Original Article

Tumor characteristics, brain functional activity, and connectivity of tinnitus in patients with vestibular schwannoma: a pilot study

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Background: The mechanism underlying tinnitus remains unclear, and when it coexists with vestibular schwannoma (VS), it can significantly diminish the quality of life for affected patients. This study aimed to determine the correlation between preoperative clinical characteristics of VS, postoperative changes in brain function, and tinnitus in patients with VS through a cohort study.

Methods: We collected data from 80 patients with VS preoperatively and 28 patients with VS preoperatively and postoperatively, and recruited 28 healthy controls. We used Chi-squared tests and unpaired *t*-tests to identify clinical characteristics with a significant preoperative effect. We used paired *t*-tests to identify brain regions where patients demonstrated significant changes in amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) postoperatively. Tinnitus severity was evaluated using the Tinnitus Handicap Inventory (THI) and Visual Analogue Scale (VAS). Pearson correlation coefficients were applied to assess the relationship between the changes in ALFF and ReHo and the changes in THI and VAS scores postoperatively. We also conducted seed- and region of interest (ROI)-based functional connectivity (FC) analyses.

Results: Before surgery, patients with VS with tinnitus (n=49) had smaller tumors (t=3.293; P<0.001), more solid tumor (χ^2=4.559; P=0.033), and less extrusion into the cerebellum brain stem (χ^2=10.345; P=0.001) than those without tinnitus (n=31). After surgery, the 28 patients with VS showed a significant reduction in ALFF in the left Cerebellum_Crus2 (a lobule in the cerebellum anatomy) (ROI 1) and a significant reduction in ReHo in the left Cerebellum_Crus1 (a lobule in the cerebellum anatomy) (ROI 2) and the right precuneus (ROI 3). Conversely, ReHo was significantly increased in the right precentral gyrus (ROI 4) [cluster-level P value family-wise error (P_{FWE}) <0.05]. The changes in ALFF values were negatively correlated with changes in the VAS score (r=−0.32; P<0.05). The FC strengths of patients between ROI 2 and the left and right posterior cingulate gyrus were significantly decreased postoperatively [false discovery rate (FDR) correction; P<0.05].

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Conclusions: Preoperative tinnitus in patients with VS may be influenced by tumor characteristics. The functional activities of brain regions are possibly altered postoperatively, which may be involved in the maintenance of postoperative tinnitus. Notably, the changes in ALFF are correlated with tinnitus.

Keywords: Vestibular schwannoma (VS); tinnitus, amplitude of low-frequency fluctuation (ALFF); regional homogeneity (ReHo); functional connectivity (FC)

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Introduction

Vestibular schwannoma (VS), also known as acoustic neuroma, derives from Schwann cells of the vestibulocochlear nerve. It is the most common benign tumor of the internal auditory canal and cerebellopontine angle (CPA), accounting for approximately 6% to 8% of all intracranial tumors and 80% to 90% of tumors in the CPA region (1,2). Tinnitus is one of the most common symptoms experienced by patients with VS, with approximately 80% of patients experiencing symptoms of tinnitus as the condition progresses. Around 10% of these patients experience tinnitus as their first symptom (3,4). Tinnitus is an auditory sensation that occurs in the absence of auditory stimuli and may be associated with various factors such as chronic hearing loss and emotional stress. The psychopathological reaction to the perceived auditory stimulus is a crucial factor in the discomfort and disability experienced by many patients with tinnitus (5). Although numerous studies have investigated the underlying mechanisms of tinnitus in patients with VS (6,7), particularly the peripheral mechanisms such as compression and ischemia, the exact mechanism is still unclear. Surgical removal of the tumor and nerve is not always effective in relieving tinnitus symptoms in patients with VS, and some patients develop tinnitus even after surgery (4). This suggests that the mechanisms leading to tinnitus in patients with VS are multifactorial and likely involve, in addition to the peripheral mechanisms mentioned above, alterations of functional plasticity in the central nervous system. Central gain refers to a condition in which the central auditory neurons are deprived of their usual sensory input, and the neurons receiving reduced input restore their typical activity level by responding more strongly to any given strength of input, which can lead to tinnitus. The persistence or even new onset of postoperative tinnitus symptoms in patients with VS may be primarily attributed to the phenomenon of central gain (8). With the development of modern surgical techniques and the application of intraoperative neurophysiological monitoring, preservation of facial nerve function or even hearing preservation in patients with VS has become an achievable goal (9), but tinnitus affecting quality of life is often ignored.

Functional neuroimaging techniques have emerged as noninvasive and reproducible methods for objective assessment of neurostructural and functional remodeling associated with tinnitus in patients with VS (10,11). These approaches can provide insights into the neurophysiologic and neuroanatomic bases of tinnitus in both the clinical and investigational realms. Brain imaging technology can be used to study the alterations in brain functional activity and functional connectivity (FC) related to tinnitus. In the study of brain functional networks, the network patterns represented by the default mode network (DMN) are related to various functions of the human brain, such as memory and cognition (12). It has been confirmed that the alterations of FC in several brain regions related or unrelated to hearing, such as the auditory cortex and hippocampus, are associated with tinnitus (13). Multimodal functional magnetic resonance imaging (fMRI) may be used to further clarify the mechanisms underlying tinnitus and may contribute to searching for potential targets of tinnitus treatment in patients with VS (14).

To this end, we attempted to identify the key clinical characteristics associated with tinnitus in patients with VS. We measured the regional functional metrics and conducted FC analysis to ultimately explore the potential to predict tinnitus and to gain a deeper understanding into the mechanisms underlying tinnitus in patients with VS. We hypothesized that surgery would induce broad functional activity changes of the brain regions in patients with VS. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-721/rc).

