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Impairments of thalamic resting-state functional connectivity in patients with chronic tinnitus

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ABSTRACT

Purpose: The phantom sound of tinnitus is believed to arise from abnormal functional coupling between the thalamus and cerebral cortex. To explore this hypothesis, we used resting-state functional magnetic resonance imaging (fMRI) to compare the degree of thalamocortical functional connectivity in chronic tinnitus patients and controls.
Materials and methods: Resting-state fMRI scans were obtained from 31 chronic tinnitus patients and 33 well-matched healthy controls. Thalamocortical functional connectivity was characterized using a seed-based whole-brain correlation method. The resulting thalamic functional connectivity measures were correlated with other clinical data.
Results: We found decreased functional connectivity between the seed region in left thalamus and right middle temporal gyrus (MTG), right middle orbitofrontal cortex, left middle frontal gyrus, right precentral gyrus, and bilateral calcarine cortex. Decreased functional connectivity was detected between the seed in the right thalamus and the left superior temporal gyrus (STG), left amygdala, right superior frontal gyrus, left precentral gyrus, and left middle occipital gyrus. Tinnitus distress correlated negatively with thalamic functional connectivity in right MTG; tinnitus duration correlated negatively with thalamic functional connectivity in left STG. Increased functional connectivity between the bilateral thalamus and a set of regions were also observed.
Conclusions: Chronic tinnitus patients have disrupted thalamocortical functional connectivity to selected brain regions which is associated with specific tinnitus characteristics. Resting-state thalamic functional connectivity disturbances may play an important role in neuropathological features of tinnitus.

1. Introduction

Chronic subjective tinnitus, a ringing or buzzing sensation in the absence of an external sound, affects approximately 9–12% of adults over the age of 65; patients with severe, chronic tinnitus often suffer from depression, anxiety and attention deficits, all of which making tinnitus more complex than simply experiencing a phantom sound [1]. Severe tinnitus can be extremely disruptive and debilitating leading many to seek medical treatment. Even though most tinnitus patients localize tinnitus to one or both ears, a surgical section of the auditory nerve often fails to eliminate or reduce the severity of the tinnitus sound [2], suggesting that the neural generator is not in the ear but in the central nervous system (CNS). On the basis of recent electrophysiological and neuroimaging studies, it has been proposed that tinnitus is generated by abnormal neuronal activity in the CNS by a variety of mechanisms such as increased spontaneous activity, increased neural synchrony, increased burst firing, tonotopic map reorganization, and aberrant neural connectivity to structures within and/or outside the auditory pathway [3].

Magnetic resonance imaging (MRI) has been used to probe the structural and functional abnormalities likely to contribute to tinnitus. Resting-state functional MRI (fMRI) of spontaneous blood

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oxygenation level-dependent (BOLD) responses has proved to be a useful noninvasive technique to assess the underlying pathogenesis of tinnitus-induced neural dysfunction [4–6]. Recently, our group found that chronic tinnitus patients with normal hearing exhibited altered amplitude of low-frequency fluctuations (ALFF) in several brain regions, such as the middle temporal gyrus (MTG) and angular gyrus, regions previously implicated in tinnitus [4]. Other resting state studies have focused on the functional connectivity among disparate brain areas; these measurements provide insights related to the temporal synchrony or interregional cooperation between two or more spatially separate regions [5,6]. Using seed-based functional connectivity methods, negative correlations were observed between BOLD response in auditory cortex and visual, attention and control networks [5]. With independent component functional connectivity method, tinnitus was linked to disrupted resting-state functional connectivity in multiple intrinsic neural networks including the attention network and default mode network (DMN) [6].

The thalamus, a key component of the cortical-basal ganglia-thalamic circuits, is regarded as a filter for sensory input to the cortex [7]. Portions of the thalamus, especially the medial geniculate body (MGB), are believed to play a key role in the perception of tinnitus. Spontaneous activity of MGB neurons are altered by ototoxic drugs that induce tinnitus [8]. Disrupted inhibitory neurotransmission between the thalamus and other CNS regions such as the inferior colliculus and auditory cortex may also contribute to tinnitus [9]. MRI studies have identified structural and functional abnormalities in the thalamus of tinnitus patients. Increased gray matter (GM) volume was seen in the thalamus using voxel-based morphometry (VBM) [10] while diffusion tensor imaging (DTI) revealed a significant increase in fractional anisotropy in the anterior thalamic radiations of patient with noise-induced tinnitus [11]. High-field proton magnetic resonance spectroscopy (MRS) showed a downregulation of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), in the thalamus of rats with chronic tinnitus [12]. Tinnitus was associated with decreased ALFF activity bilaterally in the thalamus function [4]. Other sound-evoked fMRI showed that tinnitus was associated with reduced functional connectivity between thalamus and cortex [13–15].

