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Original Article

Study of functional connectivity in patients with sensorineural hearing loss by using resting-state fMRI

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Abstract: Objective: To determine functional connectivity of the default mode network in patients with sensorineural hearing loss (SNHL) in resting state. Methods: The posterior cingulate cortex was selected as a seed for assessment of functional connectivity of the activated brain areas in resting state by using a seed-based correlation analysis of the resting state functional magnetic resonance imaging (fMRI) data. Results: The fMRI results demonstrated that, the healthy volunteers and the patients with NSHL shared certain activated brain areas with positive functional connectivity with region of interest (ROI). However, the healthy volunteers also had positive functional connectivity with ROI in bilateral middle temporal gyrus, left anterior cingulate cortex, right inferior parietal lobule and left medial superior frontal gyrus. While the patients with SNHL did with bilateral inferior parietal lobule, left medial superior frontal gyrus, right supramarginal gyrus, and left middle temporal gyrus. Compared to controls, patients with SNHL showed increased functional connectivity in the right posterior frontal lobe, right precentral gyrus, right supramarginal gyrus and left posterior cingulate cortex, and had decreased functional connectivity in the left lingual gyrus, right cuneus lobe and right superior frontal gyrus. Conclusion: The posterior cingulate cortex, precuneus lobe, medial frontal gyrus, anterior cingulate cortex, temporal lobe, angular gyrus and inferior parietal lobule constitute a default mode of network in normal resting status. And patients with SNHL have abnormal functional connectivity of default mode network and cortical reorganisation in resting status.

Keywords: Resting-status, functional connectivity, functional magnetic resonance imaging, sensorineural hearing loss

Introduction

Hearing is one of the most important functions of the human brain for gathering outside information. It has been estimated that approximately 25 out of every 1,000 school-aged children in the United States suffer from hearing losses that may significantly interfere with their education [1]. Of the affected children, about one-third suffers from bilateral, as opposed to unilateral, hearing loss. Fully one percent of school-aged children have hearing loss categorised as severe to profound. Currently, there are 20 million persons with hearing loss in China [2].

Since recent application of magnetic resonance imaging (MRI), magnetoencephalography, and neural functional imaging to auditory system research, several lines of insights have been obtained into the mechanisms underlying audio production, transmission, integration and processing, which have been particularly valuable in our understanding of deafness. In fact, resting-state fMRI can noninvasively map whole brain functional activity [3-6]. This is especially promising for study patients with difficulty in task performance such as NSHL.

Herein we explored functional connectivity of default mode network in patients with SNHL and healthy volunteers in resting state. The results indicate that, unlike healthy volunteers, patients with SNHL may have distinct functional connectivity of default mode network and different cortical reorganisation.

Methods

Participants

All participants were right-handed with no previous or current psychiatric disorders (**Table 1**). Informed consent was obtained from all sub-

Table 1. Conditions of healthy participants

Number of voxels	Peak region	BA	t value	Peak MNI coordinates		
				x	y	z
225	*L* PCC	23	5.8367	-9	-51	33
232	*R* AG	39	5.5489	50	-61	24
142	*R* PL	30	5.3872	8	-50	18
220	*L* AG	39	4.7165	-46	-64	26
110	*L* PL	30	4.5773	-8	-52	19
53	*R* PCC	23	4.0548	10	-52	24
106	*L* MPL	31	3.4958	-4	-43	36
94	*L* MSFG	32	3.0807	-7	50	25
71	*R* STG	22	2.7464	56	-57	26
56	*R* IPL	40	2.6308	48	-62	47
42	*L* ACC	24	2.4181	-2	39	18
53	*R* MTG	21	2.1487	66	-22	-13
122	*L* MTG	21	2.0756	-58	-25	-15

jects prior to their participation, and the study was approved by the Institutional Review Board of the Hebei Medical University. The subjects were divided into 2 groups based on their hearing conditions: *SNHL group*: Twenty-four bilateral, severe ototoxic drug-caused SNHL patients were included in the study, 12 males, 12 females, with age ranging from 17 to 22 years old (average 19.3 ± 1.8 years). The drugs caused hearing loss in these patients included: gentamicin, furosemide, ibuprofen. All SNHL patients were examined by ENT (Ear Nose & Throat) specialists. Histories of hearing aids, familial diseases, infection, trauma, neural diseases and other psychiatric diseases were not present, and no abnormalities were revealed on routine head MRI scans (T2WI) prior to the study in all patients. Evoked potential hearing tests were performed used to confirm their hearing function on both ears with receiving strength at 90-98 dB nHL and velocity at 21.2 m/s; *Normal hearing group* was composed of 24 healthy volunteers with no known history of hearing impairment, 12 males, 12 females, age average: 23.6 ± 1.2 years (range 22 to 25 years old).

