups (cluster-level FWE correction with $p < .05$). Compared with the HC group, the EG had significantly increased internetwork FC in the right inferior frontal gyrus (IFG) of the aDMN, left superior temporal gyrus (STG) of the
TABLE 1 Demographic and clinical characteristics of the EG, IG, and healthy volunteers

| Demographic | Tinnitus-EG (baseline, n = 35) | Tinnitus-EG (treated, n = 35) | Tinnitus-IG (baseline, n = 43) | Tinnitus-IG (treated, n = 43) | Controls (n = 52) | p value |
|-------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|-------------------|---------|
| Age, years  | 47.80 (±13.05)                  | 48.00 (±11.73)                  | 48.33 (±11.37)                  |                                | .979⁵                |
| Gender      | 13 males, 22 females            | 20 males, 23 females            | 23 males, 29 females            |                                | .692⁴                |
| Handedness  | 35 right-handed                 | 43 right-handed                 | 52 right-handed                 |                                | >.99⁶                |
| THI score   | 63.77 (±24.63)                  | 28.91 (±19.39)                  | 49.72 (±21.95)                  | 53.21 (±21.24)                  | NA                 | <.0001⁶ |
| ΔTHI score  | 34.86 (±20.29)                  | –3.49 (±16.32)                  | NA                             | NA                             | NA                 |         |
| % improvement of THI score | 55.08% (±18.52%) | –14.18% (±46.68%) | NA | NA | NA | |
| Duration, months | ≥6 & ≤48                      | ≥6 & ≤48                       | NA                             | NA                             | NA                 |         |
| Tinnitus pitch | 250–8,000 Hz                  | 250–8,000 Hz                   | NA                             | NA                             | NA                 |         |
| Laterality  | 12 left, 8 right, and 15 bilateral | 14 left, 8 right, and 21 bilateral | NA                             | NA                             | .845⁷                |

Abbreviations: EG, effective group; IG, ineffective group; NA, not applicable; THI, Tinnitus Handicap Inventory; ΔTHI score, THIbaseline – THItreated.

³One-Way ANOVA.
⁴Chi-square test.
⁵Two-Way ANOVA.

AUN, left IFG of the LFPN, bilateral insula of the SN, and middle occipital gyrus (MOG) of the IVN (Figure 1a, Table 2) and decreased FC in the anterior cingulate cortex (ACC) of the aDMN and right medial prefrontal cortex (mPFC) of the RFPN (Figure 1b, Table 2); meanwhile, the IG showed increased intranetwork FC in the bilateral IFG of the aDMN, left STG of the AUN, left IFG of the LFPN, and bilateral insula of the SN (Figure 1c, Table 2) and decreased FC in the ACC of the aDMN, right middle frontal gyrus (MFG) of the dorsal attention network (DAN, and right mPFC of the RFPN (Figure 1d, Table 2). A direct comparison between the two patient groups revealed significantly decreased FC in the right IFG of the aDMN and left STG of the AUN in the EG compared with the IG (Figure 1e, Table 2).

3.4 Altered FC between RSNs among the EG, IG, and HC group

Intergroup differences in the internetwork FC among the EG, IG, and HC group are shown in Table 3. Compared with the HCs, the EG patients showed increased positive internetwork FC between the SN and ECN (p = .004; Figure 2a, Table 3). Meanwhile, when comparing the two groups of patients, the EG also displayed weakened positive internetwork FC (SN and ECN, p = .025; pDMN and DAN, p = .011; Figure 2b, Table 3). However, we did not observe any differences in internetwork FC changes between the IG patients and HCs among the 11 RSNs.