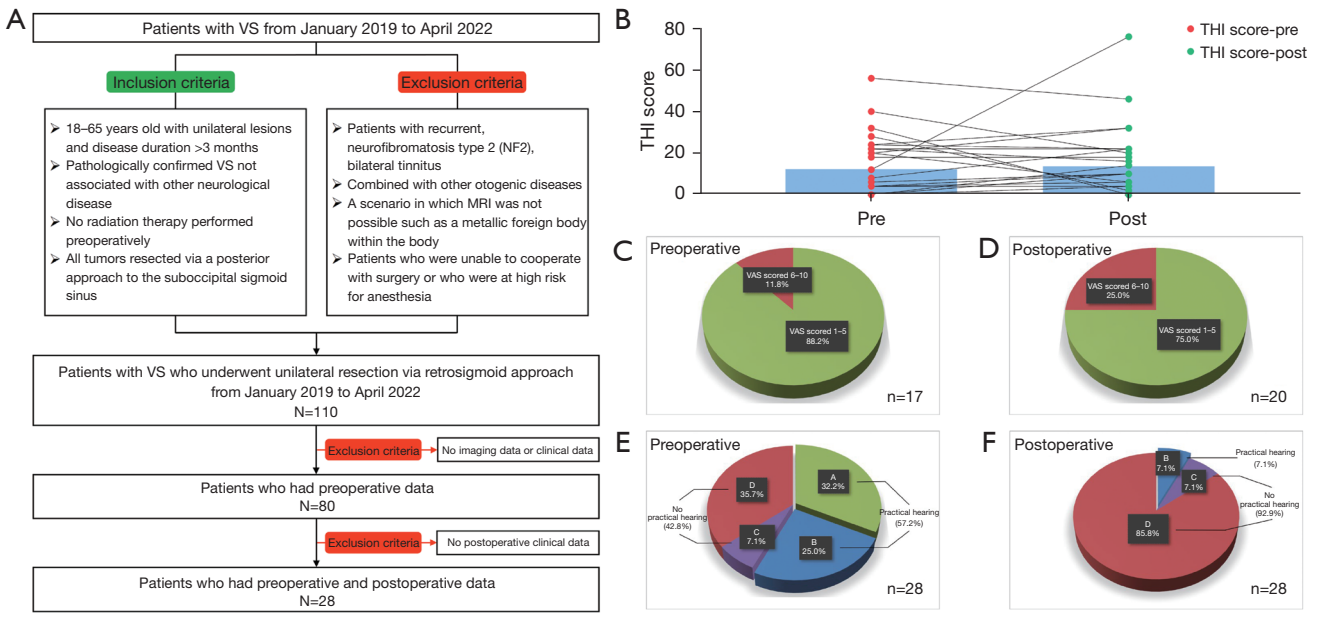

Figure 1 The flowchart of the study and the change in clinical data preoperatively to postoperatively. (A) The flowchart of the study. (B) Preoperative to postoperative changes in THI scores in patients with VS (n=28). (C,D) VAS in preoperative patients with tinnitus and postoperative patients with tinnitus (n=17 and n=20, respectively). (E,F) Changes in AAO-HNS hearing assessment grading in patients with VS (n=28). VS, vestibular schwannoma; MRI, magnetic resonance imaging; THI, Tinnitus Handicap Inventory; VAS, Visual Analog Scale; AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery.

Methods

Participants

This observational cohort study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Chinese PLA General Hospital Ethics Committee (No. S2022-335-01). All patients and their family members were fully informed of the study protocol and signed informed consent before surgery. This study included 110 patients diagnosed with VS who underwent successful operation via the retrosigmoid approach at the Chinese PLA General Hospital from January 2019 to April 2022. The inclusion criteria for patients were as follows: (I) 18–65 years old with unilateral lesions and disease duration >3 months; (II) pathologically confirmed VS not associated with other neurological disease; (III) no radiation therapy performed preoperatively; and (IV) all tumors resected via a posterior approach to the suboccipital sigmoid sinus. Meanwhile, the exclusion criteria were the following: (I) patients with recurrent, neurofibromatosis type 2 (NF2), bilateral tinnitus; (II) inability to undergo magnetic resonance imaging (MRI) due to reasons such as a metallic foreign body within the body; (III) combination with other otogenic diseases; and (IV) the inability to cooperate during surgery or at a higher risk for anesthesia. Finally, preoperative resting-state fMRI (rs-fMRI) was completed and clinical data were collected from 80 patients. Among them, 28 (the patients were followed up within 30 to 50 days postoperatively, and the patients attended the hospital for MRI and clinical scale assessment) underwent both the preoperative and postoperative rs-fMRI, and clinical data were obtained from these patients (*Figure 1A*). The patients with VS were divided into a preoperative group and a postoperative group. Patients were further divided into a tinnitus group and nontinnitus group according to whether or not they had tinnitus, which was determined by a clinical score (a score of 0 indicated no tinnitus, while other scores indicated tinnitus; for more details, see the *Clinical evaluation and outcome measures* section). In addition, 28 healthy controls (HCs) were recruited.

Surgical procedure

All patients underwent surgery for unilateral VS resection via the retrosigmoid approach. All surgeries were performed

by the same senior physician with 30 years of experience who had independently performed resection of VS via the retrosigmoid approach for more than 10 years, completing nearly 200 surgeries per year. The surgical procedure was as follows: after tracheal intubation and general anesthesia, the patient was placed in the lateral decubic position, and a straight inner hairline incision was made behind the ear according to the size of the tumor. The scalp, subcutaneous tissue, and muscle were cut, and a hole was drilled below the star point and bone flap. The open mastoid air chamber was closed with bone wax. The dura was incised in a C-type arc at the corner of the transverse sinus and sigmoid sinus, cerebrospinal fluid (CSF) was released from the cisterna magna of the cerebellum, and the cerebellum was gently tracted using a brain pressure plate. After exposure of the tumor, internal decompression of the tumor was performed within the capsule, and the tumor was gradually removed. The decision to remove the posterior wall of the internal auditory canal was determined according to the intraoperative situation. During the surgery, brainstem auditory evoked potential (BAEP) was used to monitor auditory function while facial motor evoked potential (FMEP) was used to detect facial nerve function. After tumor resection, the dura mater was sutured tightly, the bone flap was removed, and the muscle, subcutaneous tissue, and skin were sutured layer by layer. All patients underwent tumor pathological confirmation.

