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ASYMMETRY IN PRIMARY AUDITORY CORTEX ACTIVITY IN TINNITUS PATIENTS AND CONTROLS

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Abstract—Tinnitus is a bothersome phantom sound percept and its neural correlates are not yet disentangled. Previously published papers, using [^{18}F]-fluoro-deoxyglucose positron emission tomography (FDG-PET), have suggested an increased metabolism in the left primary auditory cortex in tinnitus patients. This unilateral hyperactivity has been used as a target in localized treatments such as transcranial magnetic stimulation. The purpose of the current study was to test whether left-sided hyperactivity in the auditory cortex is specific to tinnitus or is a general characteristic of the auditory system unrelated to tinnitus. Therefore, FDG-PET was used to measure brain metabolism in 20 tinnitus patients and to compare their results to those in 19 control subjects without tinnitus. In contrast to our expectation, there was no hyperactivity associated with tinnitus. Nevertheless, the activity in the left primary auditory cortex was higher than in the right primary auditory cortex, but this asymmetry was present in both tinnitus patients and control subjects. In contrast, the lateralization in secondary auditory cortex was opposite, with higher activation in the right hemisphere. These data show that hemisphere asymmetries in the metabolic resting activity of the auditory cortex are present, but these are not associated with tinnitus and are a normal characteristic of the normal brain.

Key words: tinnitus, auditory cortex, positron emission tomography (PET), laterality index, hemispheric dominance.

INTRODUCTION

Tinnitus is a phantom sound percept in the absence of an external sound-generating device. Approximately 10–15% of the general population suffers from tinnitus, and 4–5% is severely affected by it (Axelsson and Ringdahl, 1989; Heller, 2003). The perception of tinnitus causes problems with concentration, falling asleep, anxiety and feelings of depression. Hence, tinnitus can have severe negative implications on the perceived quality of life.

There are at least two forms of tinnitus, classified by their characteristics and etiology (Lockwood et al., 2002; Heller, 2003; Møller, 2006). The first form is objective tinnitus, which can be heard by an external observer. It is a very rare form of tinnitus that may be caused by e.g. a vascular or muscular condition (Perry and Gantz, 2000). The second form of tinnitus is subjective tinnitus. In contrast to objective tinnitus, subjective tinnitus can only be perceived by the patient. It cannot be heard by an external observer and no acoustic sound source can be identified. Consequently, subjective tinnitus is a phantom percept. In the current paper, we focus solely on subjective tinnitus, which will be referred to simply as 'tinnitus'.

Subjective tinnitus is believed to be the result of plastic changes and reorganization processes in the auditory pathway and brain structures, most likely caused by the deprivation of input (Møller, 2006). This deprivation of input may result from peripheral hearing loss. In animals studies it has been shown that peripheral hearing loss leads to abnormal spontaneous activity in auditory brain areas. For example, noise-induced hearing loss leads to an increase of spontaneous neural activity in the primary auditory cortex of cats (Norena and Eggermont, 2003), and in the dorsal cochlear nucleus of hamsters (Kaltenbach et al., 2004). It is conceivable that an abnormal increase of spontaneous activity in the auditory system is then perceived as tinnitus.

Several attempts have been made to record this change of activity in the central nervous system that is associated with tinnitus in humans. In their extensive review Lanting et al. (2009) have described the use of different imaging techniques for the registration of this activity with the relevant advantages and disadvantages of the different techniques that are currently available. Traditionally, positron emission tomography (PET) has

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Abbreviations: BAs, Brodmann areas; FDG-PET, [^{18}F]-fluoro-deoxyglucose positron emission tomography; HL, hearing level; IC, inferior colliculus; MFG, middle frontal gyrus; MNI, montreal neurological institute; MRI, magnetic resonance imaging; PAC, primary auditory cortex; PET, positron emission tomography; PTA, pure-tone average; ROI, region-of-interest; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; STGa, superior temporal gyrus, anterior division; THI, tinnitus handicap inventory; WFU, Wake Forest University.

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been used to measure physiological baseline metabolic activity, for example in the diagnosis of oncologic pathology. In the case of tinnitus, it may be expected that if tinnitus corresponds to enhanced neural activity, this activity would correspond to an enhanced metabolic rate.