3.5 Correlations between FC and tinnitus symptom improvement

We performed partial correlations between the internetwork/internetwork FC values and the THI scores, ΔTHI scores, % improvement in THI scores, and other clinical variables (such as duration and VAS scores) in patients with idiopathic tinnitus after controlling for age and sex. Interestingly, we detected that in the EG, the internetwork FC in the right IFG of the aDMN was negatively correlated with the % improvement of THI scores (r = –.475, p = .005; Figure 3a), whereas the internetwork FC in the left IFG of the LFPN was positively correlated with the ΔTHI scores and the % improvement of THI scores (r = .385, p = .027; r = .470, p = .006, respectively) (Figure 3b,c), and the internetwork FC in the right insula of the SN was positively correlated with the ΔTHI scores and the % improvement of THI scores (r = .415, p = .016; r = .391, p = .024, respectively; Figure 3d,e). We did not observe any associations between these variables and the brain internetwork/internetwork FC values in the IG (p > .05).

3.6 Alterations in intranetwork FC values in the right IFG of the aDMN and the left STG of the AUN as indicators

Figure 4 and Table 4 show the sensitivity and specificity of the internetwork FC changes in the right IFG of the aDMN and the left STG of the AUN in the EG for prognosis evaluation and screening patients before sound treatment. Applying cutoff values of 0.374, 0.544, and 0.710, we evaluated the prognoses and screened patients with a sensitivity of 51.4% and specificity of 86.0% using the internetwork FC change in the right IFG of the aDMN, a sensitivity of 80.0% and specificity of 74.4% using the change of internetwork FC in the left STG of the AUN, and a sensitivity of 94.3% and specificity of 76.7% using the combination of alterations in the right IFG of the aDMN and the left STG of the AUN, respectively; the resulting areas under the curve (AUCs) for the receiver operating characteristic (ROC) curve values were 0.716 (95% confidence intervals from 0.610 to 0.830), 0.827
Our latest study proved that idiopathic tinnitus patients with different outcomes (effective or ineffective) after sound therapy experienced distinct brain structural reorganization (Chen et al., 2021a). Thus, the main objective of this study was met by providing convincing data about whether the different prognoses of tinnitus patients after sound therapy can be associated with the differences in brain network connectivity. We found that similar to brain structural changes, brain network-level FC directly affected tinnitus long-term outcomes after sound therapy. In the present study, the EG showed significant tinnitus symptom relief relative to the IG (55.08% vs. 14.18%). More importantly, we found that compared with the EG, the IG showed increased intranetwork FC in the aDMN and AUN. The extent of the

FIGURE 1 Intergroup differences in intranetwork FC among the EG, IG, and HC group. Compared with the HC group, the EG exhibits (a) increased intranetwork FC in the right IFG of the aDMN, left STG of the AUN, left IFG of the LFPN, bilateral insula of the SN, and MOG of the lVN and (b) decreased FC in the ACC of the aDMN and right mPFC of the RFPN (corrected at the cluster level with FWE $p < .05$). Compared with the HC group, the IG reveals (c) increased intranetwork FC in the bilateral IFG of the aDMN, left STG of the AUN, left IFG of the LFPN, and bilateral insula of the SN and (d) decreased FC in the ACC of the aDMN, right MFG of the DAN, and right mPFC of the RFPN (corrected at the cluster level with FWE $p < .05$). (e) Compared with the IG, the EG shows decreased intranetwork FC in the right IFG of the aDMN and left STG of the AUN (corrected at the cluster level with FWE $p < .05$). ACC, anterior cingulate cortex; aDMN, anterior default mode network; AUN, auditory network; DAN, dorsal attention network; EG, effective group; FC, functional connectivity; FWE, familywise error; HC, healthy control; IFG, inferior frontal gyrus; IG, ineffective group; LFPN, left frontoparietal network; lVN, lateral visual network; MFG, middle frontal gyrus; MOG, middle occipital gyrus; mPFC, medial prefrontal cortex; RFPN, right frontoparietal network; SN, salience network; STG, superior temporal gyrus.

(95% confidence intervals from 0.736 to 0.918) and 0.899 (95% confidence intervals from 0.832 to 0.966), respectively.