Clinical evaluation and outcome measures

We used the Tinnitus Handicap Inventory (THI) and Visual Analogue Scale (VAS) as clinical data to evaluate tinnitus in patients with VS, the results of which were obtained preoperatively and postoperatively. THI quantifies the subjective perception of patients' tinnitus symptoms using 25 questions in 3 dimensions (functional, emotional, and catastrophic) to assess disease severity and quality of life (15). Patients could answer "no", "sometimes", or "yes" to each item (corresponding to a score of 0, 2, and 4 respectively) (16). The overall score was used as an indicator of tinnitus severity, with scores ranging from 0 to 100. Based on the THI score, patients were assigned different THI grades, including level 1 (very mild, score 1–16), level 2 (mild, score 18–36), level 3 (moderate, score 38–56), level 4 (severe, score 58–76), and level 5 (catastrophic, score 78–100). The changes (worsening or improvement) in a patient's tinnitus status solely depend on the changes (increase or decrease) in the THI score. This means that patients with VS and a postoperative THI score higher than their preoperative THI score were considered to be worsening, while those with postoperative THI score lower than their preoperative THI score were considered to be improving. The VAS was used to estimate tinnitus intensity in patients and ranged from "very faint" to "very loud" (17).

MRI data acquisition and preprocessing

MRI data were acquired with a 3.0T MRI scanner (Discovery 750, GE HealthCare, Chicago, IL, USA). Participants were asked to keep their eyes closed, relax, and wear earplugs to reduce noise, and foam pads were placed around their heads to minimize head motion during MRI acquisition. The rs-fMRI data were collected under the following echo-planar imaging sequence: time to echo (TE) =30 msec, time to repetition (TR) =2,000 msec, flip angle (FA) =90°, field of view (FOV) =240×240 mm^2, matrix =64×64, slice thickness =3.5 mm, slice gaP =0.5 mm, voxel size =3.75 mm × 3.75 mm × 4 mm, and volume =180 volumes.

Two senior radiologists independently reviewed the sequences and checked the image quality. The rs-fMRI data were then preprocessed using the GRETNA toolbox (18). Briefly, the preprocessing consisted of the following steps: (I) the Digital Imaging and Communications in Medicine (DICOM) images were converted to Neuroimaging Informatics Technology Initiative (NIfTI) format; (II) the top 5 time points of 180 volumes were removed; (III) the images underwent slice timing correction and correction for head motion; (IV) all images were spatially normalized with the standard Montreal Neurological Institute (MNI) space; (V) spatial smooth was performed using a 6 mm × 6 mm × 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel, and image smoothing was performed in the amplitude of low-frequency fluctuation (ALFF) calculations, but not in the regional homogeneity (ReHo) calculations; and (VI) linear trend removal and nuisance covariate regression were performed with nuisance variables including Friston 24 parameter correction, white matter (WM) signal, and CSF signal. Bandpass filtering was 0.01–0.08 Hz.

Regional functional activity analysis

Among the regional functional metrics, ALFF is a sensitive and specific approach that measures the magnitude of regional activity amplitude to reflect the intensity of local brain activity (19). Meanwhile, ReHo reflects the synchronization of local brain activity by calculating

Kendall coefficient concordance of the time series between one voxel and the adjacent voxels (20).

RESTplus software (version 1.2) was used to calculate these metrics (21). The imaging data of all patients with VS on the right side of the brain were flipped to the left side. The ALFF for each voxel was calculated as the averaged square-rooted power spectrum within the frequency band of 0.01–0.08 Hz. Next, the calculated ReHo values were smoothed with a 6-mm FWHM Gaussian kernel. Finally, *Z*-standardized ALFF and ReHo values were calculated.

A two-sample independent *t*-test was performed using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/) to identify brain regions with significant alterations in ALFF and ReHo in VS patients with or without tinnitus preoperative. A paired-sample Student's *t*-test was performed to identify brain regions with significant alterations in ALFF and ReHo in VS patients postoperatively compared with preoperatively. The significance level was set at 0.001 for voxels and 0.05 for clusters, with family-wise error (FWE) correction. The ALFF and ReHo values were extracted from cluster regions of the significantly altered brain regions in patients and in the corresponding regions in HCs. Pearson correlation coefficients were applied to assess the relationship between the changes in ALFF and ReHo and the changes in THI and VAS scores preoperatively and postoperatively. The statistical significance level was set at P<0.05. The results of all tests were corrected by false discovery rate (FDR) in order to ensure the accuracy.

