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Research paper

Tinnitus-related dissociation between cortical and subcortical neural activity in humans with mild to moderate sensorineural hearing loss

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ABSTRACT

Tinnitus is a phantom sound percept that is strongly associated with peripheral hearing loss. However, only a fraction of hearing-impaired subjects develops tinnitus. This may be based on differences in the function of the brain between those subjects that develop tinnitus and those that do not. In this study, cortical and sub-cortical sound-evoked brain responses in 34 hearing-impaired chronic tinnitus patients and 19 hearing level-matched controls were studied using 3-T functional magnetic resonance imaging (fMRI). Auditory stimuli were presented to either the left or the right ear at levels of 30–90 dB SPL. We extracted neural activation as a function of sound intensity in eight auditory regions (left and right auditory cortices, medial geniculate bodies, inferior colliculi and cochlear nuclei), the cerebellum and a cinguloparietal task-positive region. The activation correlated positively with the stimulus intensity, and negatively with the hearing threshold. We found no differences between both groups in terms of the magnitude and lateralization of the sound-evoked responses, except for the left medial geniculate body and right cochlear nucleus where activation levels were elevated in the tinnitus subjects. We observed significantly reduced functional connectivity between the inferior colliculi and the auditory cortices in tinnitus patients compared to controls. Our results indicate a failure of thalamic gating in the development of tinnitus.

1. Introduction

Tinnitus is a poorly understood hearing disorder characterized by the presence of an auditory percept in the absence of an external stimulus and is typically associated with hearing loss. It is a common disorder with prevalence estimates ranging from 7 to 20% (Hoffman and Reed, 2004). Approximately 40% of the tinnitus patients also suffer from hyperacusis, a diminished tolerance to ordinary environmental sounds (Baguley, 2003). Most patients with chronic tinnitus are continuously aware of the tinnitus percept, but are able to cope effectively with the disturbance. However, for some patients the tinnitus is more than a trivial annoyance resulting in feelings of desperation and even suicidal thoughts (Dobie, 2003).

An important role in the generation of tinnitus is currently attributed to mechanisms in the central auditory system. Animal studies have shown that manipulations that are known to be sources of tinnitus in humans (e.g. noise trauma) cause increased spontaneous neural activity or changes in neural synchrony in auditory brain structures (Noreña and Eggermont, 2003; Seki and Eggermont, 2003). A number of blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) studies have investigated the neural correlates of tinnitus in humans (for a review, see Lanting et al., 2009; Adjamian et al., 2009). BOLD fMRI is unable to register sustained increases in spontaneous activity. Consequently, these fMRI studies applied sound stimuli to probe abnormal sound processing in the brain of tinnitus patients. Measuring changes in hemodynamics as a response to sound in tinnitus sufferers revealed increased activation in the inferior

Abbreviations: AC, auditory cortex; ANCOVA, analysis of covariance; BA, Brodmann area; BOLD, blood oxygenation level dependent; CER, cerebellum; CN, cochlear nucleus; DMN, default mode network; fMRI, functional magnetic resonance imaging; EPI, echo planar imaging; FWE, family wise error; HI, hearing-impaired; HI + T, hearing-impaired and tinnitus; IC, inferior colliculus; L, left; MGB, medial geniculate body; MNI, Montreal neurological institute; PTA, pure-tone average; R, right; ROI, region of interest; TPN, task-positive network; THI, tinnitus handicap inventory

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colliculus compared to controls (Melcher et al., 2000, 2009; Lanting et al., 2008), although this may have been associated with hyperacusis rather than with tinnitus (Gu et al., 2010). In contrast to activation of the brainstem, elevated sound-evoked auditory cortex activation can be attributed to tinnitus (Gu et al., 2010). These studies all show neural correlates of tinnitus in clinically normal-hearing subjects.

The majority of tinnitus patients, however, has a significant hearing loss. As was shown in numerous animal studies, hearing loss is associated with adaptation in the central auditory system, which is likely to be related to tinnitus (for a review, see Eggermont, 2001). Since tinnitus does not develop in all hearing-impaired individuals, it must be assumed that these adaptations are different between those that develop tinnitus and those that do not. So far, differences in adaptations are supported by two models on the pathophysiology of tinnitus: one based on abnormal thalamic gating (Rauschecker et al., 2010; Zhang, 2013) and another based on thalamic hypo-activity (Llinás et al., 1999).

The aim of this explorative study was to investigate tinnitus-related abnormalities in sound-evoked hemodynamic responses in subjects with mild to moderate sensorineural hearing loss. Two relatively large subject groups were enrolled: a hearing-impaired group without tinnitus and a hearing-impaired group suffering from tinnitus. Both groups were carefully matched with respect to age and hearing loss, which allows us to identify the effects that are specific to tinnitus. In line with previous studies (Melcher et al., 2000, 2009; Lanting et al., 2008; Gu et al., 2010), we used BOLD fMRI to measure sound-evoked responses throughout the brain, and primarily focused on auditory regions since we used auditory stimuli. Differences between both groups were investigated with respect to the magnitude of brain responses, their lateralization, and the functional connectivity patterns between brain regions.