fMRI scanning

T2WI and BOLD-fMRI were performed with a GE 3.0 T superconducting scanner (USA, Signal EXCITE). During the scanning procedure, individual participant in supine position was instructed to stay awake and motionless, close their eyes, breathe calmly and refrain from systematic thinking as much as possible. Rescanning was performed if an unacceptable degree of head movement (translation > 2 mm, rotation > 2 degrees) occurred.

T2WI-FSE protocol was carried out as follows: TR = 3500 ms, TE = 102 ms, ETL = 19, BW = 62.50 Hz, FOV = 24 cm, slice thickness = 6.5 mm, slice gap = 1.3 mm, matrix = 416 × 224, NEX = 2, frequency direction = A/P. While BOLD-fMRI used the following EPI protocol: TR = 2500 ms, TE = 35 ms, FOV = 24 cm, matrix = 64 × 64, voxel size = 3.75 mm × 3.75 mm, slice thickness = 5 mm, slice gap = 1 mm, number of slices = 32, time points = 180, total scanning time = 434 s, 5760 images.

Image analysis and measurement

Functional image processing included following steps: Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm), Data Processing Assistant for Resting-State fMRI (DPARSF 2.0 Basic Edition), Resting-State fMRI Data Analysis Toolkit (REST 1.6, http://www.restfmri.net) and MATLAB 7.11.

Preprocessing protocol included the following steps: Conversion of DICOM data into NIFTI data; Removal of the first 10 time points; Slice timing correction (slice number 32, slice order "1 3 5...31, 2 4 6...32", reference slice 31); Realignment with exclusion standard as: translation > 2 mm, rotation > 2 degrees); Normalization (bounding box: -90 -126 -72; 90 90 108., voxel size: 3 mm × 3 mm × 3 mm, EPI templates); Smoothening with FWHM = 4 mm × 4 mm × 4 mm); Detrending; Filtering with 0.01 Hz to 0.08 Hz.

The functional connectivity analysis protocol consisted of following steps: Regress out nuisance covariates, consisting of six head motion parameters, the global mean signal, the white matter signal and the cerebrospinal fluid signal; Set the region of interest (ROI), by drawing a circle in the posterior cingulate cortex (PCC) (Talairach coordinates: -12 -47 32.) confirmed by Greicius et al. [7], with a radius of 6 mm (**Figure 1**); Perform seed-based correlation analysis of functional connectivity with the SPM default templates.

