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Abnormal resting-state functional connectivity study in unilateral pulsatile tinnitus patients with single etiology: A seed-based functional connectivity study

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ABSTRACT

Objective: Previous studies demonstrated altered regional neural activations in several brain areas in patients with pulsatile tinnitus (PT), especially indicating an important role of posterior cingulate cortex (PCC). However, few studies focused on the degree of functional connectivity (FC) of this area in PT patients. In this study, we will compare the FC of PCC in patients affected with this condition and normal controls by using resting-state functional magnetic resonance imaging (fMRI).
Methods: Structural and functional MRI data were obtained from 36 unilateral PT patients with single etiology and 36 matched healthy controls. FC feature of the region of interest (PCC) were characterized using a seed-based correlation method with the voxels in the whole-brain.
Results: Compared with healthy controls, patients showed significant decreased FC to the right middle temporal gyrus (MTG), right thalamus and bilateral insula. By contrast, PCC demonstrated increased functional connectivity between the precuneus, bilateral inferior parietal lobule and middle occipital gyrus. We also found correlations between the disease duration of PT and FC of PCC-right MTG ($r = -0.616$, $p < 0.001$).
Conclusions: Unilateral PT patients could have abnormal FC to the PCC bilaterally in the brain. PCC, as a highly integrated brain area, is an example of nucleus that was involved in mediation between different neural networks. It might be a modulation core between visual network and auditory network. The decreased FC of MTG to PCC may indicate a down regulation of activity between PCC and auditory associated brain cortex. Decreased FC between limbic system (bilateral AI) and PCC may reflect the emotional message control in patient group. This study facilitated understanding of the underlying neuropathological process in patients with pulsatile tinnitus.

1. Introduction

Tinnitus is defined as the sound perception without any external stimuli. It is divided into subjective and objective types. Pulsatile tinnitus (PT) is a kind of objective tinnitus, which is usually described as cardiac-synchronous annoying sounds affecting one or both side of the ears. It accounts for about 4% of all of the tinnitus populations [1].

Most of the PT patients can be diagnosed with clear etiologies. According to previous studies, focal sigmoid plate dehiscence (SPD) is one of the common etiologies of PT [1–6]. It accounts for 43%–60% populations of patients with PT [2,4,7,8]. After surgical treatment, the symptom of tinnitus could be alleviated significantly [5,9,10]. Thus, this is a kind of tinnitus with clear etiology, which is also treatable in clinic.

Apart from those anatomical abnormalities, aberrant regional neural activity observed in the non-auditory brain areas was also

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important findings in patients with PT. Those neural activities were believed as a consequence of the perception of PT sounds. One of previous studies showed positive correlations between the altered regional neural activity (reflected by the altered amplitude of low-frequency fluctuation (ALFF) value) and disease duration of PT the in the region of posterior cingulate cortex (PCC) [11]. Increased regional neural activity reflected by the increased regional homogeneity (ReHo) value was also found in this brain area [11]. Another functional connectivity study demonstrated increased long-range functional connectivity density value in the region of PCC, which was also positively correlated with disease duration [12]. The result of long-range functional connectivity density could predict the results of functional connectivity (FC) studies [13]. It indicated that the region of PCC could have more connections with other parts of the brain in patients with PT compared with normal controls. But one could not know which parts of the brain are connected with PCC by using this regional analytic method.

However, the brain always works as a whole. Different parts of the brain are widely connected with each other. Studies of regional neural activity could only reveal part of the characteristics of the brain activity. One of previous studies mainly investigated regional neural activities of brain in patients with PT. The investigations of further FC studies in patients with PT are still needed. Functional connectivity studies are highly dependent on ROI (region of interest) chosen. Those previous studies have indicated the important role of PCC in patients with PT and set a foundation for the ROI chosen for following researches. Thus, the study of the whole-brain FC pattern of PCC in patients with PT has gained traction in our research groups.

In this study, 36 unilateral (all right-sided) patients with pulsatile tinnitus and 36 healthy controls were enrolled to identify the FC characteristics between the PCC and the voxels in the whole-brain. In the light of previous investigations, we hypothesized that compared with normal controls, there is abnormal FC between PCC and other brain regions.

