Alterations of the default mode network and cognitive impairment in patients with unilateral chronic tinnitus

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Background: Previous studies have demonstrated that cognitive impairment is linked with neurophysiological alterations in chronic tinnitus. This study aimed to investigate the intrinsic functional connectivity (FC) pattern within the default mode network (DMN) and its associations with cognitive impairment in tinnitus patients using a resting-state functional magnetic resonance imaging (rs-fMRI).

Methods: Thirty-five chronic unilateral tinnitus patients, and 50 healthy controls were recruited for rsfMRI scanning. Both groups were age, gender and education level well-matched. The posterior cingulate cortex (PCC) was chosen as the region of interest (ROI) for detecting the FC changes, and determining if these abnormalities were related to a specific cognitive performance and tinnitus characteristic.

Results: Relative to the healthy controls, tinnitus patients showed increased FC between the PCC and the right medial prefrontal cortex (mPFC). Moreover, the enhanced FC between the PCC and right mPFC was correlated with the poorer TMT-B scores (r=0.474, P=0.008). These correlations were adjusted by age, gender, education level, GM volume, and mean hearing thresholds. The enhanced FC was not correlated with other tinnitus characteristics or cognitive performances.

Conclusions: The enhanced FC pattern of the PCC that is correlated with cognitive impairment in chronic tinnitus patients, especially the executive dysfunction. Enhanced connectivity pattern within the DMN may play a crucial role in neurophysiological mechanism in tinnitus patients with cognitive dysfunction.

Keywords: Chronic tinnitus; functional connectivity (FC); resting-state functional magnetic resonance imaging (rs-fMRI); default mode network (DMN); posterior cingulate cortex (PCC)

Introduction

Tinnitus is the experience of sound in the ears or head, even with the absence of an external source (1-3). Tinnitus patients often have depression, anxiety, disturbed sleep, and/or concentration difficulties that significantly influence daily life quality (4-8). Besides social and emotional problems, prior research has implicated tinnitus as impacting cognitive domains including executive functions, attention and working memory (9-11). There are only some studies adopting an objective approach to explore the nature of the cognitive impairment, although cognitive

deficits are prevalent among tinnitus patients. The cognitive dysfunction may be linked with neuropathological changes in chronic tinnitus (11-14). However, the exact neural mechanism of the cognitive impairment which is related to chronic tinnitus remains to be determined.

Resting-state functional magnetic resonance imaging (rs-fMRI) has been applied to explore the brain function network which is based on the blood-oxygenation level-dependent (BOLD) signal (15). Previous studies have used the rs-fMRI technology to investigate several resting-state networks including the auditory network, the executive control network, and the default mode network (DMN), to explore the neurological mechanisms underlying chronic tinnitus (16-18). The DMN is active at rest and suspended during cognitive activity including several important nodes such as the posterior cingulate cortex (PCC)/precuneus, anterior cingulate cortex (ACC), medial prefrontal gyrus (mPFC), and inferior parietal lobule (IPL), which may predict cognitive impairment (19,20). Using rs-fMRI, several studies have observed an enhanced functional connectivity (FC) within the DMN or between the DMN in chronic tinnitus (21-25). Vanneste et al. investigated for the first time that tinnitus patients showed cognitive deficits, which were related to abnormal activity in several brain regions including the hippocampus, anterior cingulate and insula using a resting-state source localized EEG (12). Nevertheless, the association between the alterations of DMN and cognitive impairment in chronic tinnitus is still far from clear.

As the key region of DMN, the PCC plays a pivotal role in emotion and distressing information processing (21,26). PCC contains diverse cognitive functions such as visuospatial memory, and emotional and non-emotional information processing (27,28). Moreover, the PCC is also responsible for self-referential processing and social cognition (29). During cognitive processing, the PCC is functionally linked to the DMN regions, such as the ACC and mPFC (26). Thus, cognitive deficits in tinnitus patients may be linked with the FC alterations of PCC. Our prior study has detected an enhanced amount of spontaneous neural activity in the PCC of tinnitus patients (30). Compared to the controls, tinnitus patients exhibited significantly enhanced connectivity between the right anterior insula and left PCC. However, the abnormal neural activity of the PCC related to cognitive impairment in tinnitus still remains unclear.

