Progress in Neuropsychopharmacology & Biological Psychiatry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

Lateralization effects on functional connectivity of the auditory network in patients with unilateral pulsatile tinnitus as detected by functional MRI

Han Lv[a,*], Pengfei Zhao[a], Zhaohui Liu[b], Xuehuan Liu[a], Heyu Ding[a], Liheng Liu[a], Guopeng Wang[c], Jing Xie[c], Rong Zeng[c], Yuchen Chen[d], Zhenghan Yang[a], Shusheng Gong[a], Zhenchang Wang[a,*]

[a] Department of Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China
[b] Department of Radiology, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China
[c] Department of Otolaryngology Head and Neck Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China
[d] Department of Radiology, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China

A R T I C L E I N F O

Keywords:
Neural networks
Auditory network
Pulsatile tinnitus
Resting-state
fMRI

A B S T R A C T

Unilateral pulsatile tinnitus (PT) was proved to be a kind of disease with brain functional abnormalities within and beyond the auditory network (AN). However, changes in patterns of the lateralization effects of PT are yet to be established. Relationship between the AN and other brain networks in PT patients is also a scientific question need to be answered. In this study, we recruited 23 left-sided, 23 right-sided PT (LSPT, RSPT) patients and 23 normal controls (NC). We combined applied independent component analysis and seed-based functional connectivity (FC) analysis to investigate alteration feature of the FC of the AN by using resting-state functional magnetic resonance imaging (rs-fMRI). Compared with NC, LSPT patients demonstrated disconnected FC within the AN on both sides. Disrupted network integrity between AN and several brain functional networks, including executive control network, self-perceptual network and the limbic network, was also demonstrated in LSPT patient group bilaterally. In contrast, compared with NC, RSPT demonstrated decreased FC within the AN on the left side, but significant increased FC within the AN on the right side (symptomatic side). Enhanced FC between AN and executive control network, self-perceptual network and limbic network was also found mainly on the right side in patients with RSPT. Positive FC between the auditory network and the limbic network may be a reason to explain why RSPT patients are willing to be in the clinic. Briefly, LSPT exhibit disrupted network integrity in brain functional networks. But RSPT is featured by enhanced FC within AN and between networks, especially on the right (symptomatic) side. Corroboration of featured FC helps to reveal the pathophysiological changing process of the brain in patients with PT, providing imaging-based biomarker to distinguish PT from other kind of tinnitus.

1. Introduction

Tinnitus is a prevalent hearing disorder that is described as auditory perception without an external acoustic stimulus. It is affecting about 15% of all of the populations in the world (Baguley et al., 2013; Lockwood et al., 2002). Objective tinnitus, which is usually described as pulsatile tinnitus (PT), account for about 4% of all tinnitus patients (Madani and Connor, 2009; Stouffer and Tyler, 1990).

The etiology of pulsatile tinnitus was relatively clear. According to previous studies, focal sigmoid plate dehiscence (SPD) due to focal bone defects in the region of the sigmoid sinus account for 43% to 60% of etiologies (Eisenman, 2011; Mattox and Hudgins, 2008; Mundada et al., 2015; Schoeff et al., 2014). Abnormal sound caused by the disturbance of the blood in the sigmoid sinus would be acquired by the inner ear through the bone defect. Other common etiologies include but not limited to sigmoid sinus diverticulum, persistent petrosquamosal sinus, mastoid emissary vein and dural arteriovenous fistula (Dong et al., 2015; Lansley et al., 2017). Thus, unlike NPT which is usually originated from abnormal neuronal activity, PT is not presumed to have any neural origin. But it is also characterized by abnormal neural activity alterations. Results from former studies showed several similar altered brain activity features, especially in the limbic system, among patients with PT and NPT, supporting similar emotion processing towards tinnitus related distress (Chen et al., 2017; Han et al., 2015a; Husain, 2016; Lv et al., 2016a, 2017; Pattyn et al., 2016). However, given the fact that the etiology of PT and NPT is totally different, results of brain activity studies with PT patients should be carefully discussed.

