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Research paper

Disrupted functional brain connectome in unilateral sudden sensorineural hearing loss

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ABSTRACT

Sudden sensorineural hearing loss (SSNHL) is generally defined as sensorineural hearing loss of 30 dB or greater over at least three contiguous audiometric frequencies and within a three-day period. This hearing loss is usually unilateral and can be associated with tinnitus and vertigo. The pathogenesis of unilateral sudden sensorineural hearing loss is still unknown, and the alterations in the functional connectivity are suspected to involve one possible pathogenesis. Despite scarce findings with respect to alterations in brain functional networks in unilateral sudden sensorineural hearing loss, the alterations of the whole brain functional connectome and whether these alterations were already in existence in the acute period remains unknown. The aim of this study was to investigate the alterations of brain functional connectome in two large samples of unilateral sudden sensorineural hearing loss patients and to investigate the correlation between unilateral sudden sensorineural hearing loss characteristics and changes in the functional network properties. Pure tone audiometry was performed to assess hearing ability. Abnormal changes in the peripheral auditory system were examined using conventional magnetic resonance imaging. The graph theoretical network analysis method was used to detect brain connectome alterations in unilateral sudden sensorineural hearing loss. Compared with the control groups, both groups of unilateral SSNHL patients exhibited a significantly increased clustering coefficient, global efficiency, and local efficiency but a significantly decreased characteristic path length. In addition, the primary increased nodal strength (e.g., nodal betweenness, hubs) was observed in several regions primarily, including the limbic and paralimbic systems, and in the auditory network brain areas. These findings suggest that the alteration of network organization already exists in unilateral sudden sensorineural hearing loss patients within the acute period and that the functional connectome of unilateral SSNHL patients is characterized by a shift toward small-worldization. Additionally, we hope that these findings will help to elucidate unilateral SSNHL through a new research perspective and provide insight for the potential pathophysiology of unilateral SSNHL.

1. Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as a sensorineural hypoacusis of at least 30 dB over 3 consecutive speech frequencies within 3 days (Schreiber et al., 2010). SSNHL is typically unilateral and can be associated with tinnitus and vertigo (Schreiber et al., 2010). The incidence of SSNHL has been reported to range from 3.9 to 27.5 per 100,000 people per year and is considered to be an otologic emergency (Chen et al., 2015; Nosrati-

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Zarenoe et al., 2010). Population studies of SSNHL show that the hearing loss of SSNHL is typically unilateral, has no side preference, and fewer than 5% of SSNHL patients report bilateral involvement; patients are an average of 50–60 years of age, and there is no significant sex difference (Oh et al., 2007; Schreiber et al., 2010). Although some pathophysiological mechanisms have been proposed, the precise cause of SSNHL is still unknown. What is worse, it has been reported that the hearing function of SSNHL patients will not improve even after high quality appropriate therapy (Kuhn et al., 2011), which may result in long-term negative effects for these patients lasting several years or for life.

Resting-state functional magnetic resonance imaging (fMRI) is a widely used, reliable, non-invasive method for exploring the intrinsic functional organization of the human brain. Previous functional MRI studies have revealed that SSNHL is related to the alterations in several specific functional networks, such as the default mode networks (Li et al., 2015; Wang et al., 2014b; Zhang et al., 2015b), functional networks of auditory (Suzuki et al., 2002) and executive control (Tibbetts et al., 2011), and functional networks of recognition and language networks (Liu et al., 2015a). For example, using the left/right primary auditory cortex (AI) as the region of interest (ROI), Liu et al. (2015a) evaluated the whole brain functional connectivity changes related to the auditory cortex in patients with left-sided sensorineural hearing loss and found the patient group had significant functional connectivity changes in the auditory system, recognition network, visual cortex, and language network. Zhang et al. (2015b) also found long-term unilateral SSNHL contributes to changes in the DMN, and these changes might affect cognitive abilities in patients. Additionally, Wang et al. (2014b) uncovered that unilateral hearing input damage not only alters the activity of the sensory areas but also reshapes the regional and circuit functional organization of the cognitive control network. Despite the local functional abnormalities that have been found in SSNHL, it is still unclear what alterations occur in the topological properties of brain networks (i.e., the connectome), which could be characterized using graph theoretical analysis (Fornito et al., 2015; Sporns, 2013). Graph theory offers a powerful framework to quantify topological properties of a complex network, regardless of the global or nodal properties (Bullmore and Sporns, 2009). Whole brain network analysis has been widely used to explore the alterations of the topological properties of brain networks, such as in Alzheimer's disease (Wang et al., 2013), schizophrenia (Liu et al., 2008), major depressive disorder (Luo et al., 2015b), temporal lobe epilepsy (Bernhardt et al., 2011; Wang et al., 2014a), posttraumatic stress disorder (Lei et al., 2015), and migraine suffers (Liu et al., 2015b). However, there is still a lack of systematic research examining whole brain functional or structural networks in SSNHL patients, which could aid in uncovering relative topological property alterations.