Regarding the pivotal role of the PCC in tinnitus neuropathology, we aimed to employ a seed-based method to explore the FC patterns of the PCC and its associations with the cognitive impairment in chronic tinnitus compared with healthy controls. We hypothesized that abnormal FC patterns of the PCC within the DMN could be observed in tinnitus patients with cognitive impairment and would correlate with cognitive performance deficits.

Methods

Participants

A total of 35 right-sided chronic tinnitus patients from the Nanjing First Hospital Department of Otolaryngology and 50 healthy controls through an online advertisement campaign were recruited (aged between 30 and 70 years, all right-handed and with at least 8 years of education). Both groups were age, gender, and education well-matched. Tinnitus distress was evaluated by the Iowa version of the Tinnitus Handicap Questionnaire (THQ) (31). Ten patients had mild tinnitus, 10 had moderate tinnitus, and 15 had severe tinnitus, according to guideline (32). Hearing thresholds were measured by pure tone audiometry (PTA) at the frequencies of 0.25, 0.5, 1, 2, 4, and 8 kHz. There were no statistical differences in six frequencies (mean PTA ≤25 dB) between two groups (Table 1 and Figure 1). The Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) were used to assess the depression and anxiety status (33,34). Patients with hyperacusis were excluded according to the Hyperacusis Questionnaire (35). Participants were also excluded if they acknowledged having a history of Meniere's diseases, pulsatile tinnitus, ototoxic drug therapy and surgery, hearing aid use, noise exposure, severe smoking, stroke, alcoholism, Alzheimer's disease, Parkinson's disease, epilepsy, traumatic brain injury, and major medical conditions (e.g., cancer, thyroid dysfunction, severe heart diseases, damaged liver or kidney function). This study was approved by the Research Ethics Committee of the Nanjing Medical University. Written informed consent was acquired from all subjects.

Neurocognitive tests

Objective cognitive assessment, including global cognitive tests and an extensive neuropsychological test battery, were administered to assess the neurocognitive state. Global cognitive tests contained the Mini Mental State Exam (MMSE) (36) and the Montreal Cognitive Assessment (MoCA) (37). The neurocognitive tests included the

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Table 1 Demographics, clinical, and cognitive characteristics of right-sided tinnitus patients and healthy controls

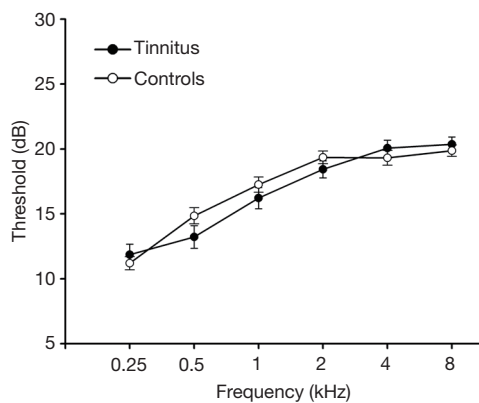| Parameter	Tinnitus patients (n=35)	Healthy controls (n=50)	P value
Age (year)	49.94±13.73	45.16±14.35	0.128
Gender (male:female)	15:20	20:30	0.104
Education levels (years)	12.46±3.04	12.84±3.13	0.576
Tinnitus duration (months)	37.71±34.58	–	–
THQ score	52.22±15.08	–	–
Hearing thresholds (left)	16.79±2.76	16.87±2.55	0.89
Hearing thresholds (right)	16.60±3.37	16.95±2.35	0.569
Hearing thresholds (average)	16.69±2.68	16.91±1.62	0.642
FD value (mm)	0.21±0.06	0.20±0.07	0.407
Cognitive performance			
MMSE	28.86±1.09	28.90±1.15	0.863
MoCA	25.71±1.79	26.02±1.32	0.393
AVLT	33.49±8.64	33.98±7.63	0.781
AVLT-delayed recall	6.60±2.55	6.86±2.04	0.603
CFT	34.37±1.74	34.52±1.73	0.699
CFT-delayed recall	16.83±2.96	16.90±2.76	0.91
DST	11.31±1.75	14.16±3.12	<0.001*
TMT-A	73.37±21.49	48.50±12.09	<0.001*
TMT-B	186.03±61.17	101.94±32.22	<0.001*
CDT	3.57±0.56	3.38±0.57	0.127
VFT	13.89±4.33	14.84±3.21	0.247
DSST	69.03±7.34	69.80±8.29	0.66
SAS	39.94±6.69	37.76±5.72	0.11
SDS	41.69±5.23	40.72±4.81	0.382

Data are represented as mean ± SD. The PTA from both ears was averaged. *, P<0.05. PTA, puretone audiometry; FD, framewise displacement; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; AVLT, Auditory Verbal Learning Test; CFT, Complex Figure Test; DST, Digit Span Test. TMT-A, Trail Making Test-Part A; TMT-B, Trail Making Test-Part B; CDT, Clock Drawing Test; VFT, Verbal Fluency Test; DSST, Digit Symbol Substitution Test; SDS, Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale.