One of the most important factors which should be considered in

* Corresponding author.
E-mail addresses: chrislvhan@126.com (H. Lv), cjr.wzhch@vip.163.com (Z. Wang).

http://dx.doi.org/10.1016/j.pnpbp.2017.09.020
Received 17 July 2017; Received in revised form 15 September 2017; Accepted 19 September 2017

studies is the perceived lateralization of tinnitus. It was proved that auditory sensory input could lead to elevated brain spontaneous activity (Barascud et al., 2016; Dykstra et al., 2016; Hurschler et al., 2015; Marinovic et al., 2015; Mayer et al., 2017; Yu et al., 2015). Conventionally, the auditory network (AN) was considered as the most affected brain network in the condition of aberrant objective sound perception (Crippa et al., 2010; Guinchard et al., 2016). Limited number of previous studies had shown different alteration features of the AN functional connectivity (FC) between left- and right-sided unilateral non-pulsatile tinnitus (NPT) patients (Lanting et al., 2008, 2014; Melcher et al., 2009). According to these studies, lateralization of sound perception should be considered as a confounding factor in studies of spontaneous brain activity. However, those results from researches on NPT may not be applicable to that of PT.

Research on spontaneous brain activity in patients with PT has been an important issue in tinnitus research field. For studies on PT patients, since the lateralization effects on the AN remain unclear, those previous studies only enrolled right-sided unilateral PT patients (Han et al., 2015a,b; Lv et al., 2016a,b). Most of previous studies excluded left-sided PT patients in order to minimize possible confounding factors (different side of PT) in neuroimaging studies. Thus, the lateralization effects on the AN caused by PT remains a major focus and need to be clarified. In order to further improve the neuroscientific research on PT, it is essential to investigate the differences of brain network activity (especially the AN) between the left- and right-sided PT patients. Relationship between the AN and other brain networks in PT patients is also a scientific question need to be answered.

Resting-state functional magnetic resonance imaging (fMRI) had been proved to be an effective tool to investigate neural activity changes in tinnitus patients (Adjamian et al., 2014; Han et al., 2015a,b, 2014; Husain, 2016; Husain and Schmidt, 2014; Lv et al., 2016a; Pattyn et al., 2016). It could identify brain networks according to the special distribution (Shirer et al., 2012). Independent component analysis (ICA) is a customized automated component selection approach to separate resting-state networks (RSNs) with high test-retest reliability (Zuo et al., 2010). It is an effective method to explore changes of AN in tinnitus patients. Furthermore, seed-based functional connectivity analysis could measure coherent neuronal activity between region of interest (ROI) and brain areas by analyzing the BOLD (blood-oxygen-level dependent) time series between voxels (Zang et al., 2015). Highly degree of synchrony of the BOLD time series between voxels suggests coherence of neural processes in those brain areas underlying same condition, i.e. functional connectivity (Biswal et al., 1995). When the AN was set as seeds, seed-based functional connectivity analysis could be conducted to investigate the relationship between the AN and other RSNs. In this way, the changes of the AN in PT patients could be fully explored by combination of these two methods, better than applying one single method alone.

In this study, we specifically focus on neural activity of the AN in PT patients. Forty-six patients with unilateral PT (23 left-sided and 23 right-sided) and age-, gender-matched 23 normal controls will be enrolled. ICA method will be applied to analyze the changes of activity in auditory cortex, followed by seed-based functional connectivity analysis to explore the relationship between the auditory cortex and other RSNs. The hypothesis is that (1) the activity of auditory network is different between left- and right-sided unilateral PT patients. (2) The imbalance features among the auditory cortex and other RSNs is different between left- and right-sided unilateral PT patient groups.