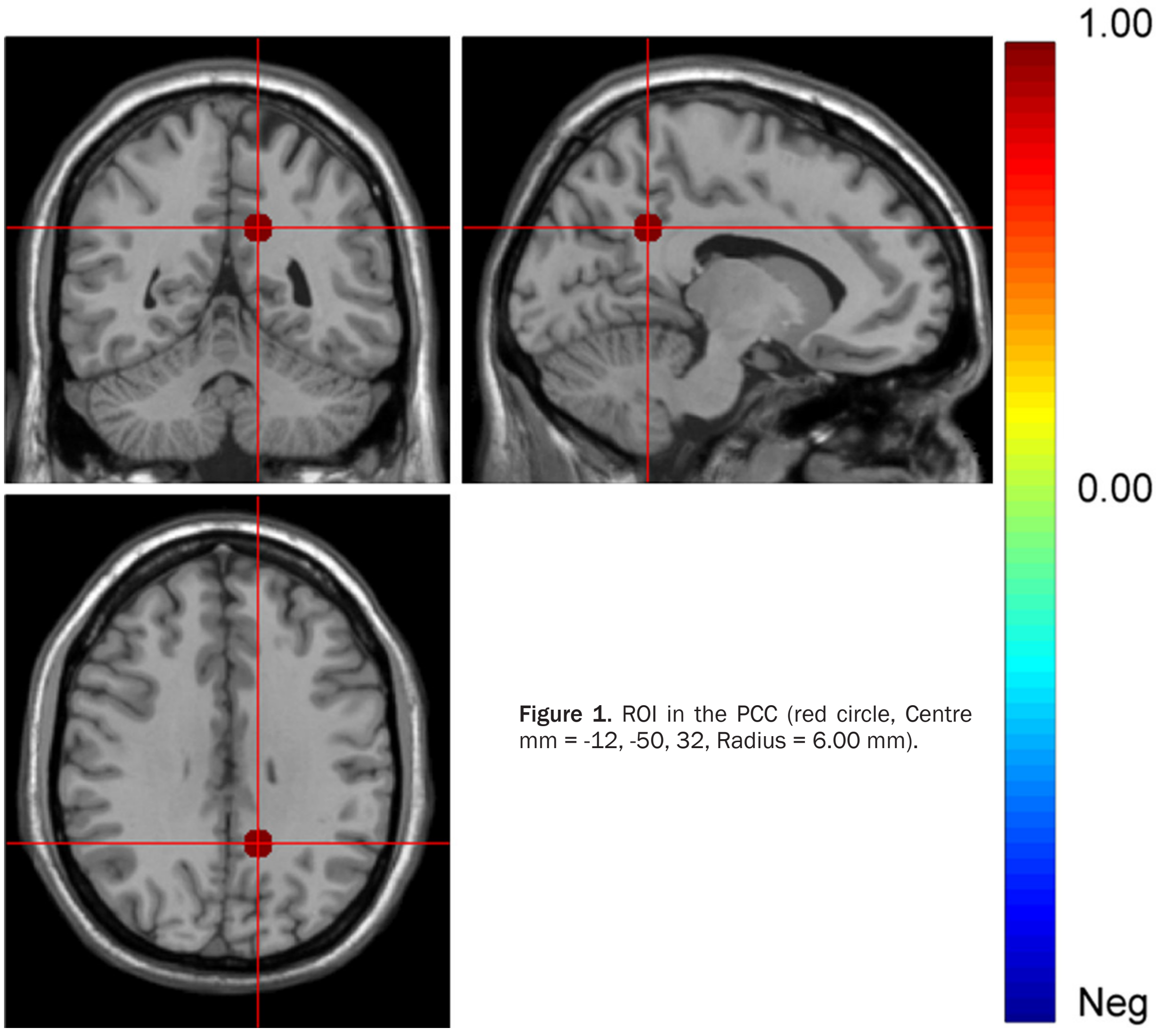

Figure 1. ROI in the PCC (red circle, Centre mm = -12, -50, 32, Radius = 6.00 mm).

Statistical analysis

Resting-State fMRI Data Analysis Toolkit (REST 1.6, http://www.restfmri.net) and XJVIEW 8 (http://www.alivelearn.net/xjview/) were used for statistics. First, one-sample t-tests were performed on all voxels independently. Second, difference of functional connectivity between the two groups was analysed by two sample t tests (no mask).

Results

Activated brain areas of positive functional connectivity with the ROI

The healthy volunteers and SNHL had different geography of activated brain areas of positive functional connectivity with the ROI in resting state. On one hand, interestingly, the two groups shared certain activated brain areas of positive functional connectivity with the ROI, i.e., bilateral posterior cingulate cortices, bilateral precuneus lobes, left medial parietal lobe, bilateral angular gyri, and right superior temporal gyrus. On other hand, the two groups also used distinct brain functional areas for connectivity in resting state. For instance, the normal individuals also relied in resting state on bilateral middle temporal gyri, left anterior cingulate cortex, right inferior parietal lobule and left medial superior frontal gyrus in resting state (**Figure 2**; **Table 1**). While in SNHL group, bilateral inferior parietal lobules, left medial superior frontal gyrus, right supramarginal gyrus, and left middle temporal gyrus were the activated brain areas were also responsible for functional connectivity (**Figure 3**; **Table 2**).