Auditory Verbal Learning Test (AVLT) (38), Rey-Osterrieth Complex Figure Test (CFT) (39), Digit Span Test (DST) (40), Trail Making Test-A and B (TMT-A and TMT-B) (41), Clock Drawing Test (CDT) (42), Verbal Fluency Test (VFT) (43), and Digit Symbol Substitution Test (DSST) (44).

MRI acquisition

The participants were scanned using a 3.0 T MRI scanner (Ingenia, Philips Medical Systems, Netherlands), with an 8-channel receiver array head coil. Subjects lay supine with their head fixed by foam pads and a belt to minimize head motion. And earplugs were used to reduce scanner noise by approximately 32 dB according to the manufacture's data sheet. The subjects were instructed to lie quietly and keep their eyes closed but not to fall asleep, not to think of anything special, and to avoid head motion during the functional MRI. Structural images were obtained using a three-dimensional turbo fast echo T1WI sequence using

Figure 1 No significant differences in auditory thresholds between chronic tinnitus patients and healthy controls. Data are presented as Mean ± SEM. SEM, standard error of mean.

the following parameters: repetition time (TR)/echo time (TE) =8.1/3.7 ms; slices =170; thickness =1 mm; gap =0 mm; flip angle (FA) =8°; acquisition matrix =256×256; field of view (FOV) =256×256 mm^2. The functional images were obtained axially using the gradient echo-planar imaging sequence as follows: TR/TE =2,000/30 ms; slices =36; thickness =4 mm; gap =0 mm; FOV =240×240 mm^2; acquisition matrix =64×64; FA =90°; and voxel size =3.75×3.75×4.0 mm^3. The SENSE is used for parallel imaging.

Data preprocessing

fMRI data was preprocessed using Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI_V2.3_170105) (45), with the following stages. The first 10 volumes were discarded, followed by a slice-timing adjustment, realignment for head-motion correction, and spatial normalization to the Montreal Neurological Institute (MNI) template (resampling voxel size =3×3×3 mm^3) in addition to smoothing with an isotropic Gaussian kernel (FWHM =6 mm), detrending and filtering (0.01–0.08 Hz). Participants with a head motion of >2.0 mm translation, or a 2.0° rotation in any direction, were excluded to minimize movement artifacts.

Structural MRI analysis

Structural MRI data were processed based on the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm). Briefly, cerebral tissues were segmented into gray matter (GM),

white matter (WM), and cerebrospinal fluid (CSF) categories using the unified segmentation model (46). Brain parenchyma volume was measured as the sum of the GM and WM volumes. The GM, WM, and brain parenchyma volumes were divided by the total intracranial volumes, to correct for variability of head size. GM intensity maps in the MNI space were acquired by the unified segmentation algorithm. Data were spatially smoothed with 8 mm full width at half maximum Gaussian kernel.

Functional MRI analysis

The region of interest (ROI) of the PCC was developed from a Brodmann template, using the WFU_PickAtlas Version 3.0.5 software (http://fmri.wfubmc.edu/software/PickAtlas) (47). Briefly, the mean time series of the PCC was obtained for use as a reference time course. Then, Pearson's correlation coefficients were calculated between the average signal change in the ROI (PCC) and the time series of each voxel. Finally, correlation coefficients were converted to z values using Fisher's z-transformation to standardize the statistical analysis (48). Six head motion parameters and a mean time series of global, WM and CSF signals were included as confounding factors in the regression analysis to remove their possible effects.

Between-group analyses were conducted to analyze FC differences between the tinnitus patients and the healthy controls using a whole-brain mask. Age, gender, education level, GM volume, and average hearing thresholds were added as the nuisance covariates. Multiple comparison corrections were performed using a threshold (P<0.01) of the individual voxel and a cluster size, based on the Monte Carlo simulations (49), corresponding to cluster-level P<0.01 by AlphaSim correction.