2. Subjects and methods

2.1. Subjects

This study was approved by the medical research ethics committees. Written informed consent was obtained from all subjects prior to enrollment. All patients and healthy volunteers were recruited at the Beijing Friendship Hospital, Capital Medical University, Beijing, China.

In this study, 46 PT patients were enrolled and then divided into 2 groups according to the side of tinnitus: 23 patients were in left-sided PT (LSPT) group, 23 patients were in right-sided PT (RSPT) group. All of the PT patients were clearly diagnosed based on their typical symptom and CTA/V and DSA examinations (Krishnan et al., 2006). Their etiology was confirmed as focal sigmoid plate dehiscence (SPD) according to its typical findings in radiological examinations (Zhao et al., 2016). Tinnitus patients were also asked to fill the Tinnitus Handicap Inventory (THI) in order to assess the severity of tinnitus. A normal control group including 23 healthy volunteers was also enrolled. All of the subjects were right-handed. Each group of subjects was age/gender matched. Subjects with non-pulsatile tinnitus, hyperacusis (evaluated by audiologists), hearing loss (hearing thresholds > 25 dB HL at frequencies of 0.250, 0.500, 1, 2, 3, 4, 6, and 8 kHz determined by puretone audiometry (PTA) examination), tumor, head injury, stroke and other neurological disease should be excluded in this study.

2.2. Data acquisition

GE (General Electric) 3.0 Tesla scanner and an eight-channel phased array coil were used to collect MR data. Functional magnetic resonance imaging (fMRI) data were obtained by using the following parameters (EPI (echo planar imaging) sequence): 28 slices with 4 mm slice thickness and 1 mm gap; 200 time points; TR = 2000 ms; TE = 35 mm; flip angle = 90°; matrix = 64 × 64; field of view (FOV) = 240 × 240 mm. Subjects were asked not to think of anything during fMRI data acquisition. They were also instructed not to fall asleep but keep eyes closed. A simple questionnaire also indicated that all of the subjects did not fall asleep during scan. Structural images were obtained by using the following parameters: 196 slices with 1 mm thickness (no gap); TR/TE = 8.8/3.5 ms; TI = 450 ms; field of view = 24 × 24 cm; matrix = 256 × 256; flip angle = 15°.

2.3. Data preprocessing

Data were preprocessed by using the Data Processing & Analysis of Brain Imaging (DPABI, http://rfmri.org/dpabi) toolbox (Yan et al., 2016) and Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing of functional data included discarded the first 20 functional volumes (allow for T1 equilibration effects), slice-timing, head motion correction, spatial normalization into the SPM8 Montreal Neurological Institute (MNI) template. Data were resampled to 3 mm × 3 mm × 3 mm voxels, and smoothed using 4 mm full width at a half maximum (FWHM) Gaussian kernel. None of the 69 subjects were excluded according to the exclusion criterion (> 1.5 degrees of head rotation or > 1.5 mm displacement) in the head motion correction step.

2.4. Group-level independent component analysis

A group-level ICA was performed using the MICA toolbox (http://www.nitrc.org/projects/cogicat/). MICA toolbox was proved to be able to generate more reliable and consistent results compared to previous group level ICA methods (Zhang et al., 2010). All subjects' preprocessed fMRI data, including 23 LSPT, 23 RSPT and 23 healthy controls, were fed into the MICA in order to make the results comparable between subgroups (Liang et al., 2015; Zhang et al., 2010). The analytic procedure of MICA was described in previous studies (Liang et al., 2015; Reineberg et al., 2015; Zhang et al., 2010): ICA decomposition was performed using the Infomax algorithm (Bell and Sejnowski, 1995) following repeated 100 times analysis in order to generate reliable and accurate results (Zhang et al., 2010). During the analysis, total neural network number was set to 30 according to previous researches (Liang et al., 2015; Reineberg et al., 2015). Then the generated neural networks were back-reconstructed to each subject. Finally, a Fisher's z-