FC analysis

FC was defined as the correlation of time series between brain areas measured by the Pearson correlation coefficient, which could reflect the temporal coherence between brain areas (22). The RESTplus toolkit was used to build FC (21). In order to analyze the changes between various brain regions and brain network connections in human brain, regions of interest (ROIs) were defined as brain regions with significant alterations in ALFF and ReHo values postoperatively, with a total of four ROIs. Based on ALFF and ReHo results, the correlation coefficients between the mean time series signals of each ROI and the whole-brain voxel signals were calculated to obtain the correlation maps. According to a previous study (13) on brain regions that may be associated with tinnitus-related networks, we chose 9 brain regions for ROI-wise FC analysis, including the bilateral middle frontal gyrus, bilateral posterior cingulate gyrus (PCG), bilateral hippocampus, bilateral amygdala and bilateral auditory cortex (which are related to the cognitive control network, the DMN, limbic system, and central auditory system). To generate the FC matrix, we calculated Pearson correlation coefficients between each of the four ROIs and tinnitus-related brain regions. Finally, the correlation coefficients were converted to *Z* values using a Fisher transform. A paired-sample Student's *t*-test was used to identify brain regions with significant FC changes in patients with VS (ROI-based: P<0.05 after FDR correction; seed-based: voxel-wise P<0.001; cluster-level P_{FWE}<0.05). A two-sample independent *t*-test was used to examine the FC strength difference between patients with VS and HCs. Pearson correlation coefficients were used to identify sensitive FC (P<0.05). The results of all tests were corrected by FDR in order to ensure the accuracy.

Statistical methods

Enumeration data were compared using the chi-squared test or Fisher exact test. The measurement data with normal distribution are presented as the mean ± standard deviation (SD). The paired-sample Student's *t*-test was used for comparison between groups of measurement data with normal distribution, the two-sample independent *t*-test was used for comparison between independent samples, and the Pearson correlation coefficients analysis method was used for correlation analysis. The statistical analysis based on voxel level was performed using SPM12 software, while SPSS 26 software (IBM Corp., Armonk, NY, USA) was used for post facto testing and related analyses.

Results

Demographic and clinical characteristics

In this study, we included 80 patients with unilateral VS preoperatively, with an average age of 46.5±12.0 years and an average tumor size of 2.4±1.2 cm. We compared the differences between preoperative patients with tinnitus (n=49) and without tinnitus (n=31) in terms of demographic information, preoperative hearing, and tumor characteristics, such as tumor nature, tumor size, cerebellum brain stem extrusion, and occupation of the internal auditory canal. The results showed that before surgery, patients with VS and tinnitus had smaller tumors (t=3.293; P<0.001), more solid tumors (χ^2=4.559; P=0.033), and less extrusion into the cerebellum brain stem (χ^2=10.345; P=0.001) than did those without tinnitus, with other factors

Table 1 Demographic characteristics in patients with VS (n=80)

Characteristics	With tinnitus (n=49)	Without tinnitus (n=31)	P value
Side			0.236†
Left	25	20	
Right	24	11	
Gender			0.405†
Male	22	11	
Female	27	20	
Preoperative hearing			0.444†
Practical hearing (AAO-HNS class A and B)	21	16	
Unpractical hearing (AAO-HNS class C and D)	28	15	
Tumor nature			0.033*†
Solid	38	17	
Nonsolid	11	14	
Cerebellum brain stem extrusion			0.001*†
+	24	27	
–	25	4	
Tumor size, cm	2.1±1.2	2.9±1.0	<0.001*‡
Occupation of internal auditory canal, cm	0.8±0.3	0.7±0.3	0.263‡

Data are presented as number or mean ± standard deviation. †, Chi-squared test; ‡, unpaired *t*-test; *, P<0.05. VS, vestibular schwannoma; AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery.

showing no significant effect (*Table 1*).

Moreover, 28 patients underwent unilateral VS resection and received clinical and rs-fMRI follow-up after the surgery. Their average age was 46.5±11.4 years, and the average tumor size was 2.2±1.1 cm. For patients with preoperative tinnitus, their THI score, THI level, and VAS score were 20.2±14.0, 1.8±0.7, and 4.3±1.9, respectively. For patients with postoperative tinnitus, their THI score, THI level, and VAS score were 19.1±17.4, 1.6±0.8, and 4.1±1.7, respectively. These measures and the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) hearing assessment grading of patients with preoperative and postoperative VS are shown in *Figure 1B-1F*. In order to analyze the factors affecting postoperative tinnitus, the patients were divided into two groups according to the postoperative tinnitus state: improved (n=5) and worsened (n=11). Other patients (n=12) were not included because their tinnitus severity did not change after surgery. We compared the differences between these two groups in terms of side, demographic information, preoperative hearing, tumor nature, tumor size, cerebellum brain stem extrusion, occupation of the internal auditory canal, preservation of the cochlear nerve, and degree of resection. The results showed that none of these factors had a significant effect on postoperative tinnitus alteration (*Table 2*).

Correlation analysis of brain activity changes and tinnitus symptoms

Before surgery, among the 80 patients with VS, there was no significant difference in brain activity in patients with tinnitus (n=49) compared with those without tinnitus (n=31). After surgery, among the 28 patients, patients with VS demonstrated a significant reduction in ALFF in the left Cerebellum_Crus2 (a lobule in the cerebellum anatomy, taken from Region 93 of the Anatomical Automatic Labeling (AAL) provided by MNI) (ROI 1) and a significant reduction in ReHo in the left Cerebellum_Crus1 (a lobule in the cerebellum anatomy, taken from Region 91 of the AAL provided by MNI) (ROI 2) and right precuneus (ROI 3)

Table 2 Factors affecting postoperative tinnitus alteration (n=16)

Characteristics	Changes of tinnitus		P value
	Improved (n=5)	Worse (n=11)	
Side (left/right)	3/2	7/4	>0.999†
Gender (male/female)	1/4	4/7	>0.999†
Preoperative hearing (class A and B/class C and D)	2/3	10/1	0.063†
Tumor nature (solid/nonsolid)	4/1	8/3	>0.999†
Cerebellum brain stem extrusion (+/–)	1/4	7/4	0.282†
Cochlear nerve preservation (+/–)	1/4	3/8	>0.999†
Degree of resection (total resection/subtotal resection)	4/1	8/3	>0.999†
Tumor size, cm	1.6±1.5	2.0±0.8	0.255‡
Occupation of internal auditory canal, cm	0.8±0.2	0.8±0.3	0.422‡

Data are presented as number or mean ± standard deviation. †, Fisher exact test; ‡, unpaired *t*-test.