2. Materials and methods

2.1. Subjects

This study included data collected from two groups of patients. The patients were recruited at the University Medical Center Groningen and via hearing aid dispensers in Groningen, the Netherlands. The first group comprised 19 hearing-impaired subjects (HI group). The second group comprised 34 subjects with a hearing impairment suffering from tinnitus (HI + T group). From the same subjects, the T1 anatomical scans of 16 HI and 31 HI + T subjects have also been included in a previous morphological study (Boyen et al., 2013). Pure-tone audiometry was performed with a clinical audiometer using six different octave frequencies (0.25, 0.5, 1, 2, 4 and 8 kHz). For all subjects, the pure-tone average (PTA) hearing threshold at the octave frequencies of 1, 2 and 4 kHz satisfied $30 \leq \text{PTA} \leq 60$ dB in both ears.

To assess handedness, a translated version of the Edinburgh Inventory (Oldfield, 1971) was completed by all subjects. In the tinnitus subjects only, tinnitus handicap was assessed by a Dutch translation of the Tinnitus Handicap Inventory (THI), a self-reported tinnitus handicap questionnaire (Newman et al., 1996). In order to assess the presence of hyperacusis, a translated version of the Hyperacusis Questionnaire (HQ; Khalfa et al., 2002) was administered to all participating subjects. Furthermore, the subjectively perceived tinnitus loudness was recorded on a numeric rating scale from zero (tinnitus not audible at the time) to ten (tinnitus sounds as loud as imaginable) before and immediately after the scanning session. None of the subjects had any major medical, neurological or psychiatric history.

This study was approved by the local medical ethics committee. All subjects were informed about the purpose of the study before giving their written consent in accordance with Dutch legislation.

2.2. Data acquisition

The imaging experiments were performed using a 3-T MRI system (Philips Intera, Philips Medical Systems, Best, The Netherlands) which was equipped with an eight-channel phased-array (SENSE) head coil. The functional scans consisted of 2200-ms single-shot T_2^*-sensitive echo planar imaging (EPI) sequences with 41 3-mm thick slices (TR 10 s; TE 22 ms; flip-angle 80°; voxel size $1.75 \times 1.95 \times 3$ mm^3; field of view $224 \times 224 \times 123$ mm^3) and were acquired using a near-coronal orientation, aligned to the brainstem when viewed on a midsagittal cross-section. Each image volume enclosed left and right cochlear nuclei (CN), inferior colliculi (IC), medial geniculate bodies (MGB) and auditory cortices (AC). The influence of acoustic scanner noise was reduced using a sparse sampling strategy (Hall et al., 1999; Langers et al., 2005a). Auditory stimuli were presented during a 7.8-s gap of scanner silence between two successive acquisitions. For each subject, three runs of 73 acquisitions were performed. Additional start-up scans that were included to achieve magnetization equilibrium and to trigger the start of the stimulus delivery were excluded from analysis. In addition, a 3-dimensional high-resolution T_1-weighted fast-field echo scan (TR 9 ms; TE 3.50 ms; flip-angle 8°; voxel size $1 \times 1 \times 1$ mm^3; field of view $256 \times 256 \times 170$ mm^3) was acquired with the same orientation as the functional scans to serve as an anatomical reference.

2.3. Acoustic stimulation and scanning paradigm

Auditory stimuli were delivered by an MR-compatible electrodynamic system (MR Confon GmbH, Magdeburg, Germany; Baumgart et al., 1998), connected to a PC setup equipped with a digital-to-analog converter controlled by Labview 6.1 (National Instruments 6052E, National Instruments Corporation, Austin, TX, USA). The stimuli consisted of dynamic ripples (Langers et al., 2003). The spectrum of a dynamic ripple is based on pink noise, but contains temporal and spectral modulations. The stimuli comprised frequency components between 125 and 8000 Hz, with a spectral modulation density of one cycle per octave, a temporal modulation frequency of two cycles per second, and a modulation amplitude of 80%. These stimuli were chosen for their potency to induce robust sound-evoked responses in the auditory pathway (Langers et al., 2003; Lanting et al., 2008, 2010).

During the gaps of scanner silence between two successive acquisitions, auditory stimuli were presented to the left (L) or the right (R) ear at either 30, 50, 70 or 90 dB SPL (L_{30}, L_{50}, L_{70}, L_{90}; R_{30}, R_{50}, R_{70} or R_{90}). In addition, a silent baseline condition was included. The stimuli were presented in a fixed pseudo-random order in each functional run. Per run, the silent condition was presented nine times and all the stimulus conditions were presented eight times each. During the functional scans, the subjects were instructed to register whether they perceived an audible stimulus using a button box: whenever they perceived an audible stimulus in the left or right ear, they pressed one of two corresponding buttons with their right thumb. This task was imposed in order to promote and monitor that the subject paid attention to the presented sound stimuli.

2.4. Data processing and linear regression analysis

The images were analyzed using SPM8 (Functional Imaging Laboratory, The Wellcome Department of Imaging Neuroscience,