Hearing Research 346 (2017) 55–61

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research Paper

Abnormal regional activity and functional connectivity in resting-state brain networks associated with etiology confirmed unilateral pulsatile tinnitus in the early stage of disease

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A R T I C L E I N F O

Article history:
Received 18 May 2016
Received in revised form
3 January 2017
Accepted 5 February 2017
Available online 7 February 2017

Keywords:
Pulsatile tinnitus
Neural networks
Resting-state
fMRI

A B S T R A C T

Abnormal neural activities can be revealed by resting-state functional magnetic resonance imaging (rs-fMRI) using analyses of the regional activity and functional connectivity (FC) of the networks in the brain. This study was designed to demonstrate the functional network alterations in the patients with pulsatile tinnitus (PT). In this study, we recruited 45 patients with unilateral PT in the early stage of disease (less than 48 months of disease duration) and 45 normal controls. We used regional homogeneity (ReHo) and seed-based FC computational methods to reveal resting-state brain activity features associated with pulsatile tinnitus. Compared with healthy controls, PT patients showed regional abnormalities mainly in the left middle occipital gyrus (MOG), posterior cingulate gyrus (PCC), precuneus and right anterior insula (AI). When these regions were defined as seeds, we demonstrated widespread modification of interaction between the auditory and non-auditory networks. The auditory network was positively connected with the cognitive control network (CCN), which may associate with tinnitus related distress. Both altered regional activity and changed FC were found in the visual network. The modification of interactions of higher order networks were mainly found in the DMN, CCN and limbic networks. Functional connectivity between the left MOG and left parahippocampal gyrus could also be an index to reflect the disease duration. This study helped us gain a better understanding of the characteristics of neural network modifications in patients with pulsatile tinnitus.

1. Introduction

About 5%–15% of people in the world suffer from tinnitus (Baguley et al., 2013; Lockwood et al., 2002). Patients hear sounds without any external stimuli. Most of the tinnitus patients are non-pulsatile tinnitus (NPT) subtypes. For pulsatile tinnitus (PT) subtype, which accounts for about 4% of all tinnitus patients, the rhythm of the abnormal sounds usually coincides with the patient's heartbeat.

Unlike NPT, PT is not a consequence of abnormal neural activities in the brain. Based on previous studies (Madani and Connor, 2009; Mundada et al., 2015; Schoeff et al., 2014; Sonmez et al., 2007; Xue et al., 2012; Zhao et al., 2016), focal sigmoid plate dehiscence (SPD) due to focal bone defects in the region of the sigmoid sinus is one of the common etiologies of PT, and accounts for 43%–60% populations of patients with PT (Eisenman, 2011; Mundada et al., 2015; Schoeff et al., 2014). Sound originated from sigmoid sinus will be acquired by the inner ear through the bone defect. Pulsatile tinnitus does not originate from abnormal neural activity, but it has neural consequences. According to our previous studies (Han et al., 2015a,b, 2014; Lv et al., 2016), pulsatile tinnitus and non-pulsatile tinnitus might partially share common neuronal

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http://dx.doi.org/10.1016/j.heares.2017.02.004
0378-5955/

dysfunctions (especially in brain networks involved in emotion and attention). However, given the fact that the physiopathology of PT and NPT is different (because the former has an objective sound source, whereas the latter is originated from abnormal neuronal activity), results of studies with PT patients should be carefully discussed.

Previous studies using resting-state functional magnetic resonance imaging (rs-fMRI) investigated regional neural activities using the amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) measurements (Han et al., 2015a,b, 2014). One of the limitations of previous studies is that the relationship between regional abnormalities and its circuit synchronization, or functional connectivity (FC), with other brain areas had not been analyzed yet. Thus, a comprehensive investigation is needed. For regional synchronization feature analyses, ReHo was proved to be a robust algorithm with remarkably high test-retest reliabilities (Jiang et al., 2015; Zuo et al., 2013). It is calculated by computing Kendall's coefficient of concordance (KCC) of the time series of a voxel with its 26 neighboring voxels (Zang et al., 2004). ReHo reflects the coherence of activity of one computed voxel and other voxels around it. Higher ReHo value indicates higher coherence of those voxels, i.e. higher local synchronization. Altered ReHo values could potentially reflect local neural activity changes in patients with Parkinson's disease, Alzheimer's disease, and attention deficit hyperactivity disorder (Cao et al., 2006; Greicius et al., 2004; Wu et al., 2009). Previous studies also proved that ReHo was effective in revealing the local neural activity of patients with pulsatile tinnitus (Han et al., 2015a,b). Thus, this computational method is one of the best candidates to study local synchronization in functional neuroimaging. However, the activity of the brain consists of both local synchronization and neural network activities. Neural network activity makes it possible to integrate resources from different brain areas (Friston, 2009; Tononi et al., 1994), serving as a possible mechanism for parallel information processing (Liu et al., 1999). Seed-based FC analysis is a popular method to reveal functional relationships among spatially distant regions by using correlation analyses of the time courses of voxels in the brain (Biswal et al., 1995). By selecting regions of interest (ROI) derived from a regional neuroimaging study (such as ReHo analysis), we are able to analyze the relationship between regional neural activity and its FC with other brain areas. Thus, if we conduct a study with a combination of these two methods, we may yield results of brain network research in PT patients better than just using either method alone.