Functional connectivity in healthy volunteers and patients with SNHL

Compared to those in healthy volunteers, patients with SNHL had increased functional

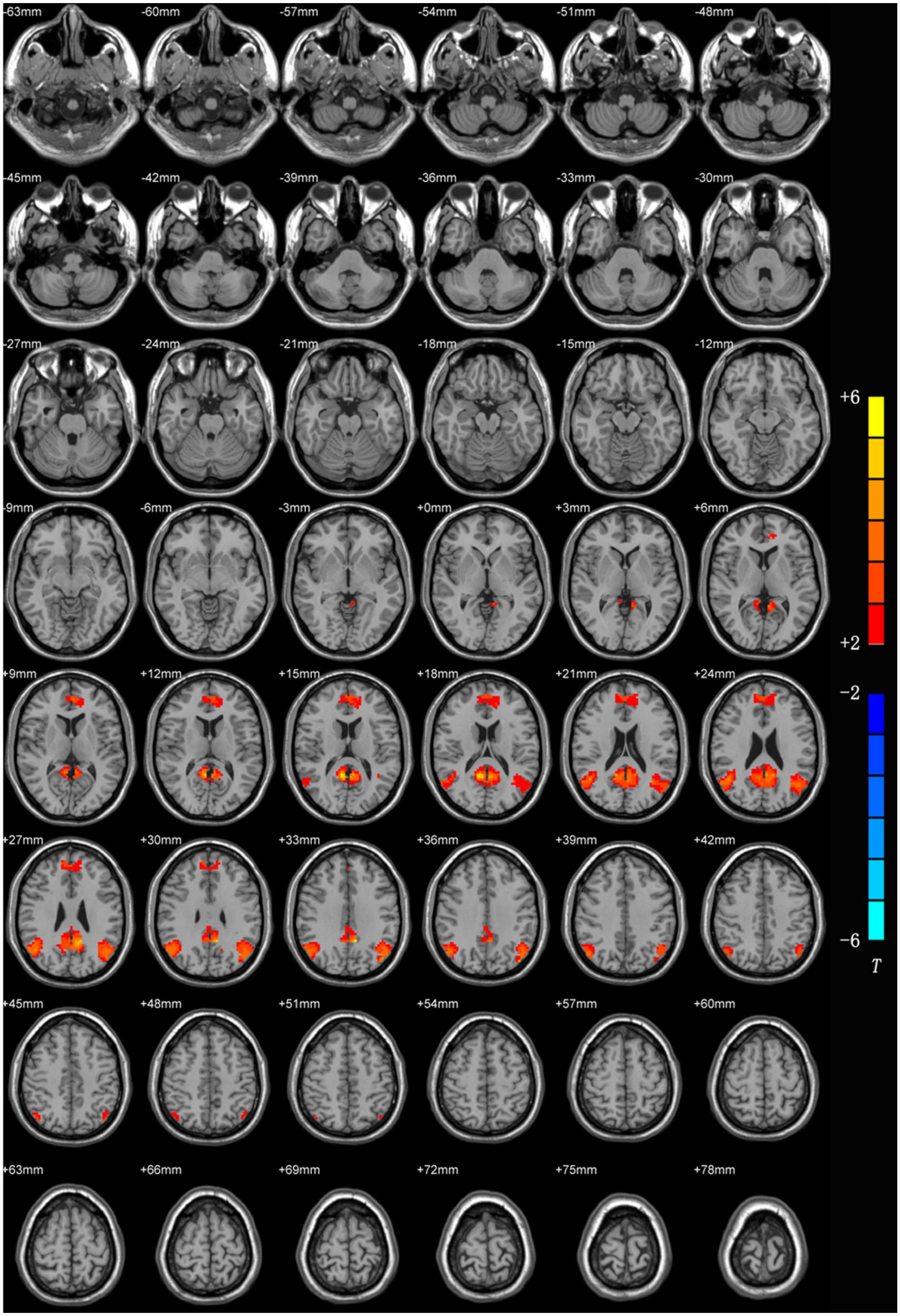

Figure 2. The positive functional connectivity map of the normal control individuals (Axial images). The colour depth gradient represents the differences in the functional connectivity of the areas. Going from red to yellow indicates a

gradually increasing intensity of positive functional connectivity with the ROI in normal control individuals. Images are displayed according to radiological convention.

