

# Headache is associated with aberrant cerebral blood flow in chronic tinnitus revealed by perfusion functional MRI

**Yu-Chen Chen**

Nanjing First Hospital <https://orcid.org/0000-0002-8539-7224>

**Jinghua Hu**

Nanjing First Hospital, Nanjing Medical University

**Jinluan Cui**

Nanjing First Hospital, Nanjing Medical University

**Song'an Shang**

Nanjing First Hospital, Nanjing Medical University

**Wei Yong**

Nanjing First Hospital, Nanjing Medical University

**Jin-Jing Xu**

Nanjing First Hospital, Nanjing Medical University

**Xindao Yin**

Nanjing First Hospital, Nanjing Medical University

**Yuanqing Wu** (✉ [cnnxdd@163.com](mailto:cnnxdd@163.com))

**Jianwei Qi**

Nanjing First Hospital, Nanjing Medical University

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## Research article

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# Abstract

**Background:** Chronic tinnitus is often accompanied with headache symptom that will affect the cerebral blood flow (CBF) and exacerbate the tinnitus distress. However, the potential relationship between headache and tinnitus remains unclear. This study will investigate whether aberrant CBF patterns exist in chronic tinnitus patients and examine the influence of headache on CBF alterations in chronic tinnitus.

**Methods:** Participants included chronic tinnitus patients (n=45) and non-tinnitus controls (n=50), matched for age, sex, education, and hearing thresholds. CBF images were collected and analyzed using arterial spin labeling (ASL) perfusion functional magnetic resonance imaging (fMRI). Regions with major CBF differences between tinnitus patients and non-tinnitus controls were first detected. The interaction effects between headache and tinnitus for CBF alterations were further examined. Correlation analyses illustrated the association between CBF values and tinnitus severity as well as between CBF and degree of headache.

**Results:** Compared with non-tinnitus controls, chronic tinnitus patients exhibited decreased CBF, primarily in right superior temporal gyrus (STG), bilateral middle frontal gyrus (MFG), and left superior frontal gyrus (SFG); decreased CBF in these regions was correlated with tinnitus distress. There was a significant interaction effect between headache and tinnitus for CBF in right STG and MFG. Moreover, the degree of headache correlated negatively with CBF in tinnitus patients.

**Conclusions:** Chronic tinnitus patients exhibited reduced CBF in the auditory and prefrontal cortex. Headache may facilitate a CBF decrease in the setting of tinnitus, which may underlie the neuropathological mechanisms of chronic tinnitus comorbid with headache.

## Introduction

Tinnitus is a common auditory disorder that affects approximately 10–15% of adult populations, which severely impairs life quality of about 1–2% of the general population [1, 2]. Chronic tinnitus patients suffer from secondary tinnitus symptoms or comorbidities, such as depression, anxiety, insomnia, and chronic pain [3–5]. Furthermore, nearly 26–47% of patients with tinnitus also suffer from headache [6]. The association between tinnitus and headaches has been described in prior studies [6–8]. Therefore, headache is a risk factor that may play an important role for tinnitus-related impairment in quality of life. However, the potential relationship between headache and tinnitus still remains unclear.

Previous researches using functional magnetic resonance imaging (fMRI) have suggested that tinnitus is associated with aberrant brain functional changes in temporal cortex and non-auditory brain areas, including the prefrontal cortex, parahippocampus, insula and cerebellum[9]. Moreover, researches using cerebral perfusion, investigated via single-photon emission computed tomography (SPECT) and positron emission tomography (PET), showed that tinnitus patients exhibit decreased or increased cerebral blood flow (CBF) in widespread brain regions [10–12]. Arterial spin labeling (ASL) is used to evaluate CBF at resting state and could serve as a marker of functional activation albeit, which achieves a direct measure

of regional CBF and independent of complicated calculations [13]. ASL perfusion fMRI, with higher resolution and accurate localization, has been applied to detect the CBF in various neurological or psychiatry disorders [14]. However, Emmert et al. did not observe any significant CBF changes between tinnitus patients and healthy controls using ASL [15], probably due to the limited sample size. Regarding the headache, previous studies showed that patients with headache or migraine exhibited hypoperfusion, hyperperfusion or no changes in whole-brain gray matter (GM) CBF [16–18]. Therefore, further research is required to investigate what regions reveal altered CBF in chronic tinnitus and to determine whether headache is involved in the fluctuation of CBF values in these regions.