4 | DISCUSSION

Our latest study proved that idiopathic tinnitus patients with different outcomes (effective or ineffective) after sound therapy experienced distinct brain structural reorganization (Chen et al., 2021a). Thus, the
**TABLE 2**  
| Brain region | RSN        | Cluster size (voxels) | Peak T-score | MNI coordinates |
|--------------|------------|-----------------------|--------------|-----------------|
| **EG > HC**  |            |                       |              |                 |
| Right IFG    | aDMN       | 19                    | 3.98         | 21 33 –6        |
| Left STG     | AUN        | 26                    | 4.62         | –39 9 –27       |
| Left IFG     | LFPN       | 71                    | 4.89         | –42 18 0        |
| Left MOG     | IVN        | 61                    | 5.74         | –27 –87 –3      |
| Left insula  | SN         | 55                    | 5.39         | –33 9 –15       |
| Right insula | SN         | 43                    | 4.93         | 21 9 –15        |
| **EG < HC**  |            |                       |              |                 |
| ACC          | aDMN       | 22                    | 4.04         | –3 27 15        |
| Right mPFC   | RFPN       | 25                    | 4.19         | 9 21 45         |
| **IG > HC**  |            |                       |              |                 |
| Right IFG    | aDMN       | 75                    | 5.51         | 30 30 –9        |
| Left IFG     | aDMN       | 28                    | 4.51         | –30 30 –3       |
| Left STG     | AUN        | 63                    | 5.72         | –51 –30 18      |
| Left STG     | AUN        | 19                    | 4.04         | –39 12 –27      |
| Left IFG     | LFPN       | 95                    | 4.82         | –48 12 9        |
| Left insula  | SN         | 65                    | 5.75         | –36 9 –15       |
| Right insula | SN         | 39                    | 5.61         | 30 18 –12       |
| **IG < HC**  |            |                       |              |                 |
| ACC          | aDMN       | 28                    | 4.70         | 9 24 18         |
| Right MFG    | DAN        | 20                    | 4.20         | 36 3 48         |
| Right mPFC   | RFPN       | 33                    | 4.30         | 3 27 39         |
| **IG > EG**  |            |                       |              |                 |
| Right IFG    | aDMN       | 5                     | 3.60         | 45 27 0         |
| Left STG     | AUN        | 32                    | 5.13         | –51 –33 15      |

Abbreviations: ACC, anterior cingulate cortex; aDMN, anterior default mode network; AUN, auditory network; DAN, dorsal attention network; EG, effective group; HC, healthy control; IFG, inferior frontal gyrus; IG, ineffective group; LFPN, left frontoparietal network; IVN, lateral visual network; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MOG, middle occipital gyrus; mPFC, medial prefrontal cortex; RFPN, right frontoparietal network; RSN, resting-state network; SN, salience network; STG, superior temporal gyrus.

**TABLE 3**  
| Functional connectivity | EG_HC | EG_IG | HC_IG |
|-------------------------|-------|-------|-------|
|                         | t     | p     | t     | p     | t     | p     |
| SN-ECN                  | 2.962 | .004  | 2.290 | .025  | –0.066 | .947 |
| pDMN-DAN                | 1.090 | .279  | 2.624 | .011  | 1.736  | .088 |
| SN-AUN                  | 0.671 | .504  | –0.133 | .894  | –0.901 | .370 |
| IVN-RFPN                | –0.308 | .656  | –1.145 | .256  | –0.880 | .381 |
| aDMN-AUN                | –1.033 | .305  | –1.057 | .294  | –0.072 | .943 |

Note: The bold values indicate significant differences between the EG and HC and between the EG and IG at baseline (p < .05, corrected).  
Abbreviations: aDMN, anterior default mode network; AUN, auditory network; DAN, dorsal attention network; ECN, executive control network; EG, effective group; HC, healthy control; IG, ineffective group; IVN, lateral visual network; pDMN, posterior default mode network; RFPN, right frontoparietal network; SN, salience network.
FIGURE 2  Intergroup differences in internetwork FC among the EG, IG, and HC group. (a) Compared with the HC group, the EG exhibits increased internetwork FC between the ECN and SN. (b) Compared with the IG, the EG shows increased internetwork FC between the ECN and SN and between the DAN and pDMN. DAN, dorsal attention network; ECN, executive control network; EG, effective group; FC, functional connectivity; HC, healthy control; IG, ineffective; pDMN, posterior default mode network; SN, salience network. The red line represents positive FC; the green line represents negative FC.
FIGURE 3  Legend on next page.
FC changes was closely associated with ΔTHI scores and % improvement of the THI scores in the EG. We also detected that, at the inter-network level, when directly compared with the IG, the EG had increased FC between the SN and ECN and the pDMN and DAN. Our findings may provide novel insights into the role of brain functional reorganization during recovery in tinnitus patients, reveal indicators that can be used for the screening of patients and making prognosis predictions before sound therapy, and further our understanding of tinnitus mechanisms.