Table 3 The detailed information of brain regions with ALFF and ReHo alterations in patients with VS postoperatively

Peak MNI coordinate region	Side	AAL	Cluster size (voxels)	MNI coordinate (mm)			Peak level	Cluster-level
				x	y	z	*t* value	P_{FWE}
ALFF								
Cerebellum_Crus2 (ROI 1)	Left	93	280	–45	–72	–39	9.01	<0.001*
ReHo								
Cerebellum_Crus1 (ROI 2)	Left	91	141	–48	–72	–36	8.01	0.001
Precuneus (ROI 3)	Right	68	109	3	–63	24	5.29	0.003
Precentral gyrus (ROI 4)	Right	2	61	27	–21	63	4.68	0.040

*, Cluster-level P_{FWE}<0.05 when the voxel-level threshold was P<0.001. ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity; VS, vestibular schwannoma; MNI, Montreal Neurological Institute; AAL, anatomical automatic labeling; FWE, family-wise error; ROI, region of interest; Cerebellum_Crus1, a lobule in the cerebellum anatomy, taken from Region 91 of the AAL provided by MNI; Cerebellum_Crus2, a lobule in the cerebellum anatomy, taken from Region 93 of the AAL provided by MNI.

postoperatively. Conversely, ReHo in the right precentral gyrus (ROI 4) was significantly increased postoperatively (ROI 1: cluster-level P_{FWE}<0.001; ROI 2: cluster-level P_{FWE}=0.001; ROI 3: cluster-level P_{FWE}=0.003; ROI 4: cluster-level P_{FWE}=0.040) (*Table 3*, *Figure 2A*). Postoperative ALFF values in ROI 1 and ReHo values in ROI 2 were significantly lower in patients with VS compared to HCs. However, the postoperative ReHo values in ROI 3 and ROI 4 did not differ significantly between patients with VS and HCs (*Figure 2A*). Among these regions, ROI 3 belongs to the region of the DMN that may be associated with tinnitus. Furthermore, changes in ALFF values were negatively correlated with changes in VAS scores on the left side [r=–0.32; 95% confidence interval (CI): –0.6180 to 0.06207; P=0.049] (*Figure 2B*).

Correlation analysis of brain FC changes and postoperative tinnitus symptoms

We used seed-based FC analysis to investigate the association between the four ROIs and whole-brain voxels but found no significant changes. Using an ROI-based FC analysis, we investigated the connections between 4 ROIs and 9 brain regions that may be associated with tinnitus (the detailed information about ROIs and brain regions is listed in *Tables 3*,*4*). After FDR correction, we observed that