To address this issue, we raise the hypothesis that chronic tinnitus would exhibit aberrant CBF compared with non-tinnitus controls and that the comorbidity of headache would aggravate the brain abnormality. This study aims to assess CBF differences between chronic tinnitus patients and matched controls using ASL perfusion fMRI and observed the effect of headache on CBF changes in chronic tinnitus patients.

## Materials And Methods

### Subjects and clinical data

Seventy-five subjects, including 45 patients with chronic bilateral tinnitus and 50 non-tinnitus controls (all right-handed and completed at least 8 years of education), were recruited through community health screening and newspaper advertisements and matched for sex, age, and education. According to the International Classification of Headache Disorders, Third Edition (beta version) (ICHD-3 beta) [19] as well as the headache symptom of each subject, tinnitus patients were divided into two groups (20 patients with headache and 25 patients without headache). The Iowa version of the Tinnitus Handicap Questionnaires (THQ) [20] as well as a pure tone audiometry (PTA) examination was used to assess the tinnitus severity, tinnitus distress, and the hearing threshold. Any participants who had hearing loss (defined as thresholds  $\geq 25$  dB HL) at the frequencies of 0.25 kHz, 0.5 kHz, 1 kHz, 2 kHz, 4 kHz, and 8 kHz were excluded from the current study. There were no significant differences of auditory thresholds between tinnitus patients and non-tinnitus controls (Figure 1). Participants were excluded if they suffered from pulsatile tinnitus, hyperacusis or Meniere's diseases, or if they had a past history of alcoholism, stroke, migraine, brain injury, anemia, Alzheimer's disease, Parkinson's disease, epilepsy, major depression or other neurological or psychiatric illness, MRI contraindications or severe visual loss, thyroid dysfunction, cancer, severe heart diseases and damaged liver/kidney function.

According to the Self-Rating Depression Scale (SDS) and the Self-Rating Anxiety Scale (SAS) (overall scores < 50, respectively), none of the participants had depression or anxiety. The pain intensity of headache was measured by the visual analogue scale (VAS) and degree of headache was measured by the Headache Impact Test-6 (HIT-6). Demographics and clinical characteristic data of the chronic tinnitus patients and non-tinnitus controls were summarized in Table 1.

### MRI data acquisition

All participants were scanned using a 3.0 T MRI scanner (Ingenia, Philips Medical Systems, Netherlands). Foam padding and earplugs were used to reduce the head motion and scanner noise. The participants were instructed to rest quietly with their eyes closed and avoiding either falling asleep or making sudden head motions, and to not think of anything in particular during MRI scan. High resolution three-dimensional turbo fast echo (3D-TFE) was acquired using the parameters as follows: repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, thickness = 1 mm, slices = 170, gap = 0 mm, flip angle (FA) = 8°, field of view (FOV) = 256 × 256 mm<sup>2</sup>, and acquisition matrix = 256 × 256. The structural sequence took 5 minutes and 29 seconds. ASL images were obtained with a pseudo-continuous ASL (pcASL) sequence with a 2D fast spin-echo acquisition and background suppression using the parameters as follows: TR = 4000 ms, TE = 11 ms, slice thickness = 4 mm, label duration=1650ms; post-label delay = 1600 ms, FA = 90°, FOV = 220×220 mm<sup>2</sup>, slices thickness = 4 mm, gap = 0.4 mm, reconstruction matrix = 672. The ASL sequence took 4 minutes and 18 seconds.

### **Imaging data processing**

A voxel-based morphometry (VBM) approach was performed to estimate whole brain volumes using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm>). DARTEL was used to improve inter-subject registration of the structural images. Briefly, cerebral tissues were segmented into GM, white matter (WM), and cerebrospinal fluid by a unified segmentation algorithm [21]. Then, resulting GM and WM images were normalized to the MNI template, followed by smoothing using an 8-mm full width at half maximum (FWHM) Gaussian kernel. Finally, the resulting voxel-wise GM volume maps were entered as covariates in the ASL data analysis.