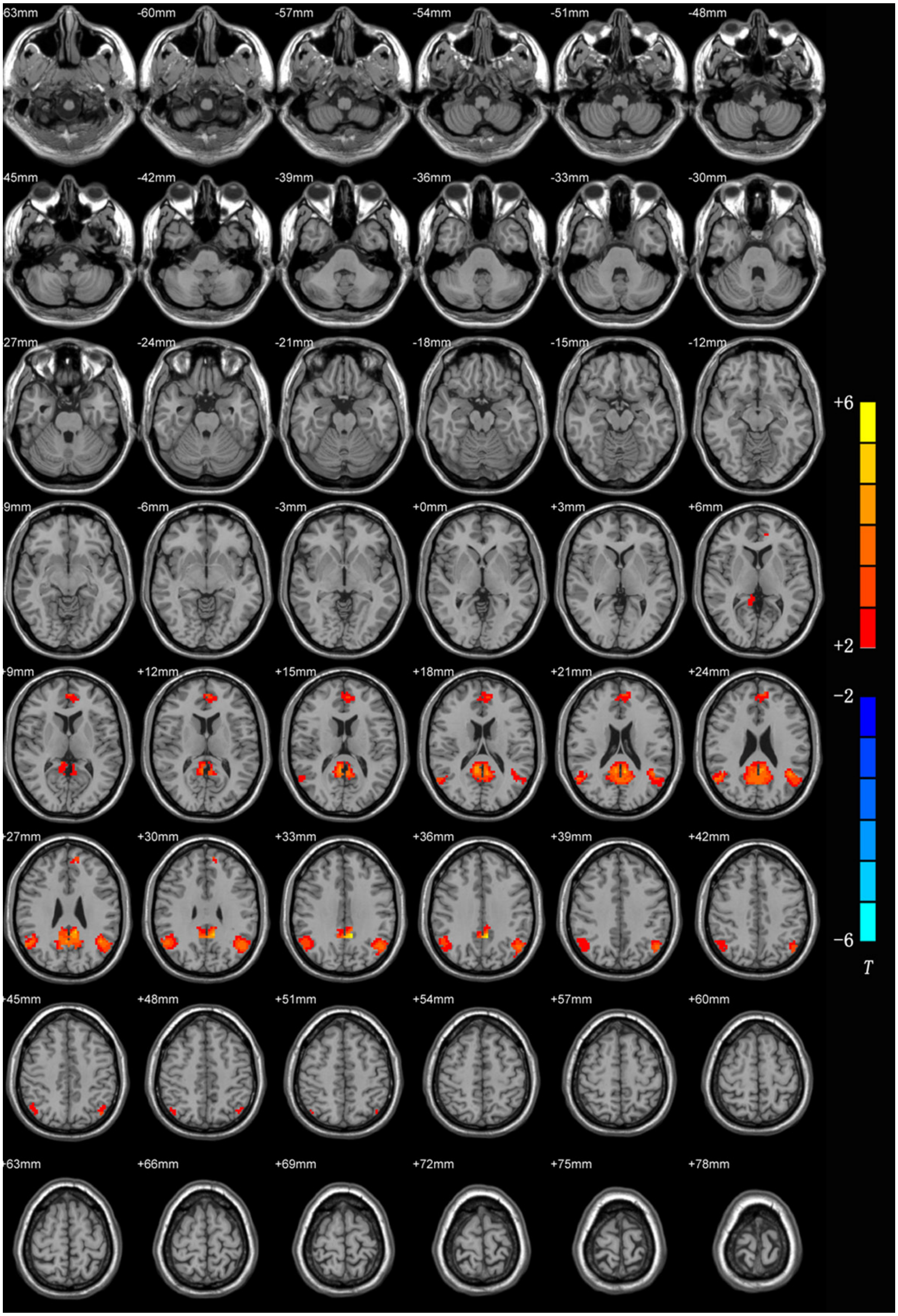

Figure 3. The positive functional connectivity map of the patients with SNHL (Axial images). The colour depth gradient represents the differences in the functional connectivity of the areas. Going from red to yellow indicates a gradually increasing intensity of positive functional connectivity with the ROI in patients with sensorineural hearing loss. Images are displayed according to radiological convention.