In this study, we will apply combined ReHo and seed-based FC analyses to investigate the altered regional activity and FC in resting-state brain networks associated with pulsatile tinnitus in the early stage of disease (less than 48 months since disease onset). On the basis of our previous neuroimaging studies, we hypothesized that 1) altered ReHo and connectivity would be detected within pulsatile tinnitus related brain networks, such as the default mode network (DMN) and attention network, and 2) these alterations might be correlated with some tinnitus characteristics, such as disease duration and the degree of tinnitus related distress (measured by Tinnitus Handicap Inventory (THI)).

2. Subjects and methods

2.1. Subjects

In order to reduce confounding factors in this study, 45 right sided unilateral pulsatile tinnitus patients and 45 age and gender matched healthy subjects were enrolled in our study. For PT patients, disease durations ranged from 6 to 48 months (within the early stage of disease). Thirty patients were recruited from Beijing Tongren Hospital, the remaining 15 patients and all of the healthy controls were recruited from Beijing Friendship Hospital. Patients in previous studies (Han et al., 2015a,b) were also included since the studies utilized the same inclusion and exclusion criteria. We did not include any patient with hyperacusis based on the evaluation by audiologists. Based on audiogram results, we excluded subjects with hearing loss, which was defined as more than 25 dB hearing loss at the frequencies ranging from 250 Hz to 8 kHz in puretone audiometry examination. All of the patients were assessed by the THI in order to assess the severity of tinnitus and the tinnitus related distress (Kam et al., 2009; Newman et al., 1996). Their etiology was confirmed as focal sigmoid plate dehiscence (SPD) due to the following diagnostic and therapeutic procedures: Firstly, all of them underwent CT Arteriography and Venography (CTA/V) and Digital Subtraction Angiography (DSA) examinations. According to the diagnostic criteria, the etiology of PT could be primarily confirmed as focal bone defect (single or multiple areas) in the region of sigmoid sinus, and other potential causes could be excluded (Madani and Connor, 2009). Then the structural and functional neuroimaging data were acquired from the patients in our research center using a magnetic resonance (MR) scanner. Thirdly, patients underwent sigmoid sinus wall reconstruction surgery. The etiology of the patients could be confirmed if their symptoms were significantly reduced after treatment. All of the enrolled subjects were right-handed. Data of the subjects were analyzed using Statistical Product and Service Solutions (SPSS) 12 software (SPSS, Inc., Chicago, IL). Fisher's exact test and two-sample *t*-tests were applied. We used a threshold of $p < 0.05$ to determine statistical significance. Written informed consent was obtained from all subjects.

2.2. Imaging acquisition

All of the structural and functional data were acquired on a 3.0 T MR scanner (General Electric, Milwaukee, WI, USA) using an 8-channel head coil. Foam pads and earplugs were applied to reduce noise and head motion during scanning. For the resting-state fMRI scan, subjects were instructed to avoid falling asleep, keep their eyes closed and avoid thinking about anything. Functional images were acquired using an echo-planar image (EPI) sequence (28 slices, 200 time points, slice thickness = 4.0 mm, gap = 1 mm, repetition time/echo time (TR/TE) = 2000/35 ms, matrix = 64×64, flip angle = 90°, field of view = 240×240 mm). Additionally, we obtained the structural images using a 3-dimensional spoiled gradient recalled sequence (3D-BRAVO sequence) (196 slices, slice thickness = 1.0 mm without gap, TR/TE/TI (inversion time) = 8.8/3.5/450 ms, matrix = 256×256, field of view = 240×240 mm, flip angle = 15°).

2.3. Data preprocessing

To reveal brain volume differences between the two groups, we performed a voxel-based morphometry analyses using Statistical Parametric Mapping 8 (SPM 8, http://www.fil.ion.ucl.ac.uk/spm). Briefly, the images acquired by the 3D-BRAVO sequence were segmented into three parts including gray matter, white matter and cerebrospinal fluid. Those images were normalized to the Montreal Neurological Institute (MNI) space using SPM default computational method. For the gray matter, the normalized images were resampled to have a 3 mm × 3 mm × 3 mm voxel size, and smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. To analyze the results, we first compared the results of two groups (PT group and normal controls) by using two-sample *t*-tests. The threshold was set to $p < 0.05$ (FDR corrected). Secondly, the normalized gray matter maps were used as nuisance