The ASL data were preprocessed to generate CBF maps using the ASL Perfusion MRI Signal Processing Toolbox (ASLtbx), which is based on SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) [22]. All images were first rearranged and adjusted to correct head movement. Next, a nonlinear transformation was performed on the CBF images of healthy controls, which were co-registered with the PET- perfusion template in Montreal Neurological Institute (MNI) space. The MNI-standard CBF template was defined as the average co-registered CBF images of healthy controls. The CBF images of all participants were then co-registered to the MNI-standard CBF template. Every co-registered CBF was removed from the non-brain tissue. Then a spatial smoothing with an isotropic Gaussian at FWHM of 6 mm<sup>3</sup> was followed. Finally, normalization was performed by dividing the cerebral blood flow per voxel by the average cerebral blood flow across the entire brain [23]. None of the participants was excluded from the study due to head movement exceeding 2.0 mm of maximum translation in any of the x, y, and z directions or 2.0° of the maximum rotation around the three axes.

### **Statistical analyses**

Clinical measures were analyzed using Statistical Package for Social Sciences (SPSS) statistics software package version 20.0 (IBM Corp., Armonk, NY, USA). The statistical significance level was set at  $p < 0.05$ , two-tailed. One-way analysis of variance (ANOVA) was used to calculate the difference among the three

groups followed by a post hoc test (t-test for means and  $\chi^2$ -test for proportions) between tinnitus patients with headache and patients without headache.

A one-way analysis of variance (ANOVA) was then performed to determine between-group differences in brain volumes, with age, sex, and education as the nuisance covariates. Between-group differences in CBF were also calculated via one-way ANOVA in SPM12 with age, gender, education level and GM volume as the nuisance covariates. Significant thresholds were corrected using false discovery rate (FDR) criterion and set at  $p < 0.01$ . A full-factorial model was utilized to detect potential interaction effects between tinnitus and headache on CBF differences. Significant thresholds were corrected using cluster-level family-wise error (FWE), and the threshold was set at  $p < 0.01$ .

The relationships between aberrant CBF and each clinical characteristic were further investigated. Firstly, regions showing significant differences between groups were extracted. Then the mean z-values of aberrant CBF region mask were calculated within every subject. Pearson correlation analysis between the mean z-values and each clinical characteristic were performed using SPSS software. Partial correlations were calculated with age, sex, education, GM volume, and average hearing thresholds as the nuisance covariates.  $P < 0.05$  was considered statistically significant.

## Results

### Structural data

There were no significant differences in the comparisons of the whole-brain volumes (GM volume, WM volume and brain parenchyma volume) between chronic tinnitus patients and controls (Table 2). After Monte Carlo simulation correction, no suprathreshold voxel-wise difference in the GM and WM volumes between chronic tinnitus patients and controls was observed.

### Group CBF differences

The CBF differences between the chronic tinnitus patients and non-tinnitus controls were shown in Figure 2A and Table 3. The tinnitus patient group exhibited decreased CBF, primarily in the right superior temporal gyrus (STG), bilateral middle frontal gyrus (MFG), and left superior frontal gyrus (SFG) ( $P < 0.01$ , FWE corrected). The interaction effect between headache and tinnitus was significant in the right STG and right MFG (Figure 2B and Table 4) ( $P < 0.01$ , FWE corrected).

### Correlation analysis

The significant correlations between the CBF changes and the clinical data were depicted in Figure 3. Regarding the tinnitus characteristics, the CBF in the right STG and the right MFG was negatively associated with THQ scores, respectively ( $r = -0.334$ ,  $p = 0.033$ ;  $r = -0.349$ ,  $p = 0.025$ ). Regarding the correlations between headache and CBF values, we observed that the HIT-6 scores were inversely correlated with the CBF in the right STG of chronic tinnitus patients ( $r = -0.364$ ,  $p = 0.019$ ). Moreover, the

VAS scores were inversely correlated with the CBF in the right MFG of tinnitus patients ( $r=-0.458$ ,  $p=0.003$ ). However, no significant correlations were observed in non-tinnitus controls.

## Discussion

The current study explored for the first time the associations between headache and tinnitus using ASL perfusion fMRI. Compared to non-tinnitus controls, tinnitus patients exhibited reduced CBF in temporal and prefrontal cortex, which was associated with tinnitus distress. Interestingly, we also observed that headache exacerbated CBF reduction in tinnitus patients, and the degree of headache was linked with decreased CBF.

Chronic tinnitus has been associated with GM changes in widespread brain regions [24–26]. We expected to observe brain atrophy in these patients, however, neither regional nor whole-brain atrophy was observed in our tinnitus patients compared to matched controls. It is possible that the absence of any hearing loss in our tinnitus population may be one reason for the different results. In addition, the MR technique and analytical method may be less sensitive for detecting subtle structural changes.