Until now eight studies with [^{18}F]-fluoro-deoxyglucose positron emission tomography (FDG-PET)-scanning in human tinnitus patients have been performed (Arnold et al., 1996; Wang et al., 2001; Langguth et al., 2003, 2006a; Eichhammer et al., 2003; Smith et al., 2007; Mennemeier et al., 2011; Schecklmann et al., 2013). Arnold et al. (1996) were the first to measure metabolic brain activity in 11 tinnitus patients compared to a control group. They found a significant higher metabolic activity in the primary auditory cortex (PAC), mostly on the left side, versus the other side. The majority of the other studies also showed a higher activity in the left auditory cortex, although in some patients the highest level of metabolism was present on the right side (Arnold et al., 1996; Langguth et al., 2006a; Smith et al., 2007). Recently a large study with 91 tinnitus patients also showed an increase of activity in the left auditory cortex versus the right auditory cortex, but this was not compared with a control group (Schecklmann et al., 2013). Considering that the higher metabolic rate is an indication for increased brain activity, the perception of tinnitus could thus be localized in the left PAC. Unfortunately, all studies mentioned above, except Arnold et al. (1996) and Wang et al. (2001) did not use a control group to compare the found lateralization.

The notion of hyperactivity in the left PAC of tinnitus patients, has motivated targeted treatment protocols of repetitive transcranial magnetic stimulation (rTMS) (Plewnia et al., 2003). This experimental treatment modality offers a noninvasive method for altering excitability of the brain (Kleinjung et al., 2005). Langguth et al. (2003) presented a patient with a 4-week reduction in tinnitus sensation after rTMS over the left PAC. Other studies with left-sided rTMS also demonstrated a significant but transient reduction in tinnitus sensation (Eichhammer et al., 2003; Kleinjung et al., 2005; Langguth et al., 2006a; Rossi et al., 2007; Smith et al., 2007; Khedr et al., 2008; Mennemeier et al., 2011). Thus although the previously reported asymmetry in the auditory cortex was not always compared to control subjects, several experimental treatments were aimed at reducing this hyperactivity.

The purpose of the current study was to verify whether left-sided resting-state hyperactivity as recorded by FDG-PET is specifically related to the presence of tinnitus. Thus, we set out to study resting-state metabolic activity by FDG-PET in subjects with bilateral tinnitus, and to compare their results to those of control subjects without tinnitus. In our analysis, we specifically focused on asymmetries between the left and right auditory cortices in order to allow for a straightforward comparison to earlier studies.

EXPERIMENTAL PROCEDURES

Subjects

Patients were recruited from our tertiary referral outpatient clinic. We included 20 right-handed chronic tinnitus patients (50% male, mean age 51.0 years, standard deviation (SD) 10.0). The mean duration of their tinnitus was 10.5 years (range 1–20 years). Tinnitus was bilateral and constantly present in all cases. Five patients reported an etiology of their tinnitus (loud noise in three, an ear infection in two cases). The tinnitus pitch was assessed by matching it to that of an external tone or 1/3-octave noise band. The median tinnitus frequency was 4000 Hz, ranging from 500 to 11,200 Hz. The tinnitus severity was assessed by the tinnitus handicap inventory (THI; Newman et al., 1996). Mean THI of our subjects was 37.9 (SD 18.5, range 12–86). Patients with any major medical, neurological or psychiatric diagnoses, specific epilepsy, severe head injury or previous cranial neurosurgery were excluded. Tinnitus patients who used drugs or medications that reduced cortical excitation such as anticonvulsants, benzodiazepines or other sedatives (e.g. antihistamines) were also excluded.

For the control group we included 19 healthy subjects, all right handed (47% male, mean age 50.8 years, SD 9.5). Exclusion criteria were equal to those in the tinnitus patients. All selected subjects were right-handed; this was confirmed with the Edinburgh handedness inventory (Oldfield, 1971).

All subjects were examined by an audiologist with a pure-tone audiometry. The pure-tone average (PTA) for the hearing loss was defined as the average hearing threshold at 1, 2 and 4 kHz. The study was approved by the local Medical Ethics committee. We obtained written informed consent from all participants, in accordance with the Declaration of Helsinki (2004). The study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

PET scanning protocol

All the scans were performed dynamically on a Siemens ECAT HR+ PET scanner. After arrival of the tinnitus patient at the scanning room, he or she had to rate the loudness and burden of their tinnitus at that moment on a scale from 0 to 100 (with 0 being very weak and 100 being very strong). To reduce auditory input, subjects used bilateral earplugs and earmuffs during the experiment. Subjects were placed in the scanner and a lead shield was placed on the subject's chest to reduce radiation artifacts originating from the chest or body of the subjects.

After these preparations ~200 MBq of FDG was injected. The subjects were asked to lie quiet in the scanner for 30 min in a quiet and dark surrounding. After this 30-min uptake time the scanning protocol started, in which the subjects remained lying quietly. The scanning protocol was divided in five blocks of 4 min without interruption.