2. Subjects and methods

2.1. Subjects

All of the enrolled subjects were right-handed. All of the patients underwent CT Arteriography and Venography and digital subtraction angiography DSA examinations to detect the etiology of PT. They Single etiology was confirmed as SPD [14–16]. Subjects with non-pulsatile tinnitus, hearing loss, head trauma, stroke, and other neurological disease will be excluded. PT patients with other kinds of etiologies were also not included. Those patients in previous studies [11,12] were also included. As the progress of study, data of 5 more patients were collected. According to the inclusion and exclusion criteria above, 2 of the 5 subjects were also included in this study. Finally, 36 right-sided pulsatile tinnitus patients and age-, gender-matched 36 healthy controls were enrolled in this study. 26 patients were recruited from Beijing Tongren Hospital. 10 patients and all of the healthy controls were recruited from Beijing Friendship Hospital. In order to assess the severity of the disease, all of the PT patients filled Tinnitus Handicap Inventory (THI) [17,18]. Written informed consent was obtained from all subjects.

2.2. Data acquisition

Data were acquired using a General Electric (GE) 3.0 T scanner and eight-channel phased array coil. Earplugs and foam paddings were applied. The structural images were obtained using 3D-BRAVO sequence: 196 slices; 1.0 mm slice thickness, no gap; TR/TE = 8.8/3.5 ms, respectively; TI = 450 ms; flip angle = 15°; field of view = 240 × 240 mm; 256 × 256 acquisition matrix. Subjects should not think of anything during the fMRI (functional magnetic resonance imaging) acquisition with their eyes closed but not falling asleep. Functional images were acquired as follows: 28 slices; 200 time points; 4.0 mm slice thickness with 1.0 mm gap; TR/TE = 2000/35 ms, respectively; 90° flip angle; field of view = 240 × 240 mm; 64 × 64 acquisition matrix).

2.3. Data preprocessing

We performed VBM analyses to reveal the GM volume alterations in both groups. Briefly, the structural images (acquired via 3D-BRAVO sequence) were firstly segmented and then normalized to Montreal Neurological Institute (MNI) space. The gray matter (GM) results were resampled to a voxel size of 3 mm^3 and smoothed (4 mm full-width at half-maximum Gaussian kernel).

The fMRI data preprocessing were based on the Data Processing & Analysis of Brain Imaging (DPABI, details are introduced on this website: http://rfmri.org/dpabi) and Statistical Parametric Mapping (SPM) 8. 180 vols in total were used for data preprocessing (first 20 vols were discarded). Slice timing, realign, normalization, detrend and bandpass filtering (0.01 to 0.08 Hz) were performed in order. Resampling voxel size was set to 3 mm^3. Quality controls were applied to exclude un-qualified results (subjects with head motion more than 2 mm translation or 2° of rotation during the fMRI scan).

Functional connectivity analyses were based on REST (http://www.restfmri.net) software [19]. We set PCC as ROI by using the results in previous study [12]. The mean time series for ROI was computed for reference time course. Cross-correlation analyses were computed between the mean signal change in the ROI and the time series of other voxels in the whole-brain. Fisher's z-transform was performed to improve the normality of the correlation coefficients [20]. Six head motion parameters, the average BOLD signals of the white matter (WM) and cerebrospinal fluid (SCF) and the global average time courses were removed by linear regression analysis.

2.4. Statistical analysis

We used SPSS 12 software to perform the statistical analysis. Fisher's exact test and two-sample *t*-tests were used. For all of the statistical analyses, $P < 0.05$ were considered to be statistically significant.

To analyze the GM differences, we performed two-sample *t*-tests between the patient group and normal control group. For within-group analysis, a one-sample *t*-test was performed based on the individual z values of patient group and normal controls group, respectively, in order to determine the brain regions which were significantly connected to PCC in each group. For between-group analysis, two-sample *t*-tests were performed using SPM 8 software to identify brain regions which showed significant functional connectivity differences to the PCC between the two groups. Analyses were performed after regress out nuisance covariates such as GM, age and gender. Results were visualized with the REST Slice Viewer and BrainNet Viewer [19,21].

We also performed Pearson's correlative analyses among the z values of abnormal FC regions and clinical data of patients with pulsatile tinnitus (such as disease duration, THI scores; controlling for GM volume, age and gender).

3. Results

Totally, 72 subjects (36 PT patients and 36 healthy controls) were included. The demographic and clinical characteristics are showed in Table 1.