Given the pivotal role that the thalamus appears to play in the pathophysiology of tinnitus, we used a seed-based approach to investigate in detail the functional connectivity of the thalamus, the region of interest (ROI), with other brain regions using cross-correlation analysis of the BOLD time signals. Using bilateral thalamus as the seed regions, we compared the functional connectivity networks in chronic tinnitus patients with well-matched control subjects. We hypothesized that resting-state thalamocortical functional connectivity in tinnitus patients would be significantly different from controls and that the disrupted thalamocortical functional connectivity would be associated with specific tinnitus characteristics such as tinnitus duration and tinnitus distress.

2. Materials and methods

2.1. Subjects

This study was approved by the Research Ethics Committee of the Affiliated Zhongda Hospital of Southeast University. Written informed consent was obtained from all subjects.

We recruited 66 subjects (all right-handed, at least 8 years of education) made up of 32 chronic tinnitus patients and 34 healthy controls; subjects were recruited through community health screening and newspaper advertisements from September 2011 to September 2013. The participants were group-matched with respect to age, sex, and education. One tinnitus patients and one healthy subject were subsequently excluded because of the exceeded limits for head motion during MR scanning. Fourteen patients reported a predominantly left-sided tinnitus, 10 a predominantly right-sided tinnitus, and 7 patients described their tinnitus as bilateral or originating within the head. The severity of tinnitus and related distress were assessed by the Iowa version of the Tinnitus Handicap Questionnaires (THQ) [16] which has three-factors, one reflecting the social, emotional, and physical consequences of tinnitus (Factor 1), a second related to hearing ability of the patient (Factor 2), and a third related to the patient's view of tinnitus (Factor 3). Hearing thresholds were determined by puretone audiometry (PTA). All the participants had normal hearing defined as hearing thresholds <25 dB HL at any of 10 measured audiometric frequencies from 250 Hz to 16 kHz. There were no significant differences in auditory thresholds between tinnitus and control groups (see Fig. 1 for average hearing thresholds). None of the participants had symptoms of depression and anxiety according to the Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) (overall scores <50, respectively) [17,18]. Participants were excluded from the present study if they suffered from hyperacusis, pulsatile tinnitus or Meniere's diseases or if they had a past history of heavy smoking, stroke, alcoholism, brain injury, Parkinson's disease, Alzheimer's disease, epilepsy, major depression, neurological or psychiatric disorders, major medical illness (e.g., anemia, thyroid dysfunction and cancer), MRI contraindications, and severe visual impairment. Table 1 summarizes the characteristics of the chronic tinnitus patients and healthy subjects.

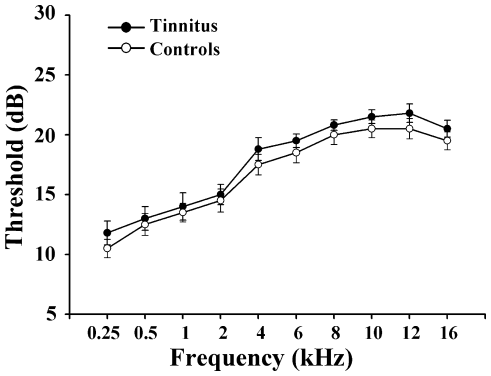

Fig. 1. Average hearing thresholds of the tinnitus and control groups. Data are presented as mean ± SEM.

Table 1
Characteristics of tinnitus patients and healthy controls.

	Tinnitus patients (n = 31)	Healthy controls (n = 33)	p Value
Age (year)	40.8 ± 13.2	45.2 ± 11.9	0.174
Gender (male:female)	18:13	18:15	0.777
Education levels (years)	11.0 ± 1.8	11.1 ± 1.6	0.802
Tinnitus duration (months)	42.6 ± 41.4	–	–
THQ total score	41.4 ± 19.7	–	–
Factor 1	44.6 ± 23.3	–	–
Social subscale	11.4 ± 6.4	–	–
Emotional subscale	16.7 ± 11.0	–	–
Physical subscale	16.5 ± 8.2	–	–
Factor 2	28.5 ± 27.0	–	–
Factor 3	55.1 ± 17.3	–	–

Data are presented as mean ± SD.
THQ, Tinnitus Handicap Questionnaire.