Table 2. Conditions of SNHL group

Number of voxels	Peak region	BA	t value	Peak MNI coordinates		
				x	y	z
201	*L* PCC	23	5.9379	-6	-51	36
218	*L* AG	39	5.7849	-42	-54	24
199	*R* AG	39	5.4132	51	-57	24
59	*L* MSFG	32	4.232	-9	54	27
52	*R* STG	22	4.1409	55	-60	23
146	*R* PL	30	3.6722	10	-51	21
77	*R* PCC	23	3.5871	9	-48	21
59	*R* IPL	40	2.7332	51	-57	43
56	*L* MTG	21	2.1948	-64	-13	-21
93	*L* PL	30	2.1273	-9	-48	18
103	*L* MPL	31	2.0967	-7	-38	36
52	*L* IPL	40	2.0167	-47	-55	48
64	*R* SMG	40	2.0089	52	-51	38

connectivity in right posterior frontal lobe, right precentral gyrus, right supramarginal gyrus and left posterior cingulate cortex, but with decreased functional connectivity in the left lingual gyrus, right cuneus lobe and right superior frontal gyrus (**Figure 4**; **Table 3**).

Discussion

Early studies of functional brain imaging assessed participants during the performance of a task. The fMRI is a new, non-invasive method for study of human physiological function, especially regarding vision and hearing. Currently, functional brain imaging in resting state is developing rapidly. However, functional connectivity in patients with SNHL is seldom studied.

Multiple human brain areas work together to process and integrate information obtained from the environment. Study of these processes in resting state by fMRI includes amplitude of low frequency fluctuation (ALFF), regional homogeneity (ReHo), and functional connectivity (FC) [8-11].

Since its introduction into the field of neuroimaging in the 1990s by Friston et al [4], functional connectivity, defined as the correlations between spatially remote neurophysiological events [9], has been widely used to study brain functions during task performance or the resting state. The alternative relationship is effective connectivity. Effective connectivity refers explicitly to the influence that one neural system exerts over another.

Functional brain imaging is a powerful tool for study of neural basis of perception, cognition, and emotion. Many brain networks have been observed to be active at rest and deactivated during active task states, such as the default network, and networks associated with motivation and attention, vision, hearing, and smell, among others [7, 12]. In fact, the default mode network is more active than other regions, consuming approximately 30% more energy [7]. And accumulating data from SPECT, PET, MEG and fMRI studies [7, 12, 13] have shown that the default mode network consists of the medial prefrontal gyrus, posterior cingulate cortex, precuneus lobe, anterior cingulate cortex, temporal lobe, hippocampus, and inferior parietal lobule. Consistent with above findings, our study revealed that, for healthy volunteers, the activated brain areas showing positive functional connectivity with our ROI consisted of the bilateral posterior cingulate cortices, bilateral precuneus lobes, left medial parietal lobe, bilateral middle temporal gyri, left anterior cingulate cortex, bilateral angular gyri, right superior temporal gyrus, right inferior parietal lobule and left medial superior frontal gyrus. We believe that these brain areas constitute the default mode network.

The posterior cingulate cortex (PCC) plays a central role in the default mode network [3]. In the present study, we found that PCC had the second-highest z score among regions that showed task-related decreases during working memory and also overlapped with regions in the default mode network. Also, we found that, comparing to ventral anterior cingulate cortex (vACC) connectivity map, the PCC connectivity