Statistical analysis

Independent t-tests and χ^2-tests were calculated to investigate the differences in the demographic variables, and cognitive performance scores between tinnitus patients and the controls. Briefly, the mean Z-values of each brain region that showed significant differences were extracted within each subject. Then we performed Pearson's correlation analyses between the mean Z-values and each variable using SPSS (SPSS 19.0, Inc., Chicago, IL, USA). Partial correlations were analyzed using age, gender, education level, GM volume, and average hearing thresholds as covariates. P<0.05 was considered to indicate a statistically

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Table 2 Comparisons of the brain volumes between right-sided tinnitus patients and healthy controls

Brain volume	Tinnitus patients (n=35)	Healthy controls (n=50)	P value
Gray matter volume (% of TIV)	31.8±2.2	32.4±2.0	0.201
White matter volume (% of TIV)	29.8±1.5	29.5±1.6	0.479
Brain parenchyma volume (% of TIV)	61.6±3.0	61.9±3.2	0.618

Data are expressed as mean ± SD. TIV, total intracranial volume.
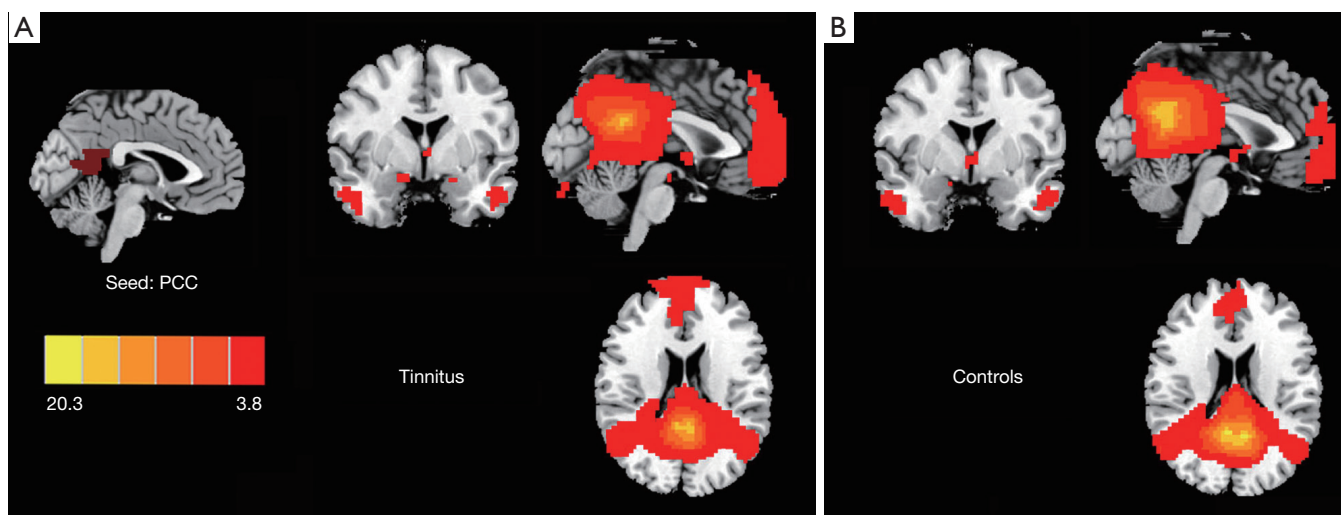
Figure 2 Significant FC patterns of the PCC in whole brain using one-sample *t*-test in chronic tinnitus patients (A) and healthy controls (B). Significant thresholds were corrected using AlphaSim criterion and set at P<0.01. FC, functional connectivity; PCC, posterior cingulate cortex.

significant difference.

Due to the effects of micro-movements from volume to volume on the FC (50), framewise displacement (FD) was calculated for every individual to represent the temporal derivative of the movement parameters. There were no significant differences of the FD values between chronic tinnitus and healthy controls. No participants had FD >0.5 mm on more than 35 volumes (*Table 1*).

Results

Demographic and neurocognitive data

The demographic and characteristic data of tinnitus patients and healthy controls were showed in *Table 1*. The two groups did not differ significantly in age, gender, education level, and average hearing thresholds. Relative to the healthy controls, tinnitus patients were revealed to have a significantly worse performance on the DST, TMT-A and TMT-B tests (P<0.05). However, the other

neuropsychological tests showed slight but no significant decreases in cognitive performance (P>0.05).

