We studied the correspondence between brain activity and tinnitus in subjects with gaze-modulated tinnitus. These subjects are able to modulate their tinnitus by peripheral gaze of the eyes. This is a rare form of tinnitus that primarily occurs in subjects that underwent acoustic schwannoma surgery. The voluntary control of the tinnitus allows for a controlled experiment to study the perceptual characteristics of tinnitus and the corresponding brain activity as assessed by functional MRI. Eighteen subjects with gaze-modulated tinnitus participated in the study. The effect of gaze on tinnitus was diverse. Most commonly, the largest effect on tinnitus was observed for horizontal gaze towards the surgery side. When the loudness of tinnitus changed, it was usually an increase. In addition, changes of the pitch and apparent bandwidth of the tinnitus were reported. Peripheral gaze corresponded to increase of activity in the cochlear nucleus and inferior colliculus, a decrease of activity in the medial geniculate body, and a reduction of deactivation in the auditory cortex. The inhibition of the medial geniculate body in the thalamus contrasts with the excitation that is typically observed in response to external sound stimuli. It suggests that abnormal functioning of the thalamus plays a role in tinnitus.
INTRODUCTION

Tinnitus is a common condition in which patients hear a sound that does not correspond to an external sound source. In some patients, an acoustic source, such as blood flow or a muscle spasm, may account for the sound. However, in the vast majority of patients, there is no acoustic source inside or outside the body. Then, the tinnitus is a phantom percept, solely based on neural activity. It has been hypothesized that many cases of tinnitus originate from brain plasticity in response to peripheral hearing loss. Noise-induced hearing loss, for example, is known to reduce spontaneous neural activity in the eighth cranial nerve, and increases spontaneous activity in the brainstem and auditory cortex (reviewed in Roberts et al., 2010). Presumably, the increase of spontaneous activity in the cortex may correspond to an auditory percept, i.e. tinnitus.

Some subjects with tinnitus can voluntarily modulate their tinnitus. This offers the opportunity to study tinnitus-related activity by neuroimaging methods, such as functional MRI. This paper explores brain activity in subjects that can modulate their tinnitus by peripheral gaze. This gaze-modulated or gaze-evoked tinnitus frequently occurs in subjects who underwent acoustic schwannoma removal surgery (Whittaker, 1982, 1983; Biggs and Ramsden, 2002). Our results have been presented in Van Gendt et al. (2012). Here, we offer an additional interpretation of those results.

MATERIAL AND METHODS

Eighteen subjects, who reported their tinnitus to be modulated by peripheral gaze, were included in this study. All these subjects underwent surgery for removal of an acoustic schwannoma, and were deaf on the surgery side (10 on the right, 8 on the left). They heard their tinnitus on the side of the surgery, regardless of gaze direction. The effect of lateral gaze on tinnitus depended on the gaze direction. The gaze direction that subjects reported to have the largest effect on tinnitus, resulted in an increase of the tinnitus loudness in 11 cases, and a decrease of loudness in four cases. In three subjects, the largest change did not correspond to a change in loudness of their tinnitus. On the side contralateral to the surgery, the hearing thresholds were near normal, showing a mild high-frequency hearing loss. In addition, nine subjects with normal hearing were included for reference.

All subjects took part in a functional MRI session. Brain activity was recorded for seven conditions: (1) no stimulation while looking straight ahead, (2) looking straight ahead, while listening to bilateral broadband rippled noise at 90 dB SPL, and (3)-(7) no sound stimulation, while gazing up, down, left, right or in the max direction, which was the direction for which subjects had reported the largest effect on their tinnitus. For the max condition, the controls were instructed to look in a direction corresponding to one of the max directions reported by the tinnitus subjects.

RESULTS

In the normal-hearing control subjects, sound stimulation resulted in significant positive responses in the bilateral cochlear nucleus, inferior colliculus, medial geniculate body and auditory cortex. In the patients, who were monaurally deaf, the sound stimulus also produced responses in the inferior colliculus contralateral to the hearing ear, and bilaterally in the auditory cortex. For lateral gaze, the data were analyzed by grouping all gaze directions and grouping the corresponding brain areas in both hemispheres (i.e. bilateral cochlear nucleus, bilateral inferior colliculus and bilateral auditory cortex). In the control subjects, peripheral gaze resulted in deactivation of the auditory cortex. In tinnitus subjects, the auditory cortex showed deactivation as well, but it was to a significantly lesser extent. Lateral gaze had no effect in the medial geniculate body of the control subjects. In contrast, the medial geniculate body showed deactivation in the tinnitus subjects. In the inferior colliculus, lateral gaze had no effect in control subjects, but did activate this region in the tinnitus subjects. The lateralization of the response was not related to the side of the tinnitus (and earlier surgery).