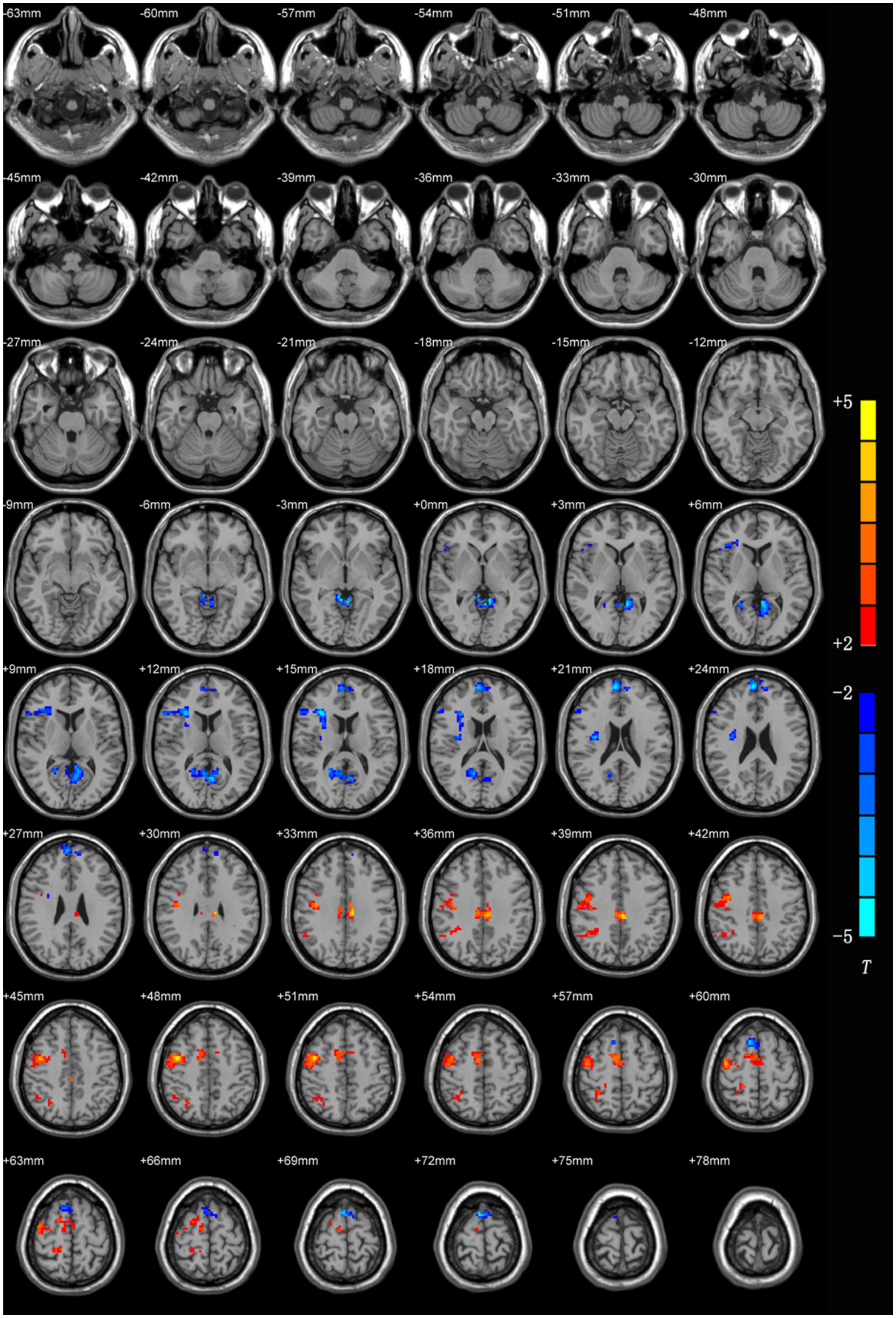
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Figure 4. The differences in functional connectivity between the SNHL group and the normal control group (Axial images). The colour depth gradient represents the differences in the functional connectivity of the areas. Going from red to yellow indicates a gradually increasing difference in the functional connectivity between the SNHL group and the normal control group, in the instances where the functional connectivity is stronger in the SNHL group than the normal control group. Going from deep blue to Cambridge blue indicates a gradually decreasing difference in the intensity of the functional connectivity between the SNHL group and the normal control group, in the instances where the functional connectivity is weaker in the SNHL group than the normal control group. Images are displayed according to radiological convention.

Table 3. Functional connectivity in healthy volunteers and patients with SNHL

Number of voxels	Peak region	BA	t value	Peak MNI coordinates		
				x	y	z
SNHL > Control						
105	*R* PFL	6	4.6630	42	-2	49
90	*L* PCC	23	4.3263	-4	-27	38
181	*R* PG	4	2.279	48	-13	40
46	*R* SMG	40	2.2062	46	-51	45
SNHL < Control						
69	*R* CL	17	-2.3298	15	-55	16
50	*R* SFG	6	-3.504	5	12	71
89	*L* LG	17	-3.5578	-5	-65	11
71	*R* SFG	10	-4.011	6	60	24

map matched better match with the default mode network. In addition, in the resting state, PCC was the only region showing inverse correlations with any of the "activated" prefrontal ROIs. Our results demonstrated that PCC is a key player in resting state.