Structural MRI

No significant differences of GM and WM volumes between tinnitus patients and healthy controls were observed (*Table 2*). Moreover, no suprathreshold voxel-wise differences of the GM and WM volume between tinnitus patients and controls were demonstrated after Monte Carlo correction.

Functional MRI

The PCC exhibited strong FC to several DMN regions, including the medial prefrontal cortex (mPFC), IPL, and precuneus in both tinnitus patients (*Figure 2A*) and healthy controls (*Figure 2B*). Compared with the healthy controls, chronic tinnitus patients showed a significantly increased FC between the PCC and the right mPFC (*Figure 3A* and *Table 3*).
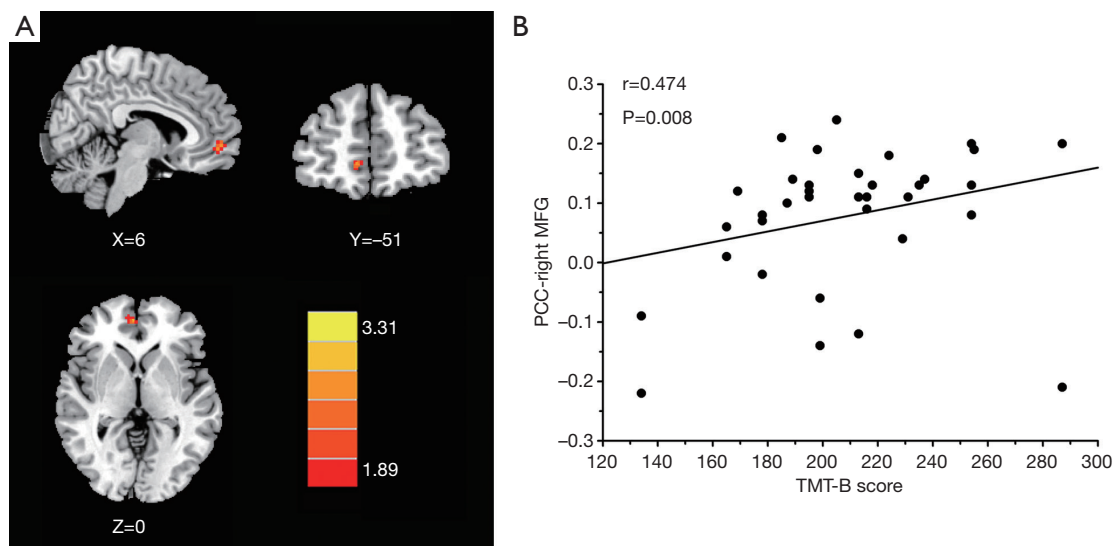
Figure 3 Significant correlations between enhanced FC and poorer cognitive performance. (A) Compared with the healthy controls, chronic tinnitus patients exhibited enhanced FC between the PCC and the right MFG (P<0.01 corrected by AlphaSim); (B) positive correlations between enhanced FC between the PCC and right MFG and poorer TMT-B scores in tinnitus patients (r=0.474, P=0.008). FC, functional connectivity; PCC, posterior cingulate cortex; MFG, middle frontal gyrus.

Table 3 Increased functional connectivity of PCC in right-sided tinnitus patients compared to healthy controls

Brain region	BA	MNI coordinates, x, y, z (mm)	T score	Voxels
R medial prefrontal cortex	10	6, –51, 0	3.2819	52

The threshold was set at a P<0.01 (AlphaSim corrected). BA, Brodmann's area; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; R, right.

Correlation analysis

After correcting for age, gender, education, GM volume, and mean hearing thresholds, chronic tinnitus patients showed enhanced FC of the PCC to the right mPFC, which was positively correlated with the poorer TMT-B scores (r=0.474, P=0.008) (*Figure 3B*). None of the enhanced FC were correlated with other tinnitus characteristics, or cognitive performances.

Discussion

In this study, the seed-based approach was used to detect the intrinsic FC of the PCC, and its associations with the cognitive impairment in unilateral chronic tinnitus patients. Relative to the controls, chronic tinnitus patients were revealed to have a significantly increased FC between the PCC and the right mPFC, which was positively and specifically linked with the poorer TMT-B scores.