The aims of this study were the following: (1) to investigate the SSNHL-related alterations in the topological organization of intrinsic functional network properties in unilateral SSNHL patients within the acute period using the graph theoretical network analysis method and (2) to determine if hearing impairment is associated with functional network property alteration in unilateral SSNHL patients. To the best of our knowledge, no previous studies have examined the SSNHL-related alterations in the topological properties of the whole brain functional networks and no studies have uncovered the correlation between these altered topological properties and a clinical index, such as disease duration, hearing level or tinnitus handicap inventory scores, in unilateral SSNHL patients. We hope our results will complement previous studies and help to characterize unilateral SSNHL pathophysiology.

2. Materials and methods

2.1. Subjects

This study included data collected from two groups (left and right side unilateral SSNHL) of patients and a healthy control group with, in total, 170 right-handed subjects (Oldfield, 1971). Eighty-five patients were recruited at the outpatient otorhinolaryngology department of Union Hospital, which is the tertiary class A teaching hospital of Tongji Medical College, Huazhong University of Science and Technology, and 85 age-matched right-handed healthy adults were recruited from the radiology department of Union hospital from 2013 to 2015. All subjects' racial category was Chinese Han. The left side unilateral SSNHL (lSSNHL) group had 41 (20 males) patients, and the right side unilateral SSNHL (rSSNHL) group had 44 (24 males) patients. The healthy control (HC) groups consisted of 85 (40 males) subjects. Pure-tone audiometry was performed with a clinical audiometer using seven different octave frequencies (0.125 0.25, 0.5, 1, 2, 4 and 8 kHz) to measure the pure tone average (PTA) and to determine the hearing level. All of the unilateral SSNHL patients were included if the PTA hearing threshold at the octave frequencies 0.5, 1 and 2 kHz was greater than 30 dB in the ear having the unilateral hearing loss. All healthy control group subjects had normal hearing (defined as hearing loss of no more than 25 dB at any of the 7 frequencies). Additionally, individuals with noisiform or pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, psychiatric illnesses, head injury, neurosurgery, neurological disorders, such as brain tumors, and individuals being treated for mental disorders were excluded from the study to obtain a more homogeneous sample (Schneider et al., 2009). These criterions were also used in our previous study (Fan et al., 2015).

This study was approved by the Tongji Medical College of Huazhong University of Science and Technology medical ethics committee. All subjects were informed about the purpose of the study before giving their written consents in accordance with Chinese legislation.

2.2. Data acquisition

All patients were scanned before any drug treatment. The imaging experiments were performed using a 3 T MRI system (Siemens Trio Tim, Erlangen, Germany) that was equipped with a 12-channel head coil. Patients were asked to lay still supine, and their ears covered with headphones to remove noise during scanning. A foam cushion was used to fix the head to reduce motion artifacts produced by head movements. All participants were instructed not to focus their thoughts on anything in particular and were remained to be still in the scanner, to keep their eyes closed and to not fall asleep during the MR acquisition. After the scan, a technician verified with each participant whether these instructions were followed, and all subjects in this study complied with these instructions (Zhang et al., 2015a). Anatomical images were acquired using a 3-dimensional high-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence. The sequence parameters were the following: repetition time (TR) = 2250 ms, echo time (TE) = 2.26 ms, inversion time (TI) = 900 ms, flip-angle = 9°, voxel size = 1.0 × 1.0 × 1.0 mm^3, field of view (FOV) = 256 mm × 256 mm, slice thickness = 1.00 mm and 176 sagittal slices covering the whole brain. Based on the geometry of the anatomical images, 240 functional images were acquired with a gradient echo type echo planar imaging (EPI) sequence (TR = 2000 ms; TE = 30 ms; flip-angle = 90°; voxel size = 3.1 × 3.1 × 3.5 mm^3; and FOV = 200 mm × 200 mm). A t2-spc-rst-tra-iso (T2 weighted) sequence was also acquired to evaluate the status of the peripheral auditory system. The t2-spc-rst-