In this study, main effects of chronic tinnitus were primarily in auditory cortex and prefrontal cortex. Our tinnitus patient group exhibited decreased CBF primarily in the right STG, which was associated with THQ scores. Dysfunction of the temporal gyrus is associated with affective disturbance, which has been proved to be linked with headache [27–29]. The tinnitus comorbid with headache may lead to more complex dysfunction in the cortico-limbic network. Moreover, prior fMRI researches have revealed the associations between aberrant neuronal activity and functional connectivity of the STG and tinnitus distress [30–34]. However, Emmert et al. found no significant CBF alterations within the auditory cortex in tinnitus patients using ASL [15], partly due to a small sample size ( $n = 14$ ). Thus, we infer that the decreased brain perfusion of temporal cortex in tinnitus perception might contribute to the disruption of emotional regulation in tinnitus patients with headache.

Furthermore, the prefrontal cortex, including the MFG and SFG, exhibited decreased CBF in tinnitus patients compared with non-tinnitus controls. The prefrontal cortex plays a critical role in emotional processing and executive function [35]. Disrupted brain activity was observed within the executive control of attention network, including the MFG and SFG [36]. Previous resting-state fMRI studies have also pointed out the abnormalities of the prefrontal cortex could act as a direct mechanism of tinnitus chronification [34, 37, 38]. Therefore, these findings suggested that the CBF alterations in the prefrontal cortex may be one important brain characteristic of chronic tinnitus. Nevertheless, the specific clinical implication for reduced CBF in the MFG and SFG is unclear and requires to be further investigated.

Previous studies showed that patients with headache exhibited reduced perfusion in temporal and prefrontal cortex [16, 17]. Our data support and extend these findings by identifying a significant interaction between tinnitus and headache for CBF in the STG and MFG, indicating that the existence of headache accelerates the decrease in CBF in the setting of tinnitus, resulting in impaired attention and executive function. In addition, the degree of headache is negatively associated with decreased CBF in

tinnitus patients, which was consistent with some researches about migraine without aura attacks [16–18]. We speculate that increased degree of headache will aggravate the tinnitus distress and severity, reflecting the aberrant perfusion in specific brain regions. Nevertheless, the association of the headache with the chronic tinnitus has not been substantially elucidated and also needs to be corroborated in future studies.

Several limitations should be acknowledged in the current study. Firstly, due to the strict inclusion and exclusion criteria, our sample size was not large enough that may affect the statistical reliability of our results. We will further expand the sample size and obtain more reliable results in future studies. Secondly, the characteristics of headache were just assessed using HIT-6 and VAS scores in this study. More neuropsychological tests are needed to assess the headache symptom of the migraine, such as the Migraine Disability Assessment Questionnaire (MIDAS) [39] and Visual Light Sensitivity Questionnaire-8 (VLSQ-8) [40]. Furthermore, although we try to diminish the MR scanner noise using earplugs, the tinnitus patients cannot be completely prevented from scanner noise that probably affects the CBF perfusion to varying degree. This confounding factor should be taken into account for all perfusion fMRI studies related to the auditory system. Finally, we only measured the CBF changes within each brain regions but did not prove the possibility of CBF functional connectivity among different brain areas. A data-driven approach to whole-brain CBF connectivity analysis will be considered in our future study.

## Conclusion

In summary, this study provided evidence that chronic tinnitus patients exhibited reduced CBF in auditory and prefrontal cortex, and that decreased CBF in tinnitus patients was associated with tinnitus severity. Headache may exacerbate CBF reduction in tinnitus patients, and the degree of headache was negatively associated with CBF levels. These findings suggest that abnormalities in CBF perfusion may contribute to the neuropathological mechanisms of chronic tinnitus with headache condition.

## List Of Abbreviations

fMRI, functional magnetic resonance imaging; SPECT, single-photon emission computed tomography; PET, positron emission tomography; CBF, cerebral blood flow; ASL, arterial spin labeling; GM, gray matter; WM, white matter; THQ, Tinnitus Handicap Questionnaires; PTA, pure tone audiometry; SDS, Self-Rating Depression Scale; SAS, Self-Rating Anxiety Scale; VAS, visual analogue scale; HIT-6, Headache Impact Test-6; FDR, false discovery rate; FWE, family-wise error; STG, superior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus.