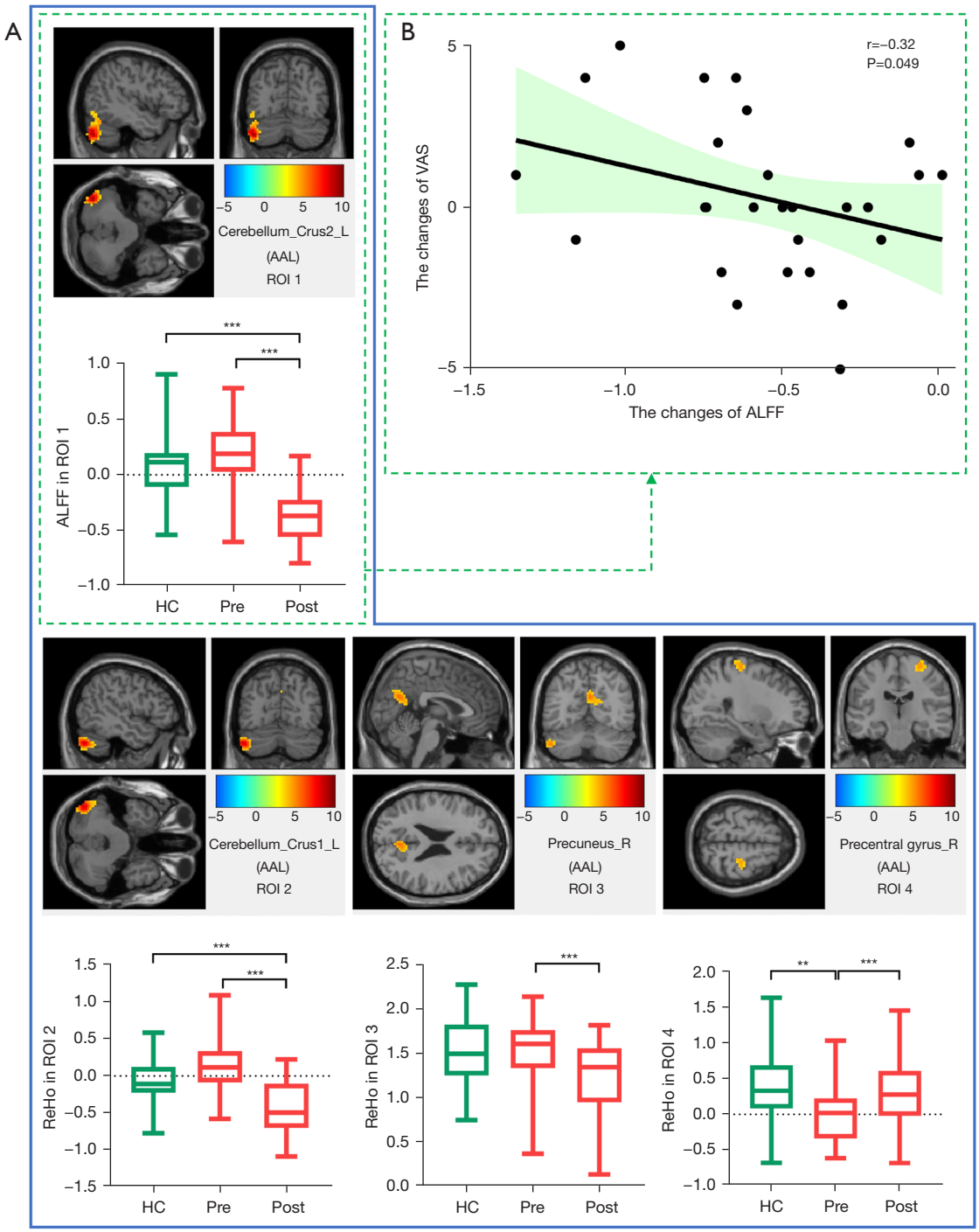

Figure 2 Brain regions with ALFF and ReHo alterations in patients with VS postoperatively. (A) Graph of the differences in ALFF and ReHo of ROIs 1–4 between HCs and patients with VS preoperatively and postoperatively. (B) The changes in ALFF values of patients with VS were negatively correlated with the changes in VAS scores on the left side. The orange area in (A) represents the regions with significant alterations in brain activity in patients with VS postoperatively. The results of all the significance tests in (A) are two-tailed, and the result of the significance test in (B) is one-tailed. **, P<0.01; ***, P<0.001. AAL, anatomical automatic labeling; ROI, region of interest; HC, healthy control; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity; Cerebellum_Crus2_L, left Cerebellum_Crus2; Cerebellum_Crus1_L, left Cerebellum_Crus1; Precentral gyrus_R, right precentral gyrus; Precuneus_R, right precuneus; VS, vestibular schwannoma; VAS, Visual Analog Scale.

the patients' FC strengths between ROI 2 and the right PCG (PCG.R) as well as between ROI 2 and the left PCG (PCG.L) were significantly decreased postoperatively (FDR correction; ROI 2 to PCG.R: P=0.048; ROI 2 to PCG.L: P=0.029). Before surgery, the FC intensity between ROI 2 and PCG.R was significantly higher in patients with VS than in HCs, and it decreased postoperatively with no significant difference compared to HCs. Similarly, the FC intensity between ROI 2 and PCG.L decreased postoperatively in patients with VS, with no significant difference compared to HCs (refer to *Figure 3A-3C*). It is interesting to note that similarly to ROI 3, in which brain activity changes occur, the PCG is also an important component of the DMN (*Figure 4*). The postoperative changes in the DMN-related FC in patients with VS may indicate changes in the pattern of neural interactions between brain regions.

Table 4 Information on the diagram of brain regions which may associated with tinnitus

Brain regions	Abbreviation	Side	Brain atlas
Middle frontal gyrus	MFG	Left/right	7/8[†]
Posterior cingulate gyrus	PCG	Left/right	35/36[†]
Hippocampus	HIP	Left/right	37/38[†]
Amygdala	AMYG	Left/right	41/42[†]
Auditory cortex	AUC	–	41/42[‡]

[†], AAL (anatomical automatic labeling); [‡], BA (Brodmann area).