We performed multidimensional neurocognitive tests to assess the cognitive function of every subject in this study. However, except for the DST, TMT-A and TMT-B, most tests exhibited insignificant differences between groups. The DST and TMT scores in tinnitus, exhibited significant reducing trends when compared to the scores in the control group, suggesting that long-term tinnitus perception may lead to overt damage to memory and executive function in tinnitus patients.

No structural changes of GM and WM volumes were detected between tinnitus patients and healthy controls. Prior studies have reported decreases or increases in GM volume in tinnitus patients compared with healthy controls in several brain regions (51-55). However, this was in accordance with our previous studies (30), which could probably be due to the absence of any hearing loss up to 8 kHz in normal hearing tinnitus patients. Moreover, the MRI analyzing technique may result in the discrepancy,

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which was not sensitive enough to detect any differences in GM volume of the patients. Nonetheless, the current results imply that aberrant FC within the DMN related to tinnitus may occur prior to any major structural abnormalities.

DMN disruptions have been previously documented in chronic tinnitus patients (16,56,57). However, no current study has discussed the association between the DMN abnormalities, and cognitive impairment. Our study showed a decreased FC within the DMN was associated with poorer cognitive performance in the chronic tinnitus patients, suggesting that the DMN may be vulnerable to chronic tinnitus with mild cognitive impairment at the early stage. Within the DMN, the PCC functions as the central hub, as well as being a metabolically active and highly connected region in the brain (26). This region is responsible for memory, mediation, emotion, and intrinsic control networks. Decreased FC of the PCC may therefore have contributed to the patients' poorer DST performance. Our prior studies have detected aberrant spontaneous brain activity of the PCC in chronic tinnitus (30), but it did not demonstrate the relationship with the cognitive dysfunction due to tinnitus. Anyhow, this neurocognitive relationship probably supports the hypothesis that an abnormal FC pattern of the PCC may play an important role in tinnitus-related cognitive dysfunction.

Furthermore, the prefrontal cortex is involved in executive function and emotional processing (58). Previous fMRI studies have detected an enhanced connectivity of the mPFC in chronic tinnitus patients (53,59-61). Similarly, when compared to healthy controls, our tinnitus patients exhibited increased PCC connectivity to the mPFC, which was correlated with a poorer TMT-B performance. TMT-B score is a neurocognitive test that reflects the function of the prefrontal cortex, and it has been commonly used to define cognitive impairments, especially the executive dysfunction (62). Moreover, the mPFC is considered as an important brain region that integrates both the emotional and sensory aspects for tinnitus (63). Araneda *et al.* suggested that executive dysfunction caused by mPFC abnormalities may play a key role in the generation and maintenance of chronic tinnitus (60). Besides, our prior study detected higher FC within the attentional control network involving the mPFC (30). Therefore, enhanced FC between the PCC and the mPFC may imply that the mPFC serves as a main hub within specific functional network affected by tinnitus perception.

This study has several limitations. First, we acknowledge that it is impossible to make causal relations between the enhanced FC, and the cognitive impairment in unilateral chronic tinnitus patients. This is because of the cross-sectional design, and the smaller population size. Thus, further studies involving a larger number of participants will be needed to confirm the present conclusions. Second, no diagnostic criteria was used for assessing cognitive dysfunction for tinnitus, and this lack of specific and objective cognitive evaluation limited the interpretation of our results. Moreover, we only chose the PCC as ROI to explore the FC patterns of DMN in tinnitus. The seed region can be extended to other DMN regions, such as ACC and precuneus. Additionally, more researches are needed to acquire structural changes, such as diffusion tensor imaging (DTI), to investigate the basis of the functional dysconnectivity within the DMN. Furthermore, due to the limited sample size, we did not compare the FC patterns in subgroups according to the classification of their tinnitus severity, which needs to be considered in future work. Finally, the scanner noise cannot be completely reduced, which may influence the resting-state functional networks between tinnitus and controls, especially the attention network, which requires to be considered in future researches.

Conclusions

To conclude, the current study mainly identified the increased FC patterns within the DMN regions that were associated with specific cognitive dysfunction in unilateral chronic tinnitus patients. These findings will illustrate the possible role of the DMN in tinnitus that may bring about a better understanding of the neurophysiological mechanisms underlying chronic tinnitus.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Research Ethics Committee of the Nanjing Medical University. Written informed consent was acquired from all subjects.

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