The auditory cortex is divided into three parts from anterior to posterior: the APT, Heschl's gyri, and the planum temporal gyrus [14-16]. In previous studies [17] of adult participants with normal hearing, the presentation of monaural stimuli produced a contralaterality effect in the superior temporal gyrus. This asymmetric cortical response is termed contralateral hemispheric dominance, and has been attributed to differences in anatomical organisation. Crossing auditory pathways may have greater numbers of fibres and faster transmission speeds relative to ipsilateral pathways [18]. These characteristics aid audition and are valuable for sound localisation. Our results did not show contralateral hemispheric dominance in the primary and secondary auditory cortices of participants with normal hearing. The discrepancy needs further investigation, and other regions including the middle frontal gyrus, anterior cingulate cortex, posterior cingulate cortex, superior temporal gyrus, Broca's area, striatum, parahippocampus should be explored as well, as they are reportedly important for processing auditory information, in memory and in distinguishing between different tones in music and different speech sounds [19-21]. Our findings were not completely consistent with the results of other studies. This could be due to a reorganisation of resting-state functional connectivity in patients with SNHL.

Schmithorst did a preliminary functional MRI investigation [22] with 4 subjects with left unilateral sensorineural hearing loss (USNHL) and 4 with right USNHL. The data showed disparate neural circuitry supporting auditory processing in individuals with left and right USNHL. In Propst et al. [23] series, significant differences in the cortical processing of sound existed between children with severe to profound USNHL and children with normal hearing. In contrast, our results showed that neither individuals with normal hearing nor patients with SNHL exhibit contralateral hemispheric dominance. This phenomenon needs further studies. One explanation could be cross-modal plasticity [24-29] if an intrinsic modality structure loses its input, the function of this brain structure would be reorganized and new functions would be assigned to it.

In individuals undergoing monaural stimulation, normal-hearing individuals displayed activation lateralised to the contralateral side, while unilaterally deaf individuals displayed bilateral activation patterns, indicating a functional reorganisation of the auditory pathways [30]. Studies have shown reorganisation of auditory and language pathways in patients with USNHL. In our study, compared with persons with normal hearing, patients with SNHL had increased functional connectivity in the right posterior frontal lobe, right precentral gyrus, right supramarginal gyrus and left PCC, and decreased functional connectivity in the left lingual gyrus, right cuneus lobe and right superior frontal gyrus. The cingulate cortex, a part of the limbic system, performs functions related to self-knowledge, working memory and emotional processing, among others. The reproduction of related events, such as working memory in the posterior cingulate cortex, is associated with the process of active allocation of attention. These two mental processes are the primary components of working memory [31]. In this study, increased functional connectivity in the left posterior cingulate cortex in patients with SNHL had could be associated with maintained vigilance, regulated attention and increased active allocation of attention.

A study by Geng et al. [32] showed that under a proper pure tone stimulus the activation of the auditory cortex can be elicited in both healthy participants and in participants with SNHL. We found that, individuals with SNHL had increased functional connectivity in the right posterior frontal lobe, right precentral gyrus and right supramarginal gyrus, which is consistent with Geng and colleagues' results. Our results demonstrated that planning independent movement, controlling such movement and movement execution were more intensive in patients with hearing loss than in healthy individuals. Simultaneously, they had an increased ability to maintain attention and vigilance.

The lingual gyrus and the cuneus lobe of the medial occipital lobe belong to the sensory cortex of the primary visual cortices, namely the striate cortex, and they participate in processing visual information. The findings of this study showed that participants with SNHL exhibited decreased functional connectivity in the left lingual gyrus and right cuneus lobe, which potentially indicates that auditory functional reorganisation partly compensates for the needs of the visual system.

The superior frontal gyrus, middle frontal gyrus, and posteroinferior parietal lobule play a major role in linguistic thinking [19-21]. In the current study, patients with SNHL exhibited decreased functional connectivity in the right superior frontal gyrus, which may be associated with the changes in the manipulation of language memory. It is difficult to reach a firm conclusion based on a small sample size. Further prospective studies with larger sample size should be pursued.

Disclosure of conflict of interest

None.

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