## Declarations

**Ethics approval and consent to participate**

Study protocol was approved by the Research Ethics Committee of the Nanjing Medical University prior to study initiation. All the subjects provided written informed consent before any study procedures.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Clinical, neuroimaging and statistical data will be available upon request from any qualified investigator.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Author contributions**

Y-C C and JH designed the study, performed the experiments, and wrote the manuscript. JC, SS, WY, J-J X, and XY performed the experiments and analyzed the data. YW and JQ revised the manuscript. All authors read and approved the final manuscript.

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## Tables

Due to technical limitations, Tables 1 - 4 are only available for download from the Supplementary Files section.

## Figures

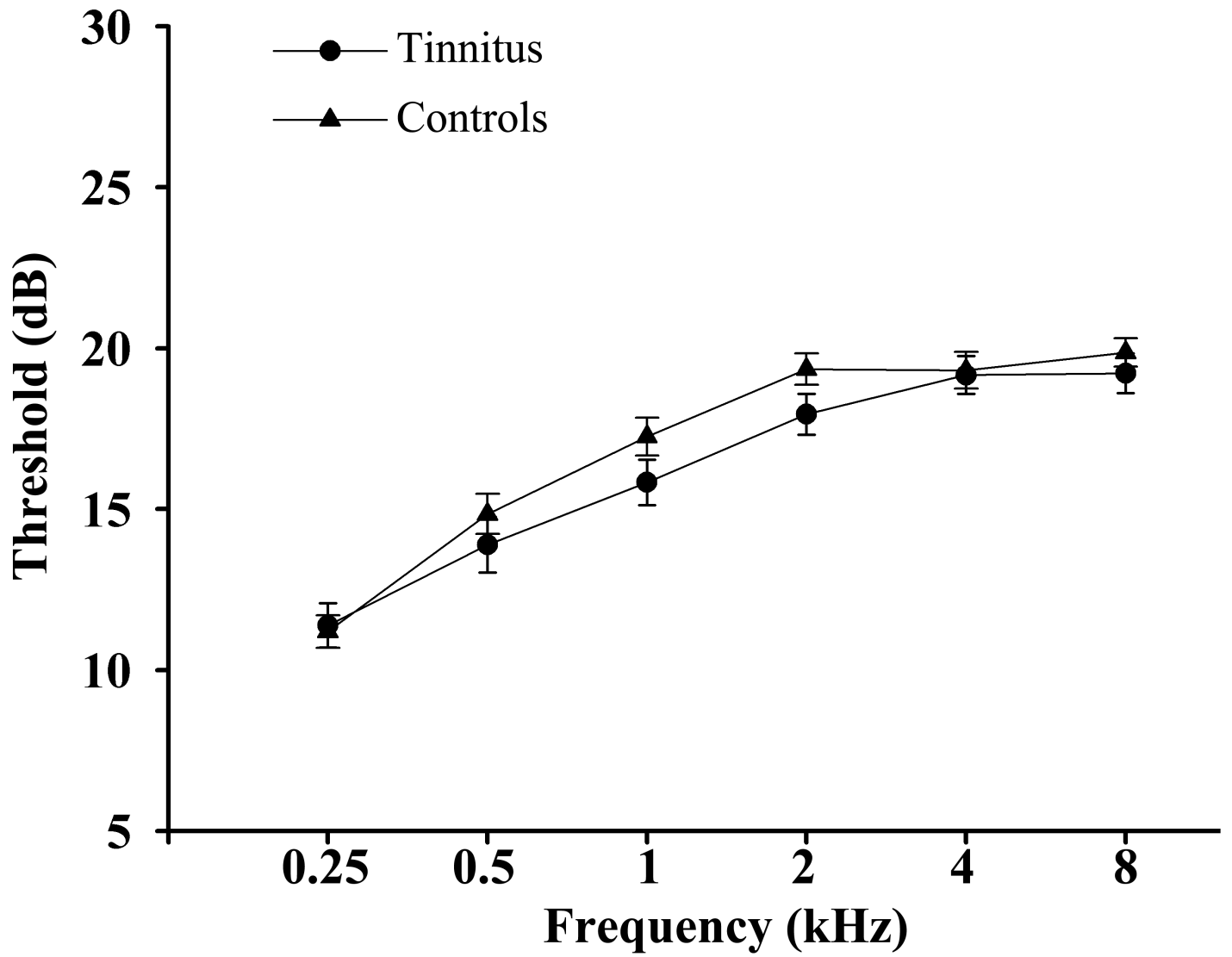
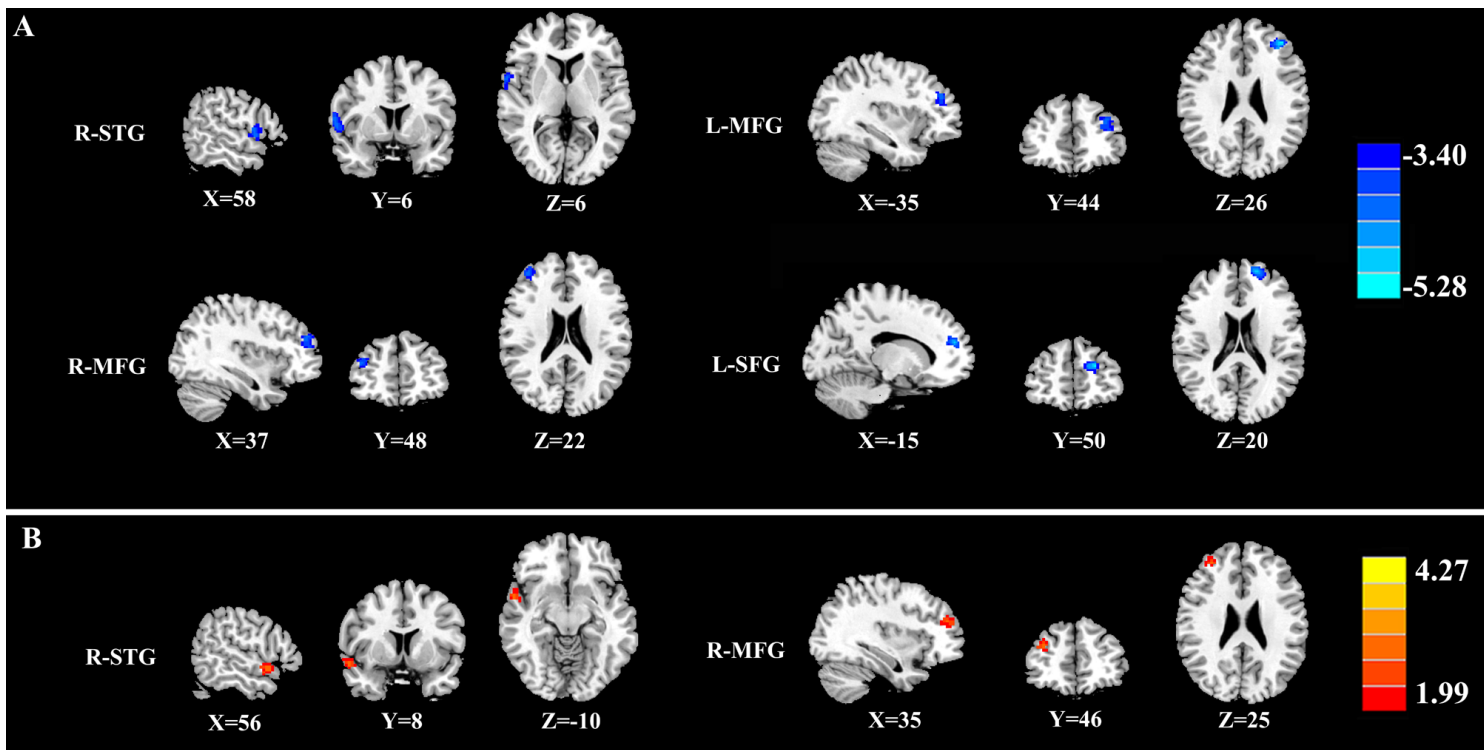