4.1 Altered FC within RSNs among the EG, IG, and HC group

In the present study, we found significantly changed (increased or decreased) intranetwork FC within the AUN, aDMN, LFPN, IVN, DAN, and SN in the EG and/or IG compared with the HC group. As an auditory phenomenon, tinnitus has been repeatedly reported to be associated with alterations in the AUN (or auditory regions; Cai, Li, Yang, & Zhang, 2019; Hu et al., 2021; Husain, 2016; Husain et al., 2011; Lan et al., 2021; Schmidt, Akrofi, Carpenter-Thompson, & Husain, 2013), which indicates the important role of the AUN in tinnitus generation. As the center of the primary auditory cortex, the STG is also considered to be an important multisensory functional brain region that integrates visual, auditory, and language information (Mtui, Gruener, & Dockery, 2016). Thus, the increased intranetwork FC in the STG of tinnitus patients suggests hyperactivity in the central auditory pathway, which may be caused by Bayesian inference in the brain (De Ridder, Joos, et al., 2014; De Ridder, Vanneste, et al., 2014).

Moreover, we observed both increased and decreased connectivity in different regions of the aDMN in both EG and IG patients. The DMN is related to both cognitive and emotional control (Whitfield-Gabrieli et al., 2011), is most active at rest and shows reduced activity when entering a task-based state involving attention or goal-directed behavior (Shulman et al., 1997). The aDMN connectivity changes (increased or decreased FC) in our study may represent dysfunction, as some previous studies have reported (Lanting, WozAniak, van Dijk, & Langers, 2016; Schmidt et al., 2013). They considered that the DMN somehow plays a role in “hearing” internally generated sound, whether it is meaningful (in schizophrenia patients) or not (in tinnitus patients).

As a lateraled and independent network (Smith et al., 2009), the frontoparietal network (FPN) supports decision-making and cognitive control functions (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Studies have reported tinnitus-related changes in the LFPN or RFPN (Chen et al., 2021b; Lanting et al., 2016). In line with these studies, we considered that the intranetwork FC changes in the FPN in our study may indicate that the brain regions related to executive control, advanced cognition, and language are in an abnormal or dysfunctional state in tinnitus patients.

Regarding the FC changes in the IVN (nonprimary regions of the visual cortex), consistent with one of our prior studies (Chen et al., 2021b), we speculated that because of the increased compensatory stimulation between the auditory and visual networks caused by tinnitus through the thalamus, the relay station (Chen et al., 2019), the increased intranetwork FC in the MOG may reflect an abnormal overactive state of the visual network in tinnitus patients. Meanwhile, we also observed decreased intranetwork FC in the DAN. The DAN is involved in visual attention (Gitelman, 2003). Previous studies have
shown increased FC between the DAN and other RSNs (such as the DMN; Chen et al., 2021b; Schmidt et al., 2013), and the authors suggested that this change could be a compensatory attempt to transfer the phantom stimulus to the limbic system (Golm, Schmidt-Samoa, Dechent, & Kröner-Herwig, 2013; Ooms et al., 2013). Thus, increased FC in the DAN of IG patients may represent abnormal compensation caused by the enhanced connectivity between the DAN and other RSNs, although the exact mechanism is still not clear.