Discussion

The neuroplasticity of the brain is affected by many factors

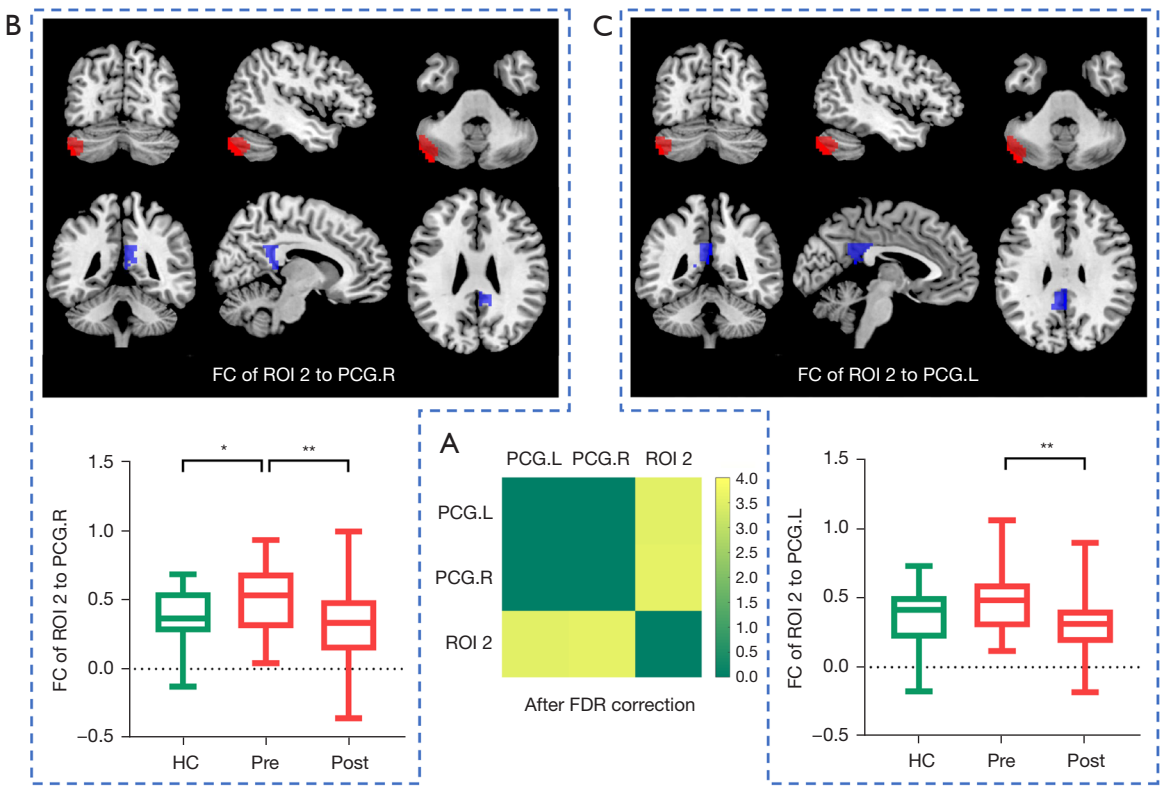

Figure 3 Regions with altered FC in patients with VS postoperatively. (A) Heatmap of the relationship with significant changes in the FC between ROIs and brain regions in patients with VS postoperatively (after FDR correction). (B,C) Graphs showing the reductions in FC strengths of related regions in patients with VS postoperatively and the differences in FCs between HCs and patients with VS preoperatively and postoperatively. The red area in (B,C) represents ROI 2; the blue area represents PCG.R in (B) and represents PCG.L in (C). The results of all the significance tests in (B,C) are two-tailed. *, P<0.05; **, P<0.01. FC, functional connectivity; VS, vestibular schwannoma; ROI, region of interest; PCG.L, left posterior cingulate gyrus; PCG.R, right posterior cingulate gyrus; HC, healthy control; FDR, false discovery rate.

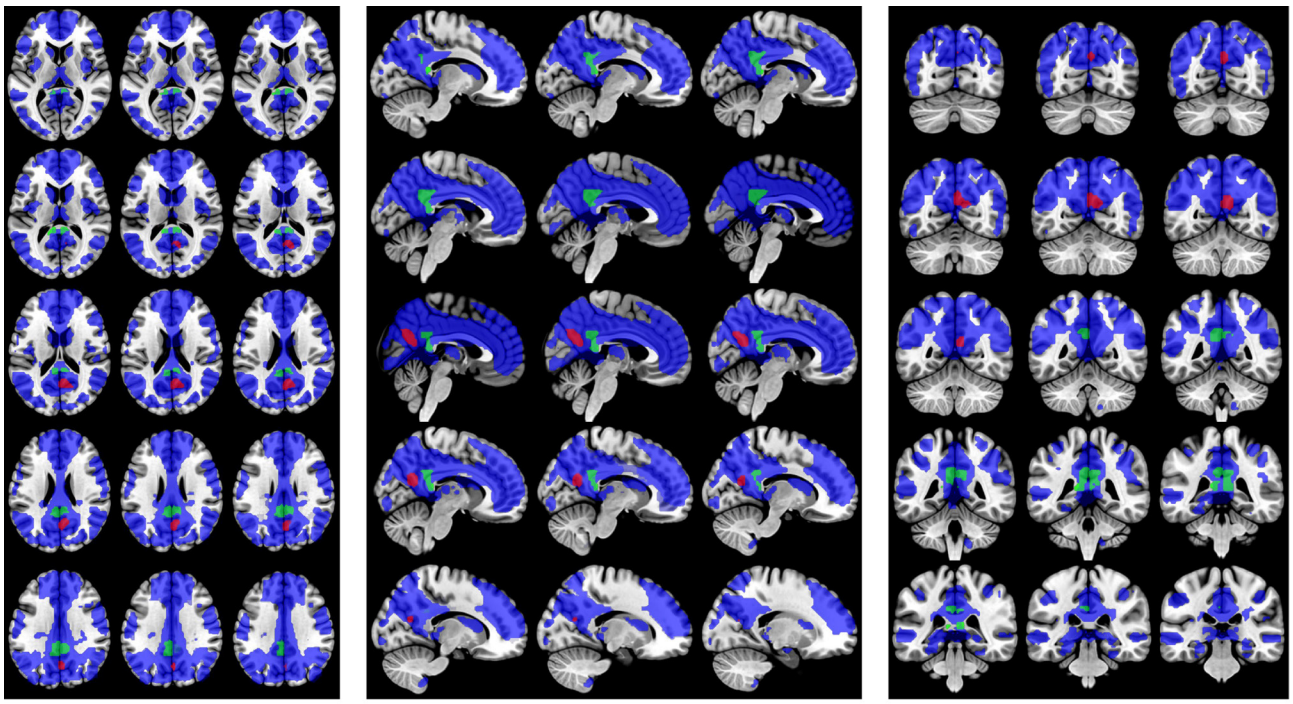

Figure 4 The schematic figure of the DMN and the related to the DMN in this study. The blue area represents DMN, the red area represents ROI 3, and the green area represents PCG. ROI 3 is the region associated with changes in brain activity in patients with VS, and PCG is the region associated with changes in FC in patients with VS. DMN, default mode network; ROI, region of interest; PCG, posterior cingulate gyrus; VS, vestibular schwannoma; FC, functional connectivity.