MRI responses were also related to the perceived tinnitus loudness. Then, an increase in tinnitus loudness corresponded to a decrease of inhibition in the cortex and an increase of activity in the inferior colliculus. In the medial geniculate body, the activity decreased with peripheral gaze, as described above. However, this decrease was not related systematically to the loudness of the tinnitus.
DISCUSSION

Functional MRI (fMRI) allows the measurement of brain activity in response to external stimuli. Typically, it relies on the comparisons of MRI images that were obtained for two or more activation states of the brain, respectively. If the neural activity of a particular region in the brain is larger in one state as compared to another state, the MRI scanner will record a larger signal from these areas. This signal is referred to as the BOLD response, where the acronym refers to the Blood Oxygenation Level Dependence of the MRI signal from the activated brain region. If a brain area is active, the increased oxygen demand is compensated by a local increase of oxygenated blood. Thus, functional MRI indirectly measures brain activity by recording local increases of blood supply.

In response to sound, fMRI may record significant responses of brain areas throughout the auditory system. That is, it records responses from the cochlear nucleus and inferior colliculus in the brainstem, from the medial geniculate body in the thalamus and from the auditory cortex on the temporal lobe. In the cortex, responses can be identified to levels which exceed the threshold of hearing by only 10-20 dB (Langers et al., 2007). In the lower brainstem, sound-evoked responses are often labeled as originating from the cochlear nucleus, but these responses may also included contribution from the superior olivary system.

There are two characteristics of fMRI responses to external sound stimuli, which are of relevance to the interpretation of the tinnitus data presented in this paper. First, the fMRI response of auditory brain areas in the brainstem, thalamus and auditory cortex monotonously increases with the intensity and loudness of the stimulus (Langers et al, 2007; Röhl and Uppenkamp, 2012). At high stimulus levels, the response may saturate, possibly due to saturation of neuronal circuits or to a saturation of the blood flow response. However, as a rule of thumb, higher responses correspond to louder stimuli. Second, in the case of monaural stimulation, the fMRI responses are lateralized: in the cochlear nucleus, the largest response is observed on the side ipsilateral to the stimulated ear. In the inferior colliculus, medial geniculate body and the auditory cortex, the largest response is observed on the contralateral side. This lateralization of the responses may also be formulated by taking an area in the brain as a viewpoint: the auditory cortex, inferior colliculus and medial geniculate body on each side of the brain, respond strongest to sound stimuli on the contralateral ear.

In this paper, we measured sound responses to binaural presentation of a broad-band stimulus. In the normal hearing subjects, the responses in the auditory system were approximately symmetrical, with equal response amplitudes on both sides of the brain. This is consistent with equal stimulation of both ears. In the patients, who were deaf on one ear, the responses were lateralized consistent with monaural stimulation on the hearing ear: the largest response was observed in the contralateral inferior colliculus, medial geniculate body and cortex. So, these responses correspond to previous results on lateralization of the response to external sound stimuli.

The correspondence between the perceptual characteristics of tinnitus and the MRI responses partly agrees with that observed for external sound stimuli. Gaze directions that resulted in an increase of tinnitus loudness, also gave more positive responses in the auditory cortex and inferior colliculus. That is, in the cortex the amount of deactivation due to gaze was reduced. However, in the medial geniculate body (MGB), peripheral gaze resulted in a decrease of neural activity, which is in contrast to the colliculus and cortex, and also is not consistent with the relation between loudness and activity to external sound. Also, the response lateralization in the cortex, colliculus and MGB, in response to peripheral gaze, was not consistent with that in response to monaural sound: although the tinnitus was clearly monaurally perceived in all subjects, the activation in these brain areas was not lateralized to the contralateral side.

The abnormal lateralization of tinnitus-related brain activity indicates differences in brain mechanisms involved in the perception of tinnitus, as opposed to those involved in the processing of external sound stimuli. Also, the deactivation of the medial geniculate body in tinnitus subjects, suggests abnormal function of this thalamic structure. Interestingly, a model of tinnitus suggested by Llinas et al. (1999) also proposes the abnormal function of the MGB in tinnitus. Llinas provides evidence for hypoactivity of the MGB in tinnitus, which leads to abnormal activity in the cortex. Our results support this model of tinnitus for the very special group of tinnitus subjects that underwent acoustic schwannoma surgery.

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REFERENCES