We observed increased intranetwork FC in the bilateral insula of the SN. As one of the core hubs of the SN, the insula serves to identify the most relevant salient stimuli and forward them to higher cognitive regions to guide behavior, such as the limbic system (Menon & Uddin, 2010). Thus, the increase in FC in the insula may again prove the hyperactivity of the limbic system in tinnitus patients caused by the loss of peripheral sensory sound perception through a Bayesian inference network.

More interestingly, we found that the intranetwork FC changes in the left IFG of the LFPN and the right insula of the SN were independently and positively correlated with the changes and % improvement of THI scores in the EG. As the primary outcome of our study, the changes and improvement in THI scores indicated that patients in the EG showed significant improvement in tinnitus symptoms. Thus, in this study, the correlations between the FC changes and THI improvements in the EG, compared to the IG, indicated that in patients with optimal treatment outcomes, the more obvious their network-level functional alteration was, and the better their prognosis.

One of the most interesting findings of our study was significantly increased intranetwork FC in the right IFG of the aDMN and left STG of the AUN in the IG compared with the EG. In particular, the mean FC strengths in the right IFG were negatively correlated with improvements in THI scores in the EG. As mentioned above, the AUN and aDMN are closely related to tinnitus, and the IFG and STG are the main parts of these two networks. Additionally, our recent study showed that FC in the aDMN in patients with idiopathic tinnitus changed significantly from before to after acoustic therapy (Chen et al., 2021b). In addition, tinnitus is considered to retrieve auditory memories in the brain through a Bayesian inference network to reduce the uncertainty caused by decreased peripheral sound perception (De Ridder, Joos, et al., 2014; De Ridder, Vanneste, et al., 2014). Therefore, based on these findings, we speculated that increased FC in these RSNs may be an overactivity (enhanced FC) in the brains of tinnitus patients caused through a Bayesian inference manner. The correlation between FC strength in the aDMN and improvements in THI scores indicated that the more FC changed in the aDMN, the poorer the prognosis in tinnitus patients. That is, idiopathic patients with FC changes in the aDMN were insensitive to sound therapy.

Taken together, our study provided evidence that idiopathic tinnitus can result in significant brain network-level functional reorganization in auditory-related and nonauditory-related RSNs. The functional remodeling in the aDMN and AUN may be an indication that the therapeutic effects in these tinnitus patients was unsatisfactory after sound therapy and that patients with these changes may not be suitable for this treatment.

### Table 4: Results of receiver operator characteristic (ROC) curve analysis of the intranetwork functional connectivity in the aDMN and AUN as prognostic indicators

| Brain region | RSN      | AUC     | Sensitivity% | Specificity% | p value% | Cutoff | PPV%  | NPV%  |
|--------------|----------|---------|--------------|--------------|----------|--------|-------|-------|
| Right IFG    | aDMN     | 0.716   | 51.4         | 86.0         | .001     | 0.374  | 70.8  | 68.5  |
| Left STG     | AUN      | 0.827   | 80.0         | 74.4         | .000     | 0.544  | 71.8  | 82.0  |
| Right IFG + left STG | AUN | 0.899   | 94.3         | 76.7         | .000     | 0.710  | 75.0  | 94.3  |

Abbreviations: aDMN, anterior default mode network; AUC, area under curve; AUN, auditory network; IFG, inferior frontal gyrus; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operator characteristic; STG, superior temporal gyrus.

In addition to the distinct intranetwork connectivity changes between the EG and the IG observed in this study, we also found that the EG, compared with the IG, showed increased internetwork FC between the SN and ECN and the pDMN and DAN. There is evidence in patients with idiopathic tinnitus that FC between RSNs (auditory or nonauditory-related networks) undergoes significant changes (Chen et al., 2021b; Husain & Schmidt, 2014; Schmidt et al., 2013). For example, in the study by Schmidt et al. (2013), they found that connectivity increased among the DMN, DAN, and AUN, and therapies that mitigated the increased connectivity among them and the decreased coherence of the DMN could be effective in reducing tinnitus-related distress. Moreover, one recent study reported that the changed internetwork FC between RSNs may reflect abnormal large-scale functional interactions among the functional networks (Chen et al., 2021b). Therefore, we speculated that, in line with these studies, the increase in FC between these networks may be the result of abnormal brain network interactions after tinnitus or a reflection of the abnormal state caused by tinnitus (Chen et al., 2021b), while the exact mechanisms are still not very clear.