(23,24), and the mechanisms regarding the occurrence of tinnitus due to VS are quite complex and cannot be explained by a single factor. Baguley *et al.* (25) suggested four possible mechanisms for tinnitus caused by VS: (I) ephaptic coupling (ephaptic excitation of one nerve fiber by neighboring nerve fibers and synchronization) of cochlear nerve fibers by compression; (II) cochlear dysfunction via ischemia or biochemical degradation; (III) efferent system dysfunction following compression of the efferent fibers in the inferior vestibular nerve; and (IV) cortical reorganization following hearing loss. It was previously thought that the development of tinnitus is closely related to the peripheral tumor mechanism and may include ephaptic coupling of cochlear nerve fibers by compression (7). In our study, similar to previous reports (25,26), we found that the differences in tumor characteristics, such as tumor size and tumor nature, and cerebellum brain stem extrusion may significantly affect tinnitus in patients with preoperative VS. It is generally believed that the clinical symptoms of patients with VS are aggravated with the increase of tumor size. However, our study showed that patients with small tumor size are more likely to develop tinnitus symptoms, but further studies are needed to confirm this. In addition, we found that patients with VS do not necessarily experience alleviation of tinnitus symptoms after removal of the tumor to relieve the tumor compression or cut the auditory nerve, with some patients still experiencing persistent tinnitus symptoms and others experiencing a new onset of tinnitus. Therefore, we believe that the peripheral tumor mechanism, among other causes, may contribute to tinnitus in patients. Additionally, we speculate that the persistence of postoperative tinnitus in patients with VS may be a central mechanism. The concept of central gain posits that a decrease in auditory input, often through hearing loss, leads to an increase in the gain of central auditory pathways, producing the patient's symptoms of tinnitus (8). The purpose of this gain is to adapt neural sensitivity to the reduced sensory inputs, preserving a stable firing and neural coding efficiency. Due to the overall increase of gain, "neural noise" is amplified, ultimately resulting in the generation of tinnitus (27). Patients with VS basically do not retain hearing function after surgical operation. Therefore,

we speculate that central gain may be the underlying mechanism for the persistence of postoperative tinnitus in patients with VS. The key to understanding central gain is recognizing the differences in brain functional activity between those with and without tinnitus, and thus we conducted functional imaging studies.

Jastreboff (28) proposed that tinnitus arises due to the subcortical auditory center processing the signal of faint neural activity to the terminals, which is finally perceived as tinnitus by the temporal cortex of the brain. One study found that any lesion on the auditory conduction pathway may trigger tinnitus, and both the auditory conduction pathway and nonauditory conduction pathway may be associated with tinnitus (29). A few fMRI studies in patients with tinnitus reported that compared with that in a nontinnitus group, the ReHo of a tinnitus group increased in the inferior frontal gyrus, middle temporal gyrus, insula, and superior margin gyrus and decreased in the cuneus (30,31). The results from the cuneus are consistent with our own, and the precuneus is one of the key brain regions of the DMN. Other studies based on rs-fMRI have shown that the remodeling of central neural networks including the DMN may be the potential underlying mechanism of tinnitus (32,33). In addition, our study found changes in ROI 1 and ROI 2 in patients with VS. It has been reported that ROI 1 and ROI 2, although located in the cerebellum, are also potential regions associated with tinnitus and hearing (34,35), and the cerebellum may play an important role in the emergence of tinnitus (36). We believe that these regions may induce tinnitus by affecting the auditory pathway and thus may be potential therapeutic targets for tinnitus in patients with postoperative VS. We also found changes in the precentral gyrus, and considering that the vestibule is one of the key mechanisms of motor regulation, we speculate that the issues in the precentral gyrus are mainly a manifestation of impairment in motor regulation and may be a side effect of surgery. Therefore, the brain regions related to the DMN and cerebellum may be centrally involved in tinnitus in patients with VS and thus warrant further investigation.

Our study also found that the FC between ROI 2 and PCG.R in patients with VS is an important factor in maintaining tinnitus. The FC between ROI 2 and PCG.R in patients with VS was altered postoperatively in our study. Some studies reported the FC of different brain regions being altered in tinnitus patients. Tinnitus can induce changes in FC, multiple brain regions, and brain networks, including the DMN, auditory cortex, precuneus, hippocampus, limbic system, and visual network, among others (13,37-39). In our study, the changes of FC in the PCG region, a key region of the DMN, may be an important cause of tinnitus in patients with postoperative VS. In addition, the DMN is related to distress, depression, and other feelings of loss in patients with tinnitus, and the FC changes between the regions and the interaction with auditory regions may affect the degree of irritability in these patients and cause cognitive impairment (40-42). Therefore, consistent with our previous research (43), changes in relevant areas, such as the DMN, may be used as a predictive marker of postoperative tinnitus in patients with VS and help us to better understand and explore the related central nervous mechanism and pathological and physiological mechanisms of postoperative tinnitus in patients with VS. The neural circuit of the DMN and cerebellum may be an important mechanism for the maintenance of postoperative tinnitus in patients with VS and should thus be further explored.

This study also has some limitations that should be mentioned. (I) Due to the coronavirus disease 2019 (COVID-19) pandemic, only a portion of patients completed postoperative follow-up, restricting the sample size, and thus a larger sample size is needed to further confirm the conclusions drawn from our findings. (II) The imaging data of the patient were flipped contralaterally, which might have produced some errors. (III) Although patients wore earbuds, the influence of noise generated during instrument scanning on their brain neural activity could not be completely avoided. Noise may activate the auditory pathway of patients and thus affect the collections of clinical scores related to tinnitus symptoms of patients. (IV) The effect of hearing loss on patients with tinnitus cannot be completely ruled out. According to these limitations, further studies should be designed and conducted to verify our findings.

Conclusions

Differences in tumor characteristics, such as tumor size and tumor nature, and cerebellum brain stem extrusion may exert a significant effect on tinnitus in preoperative patients with VS. Surgery via a retrosigmoid approach can significantly alter the spontaneous activity and default mode of the tumor-side cerebellum or other regions in patients with VS and change the FC associated with the DMN, suggesting that brain regions both related or unrelated to hearing can influence the postoperative brain changes

in patients with VS. Central gain may be the underlying mechanism of the persistence of tinnitus in patients with VS postoperatively. Further exploration is needed to determine the exact mechanism, predict clinical outcomes, and identify potential therapeutic targets.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-721/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-721/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and with the approval of the Chinese PLA General Hospital Ethics Committee (No. S2022-335-01). All patients and their family members provided written informed consent.

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