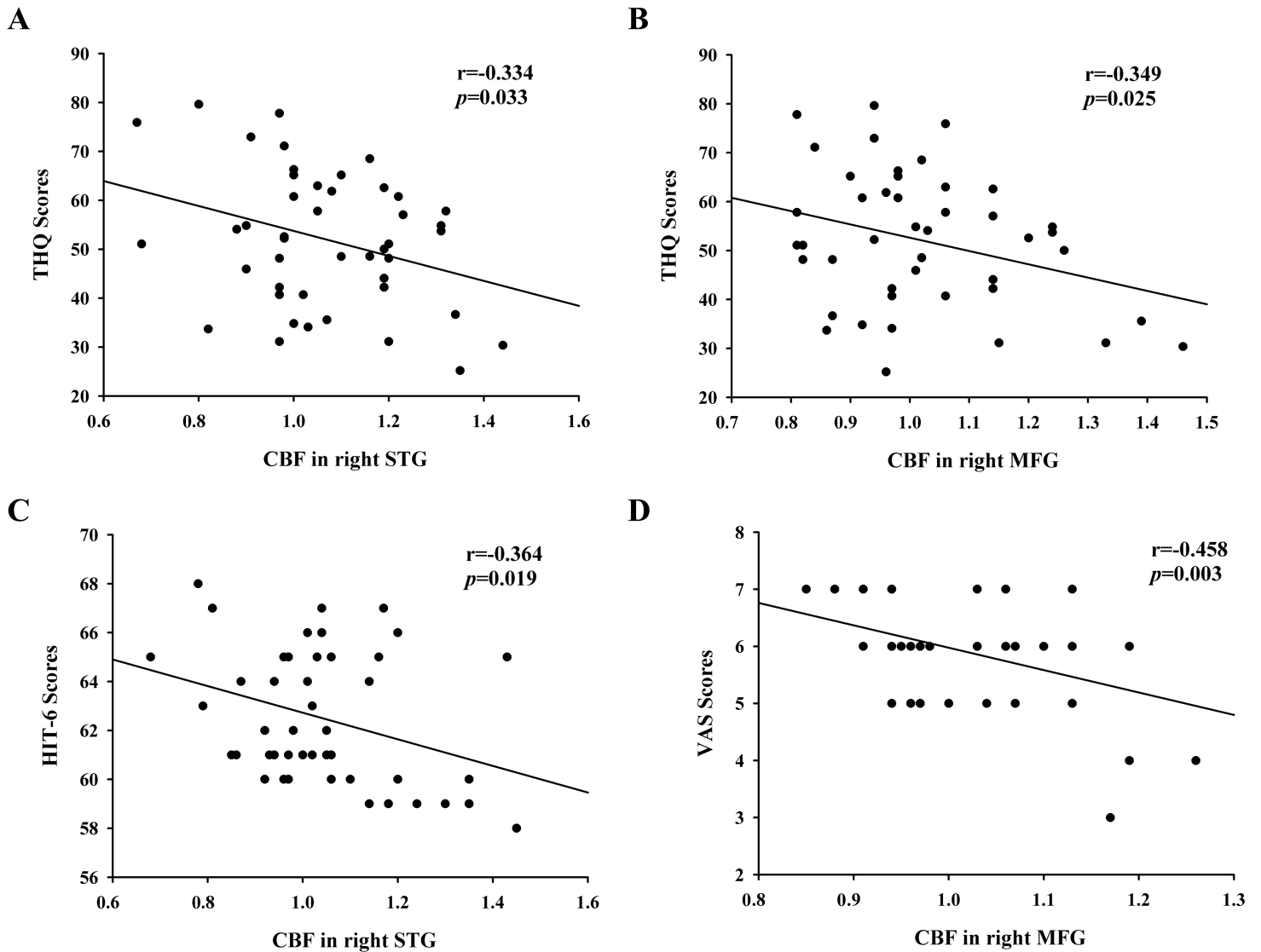
Figure 1

Mean hearing thresholds of the chronic tinnitus patients and non-tinnitus controls. Data are presented as Mean $\pm$ SEM.



**Figure 4**

The CBF differences between the chronic tinnitus patients and non-tinnitus controls. (A) The tinnitus patients exhibited decreased CBF in the right superior temporal gyrus (STG), left and right middle frontal gyrus (MFG), and left superior frontal gyrus (SFG) ( $P < 0.01$ , FWE corrected); (B) The interaction effect between headache and tinnitus in the right STG and right MFG ( $P < 0.01$ , FWE corrected).



**Figure 6**

The significant correlations between the CBF changes and the clinical data in chronic tinnitus patients. (A) CBF in the right STG was negatively associated with THQ scores ( $r = -0.334$ ,  $p = 0.033$ ); (B) CBF in the right MFG was negatively associated with THQ scores ( $r = -0.349$ ,  $p = 0.025$ ); (C) CBF in the right STG was inversely correlated with the HIT-6 scores ( $r = -0.364$ ,  $p = 0.019$ ); (D) CBF in the right MFG was inversely correlated with the VAS scores ( $r = -0.458$ ,  $p = 0.003$ ).

## Supplementary Files

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