Therefore, based on the information above, our study proved that tinnitus could result in significant FC alterations between RSNs, and the internetwork FC changes between the SN and ECN and between the pDMN and DAN in the EG may have indicated that the therapeutic effects in these tinnitus patients was perfect after sound therapy. These findings may be valuable indicators to assess treatment effects by monitoring dynamic brain functional reorganization during treatment.
4.3 Alterations in intranetwork FC values in the right IFG of the aDMN and the left STG of the AUN as indicators

In the present study, by applying the combination of the altered intranetwork FC value in the right IFG of the aDMN and the left STG of the AUN as a possible indicator, at the cutoff value of 0.710, we obtained a sensitivity of 94.3%, specificity of 76.7%, and AUC value of 0.899, and the positive (PPV) and negative (NPV) predictive values were 75.0 and 94.3%, respectively. Notably, these results show that these factors could be used as valuable imaging indicators for idiopathic tinnitus patient screening and making prognosis predictions before sound therapy.

To date, few studies have applied brain alterations to predict therapeutic outcomes or even screen patients before sound therapy (Chen et al., 2021a; Han, Yawen, et al., 2019; Han, Na, et al., 2019). For example, (Han, Yawen, et al., 2019; Han, Na, et al., 2019) used neural network nodes to predict the improvements in patient symptoms after sound therapy and found that features of the bilateral thalami were the best indicators, with adjusted AUC values of under 0.8. In another study (Chen et al., 2021a), they found that the gray matter and WM microstructure in combination could be an optimal imaging biomarker to predict the efficacy of sound therapy in patients with tinnitus. In our study, we applied the combination of intranetwork FC changes in the right IFG of the aDMN and the left STG of the AUN as an indicator to screen patients and evaluate the prognosis before sound intervention, which reached relatively ideal specificity and sensitivity and PPV and NPV simultaneously.

4.4 Strength and limitations

Our study has strengths. All of the patients and controls were prospectively recruited and studied using a standardized protocol. Intranetwork and internetwork FC were analyzed in all subjects in the whole brain without any prior hypotheses. Functional brain alterations were applied to predict therapeutic outcomes, and optimal specificity and sensitivity were obtained.

Some limitations should be noted. First, even though this was a relatively large sample of idiopathic patients, our sample size did not allow us to run more complex multivariable or multi-subgroup analyses. In addition, the cross-sectional nature of this study did not allow us to evaluate the progression over time of the distinct brain functional changes in the EG and IG from before to after sound therapy. Moreover, we need to recruit left- and right-handed subjects in future studies to eliminate the possible effect of handedness on the results. Furthermore, a proportion of the patients had varying degrees of hearing loss in this study. Further studies are needed to recruit patients with tinnitus without hearing loss and patients with hearing loss without tinnitus to investigate the possible different therapeutic effects of sound therapy on tinnitus and hearing loss in the future. Finally, we did not apply any sham therapy on patients and HCs in this research, which we will apply to them in future studies.

5 CONCLUSION

In general, our study indicated that idiopathic tinnitus can cause significant alterations in auditory and/or nonauditory-related intra- or internetwork FC. More importantly, tinnitus patients with different outcomes demonstrated distinct functional reorganization patterns. Intranetwork FC changes in the aDMN and AUN were predictive of poor prognosis, whereas greater increased FC between the SN and ECN and between the pDMN and DAN was associated with greater improvements in tinnitus symptoms after sound therapy. The intranetwork FC in the aDMN and AUN may be indicators that can be used to predict prognoses in patients with idiopathic tinnitus and to screen patients before sound therapy, and future sound therapy or related interventions should target these regions.

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CONFLICT OF INTEREST

The authors declare no financial or other conflict 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, 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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