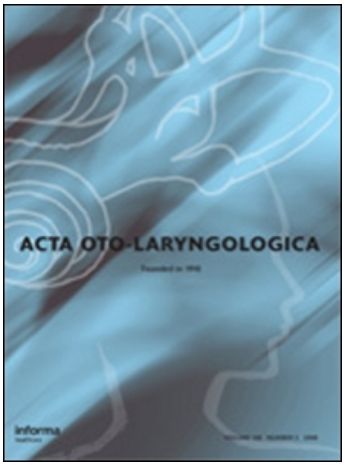

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Functional imaging of unilateral tinnitus using fMRI

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ORIGINAL ARTICLE

Functional imaging of unilateral tinnitus using fMRI

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Abstract

Conclusions. This article shows that the inferior colliculus plays a key role in unilateral subjective tinnitus. *Objectives.* The major aim of this study was to determine tinnitus-related neural activity in the central auditory system of unilateral tinnitus subjects and compare this to control subjects without tinnitus. *Subjects and methods.* Functional MRI (fMRI) was performed in 10 patients (5 males) with unilateral tinnitus (5 left-sided, 5 right-sided) and 12 healthy subjects (6 males); both groups had normal hearing or mild hearing loss. fMRI experiments were performed using a 3T Philips Intera Scanner. Auditory stimuli were presented left or right and consisted of dynamically rippled broadband noise with a sound pressure level of 40 or 70 dB SPL. The responses of the inferior colliculus and the auditory cortex to the stimuli were measured. *Results.* The response to sound in the inferior colliculus was elevated in tinnitus patients compared with controls without tinnitus.

Keywords: *fMRI, tinnitus, central auditory system, auditory cortex, inferior colliculus*

Introduction

Tinnitus is an auditory sensation without the presence of an external acoustic stimulus. Almost all adults have experienced some form of tinnitus, mostly transient in nature. However, in 6–20% of the adults, tinnitus is chronic and for 1–3% tinnitus severely affects the quality of life. Tinnitus is more prevalent in men than women and the prevalence increases with advancing age [1,2].

Tinnitus can be differentiated into subjective and objective tinnitus. For objective tinnitus there is some auditory source inside the body. Possible sources of objective tinnitus commonly have a vascular or muscular origin. Due to a vascular anomaly, vibrations of pulsatile blood flow near the middle or inner ear [3,4] can become an acoustic source. Also contractions or spasms of the tympanic membrane [5] or stapedius muscle may cause clicking and thereby act as a sound-generating source.

With subjective tinnitus, however, there is no acoustic stimulus present. Common forms of sensorineural hearing loss, such as presbyacusis or noise-induced hearing loss, may be associated with subjective tinnitus.

The sensorineural processes that underlie the perception of objective and subjective tinnitus must be quite different. In objective tinnitus, sound generated in the body is transduced in the inner ear. It stimulates the hair cells in the cochlea, which subsequently leads to a neural response. In contrast, in subjective tinnitus there is no sound to stimulate the cochlea.

There is a relation between subjective tinnitus and hearing loss [6]. Many (but not all) patients with subjective tinnitus have some form of hearing loss. Since the hearing loss usually has a peripheral origin, it has been thought for many years that the tinnitus activity must also originate from a peripheral source, e.g. the cochlea. However, many observations indicate that this view cannot be correct for all forms of tinnitus. In patients that underwent sectioning of the eighth cranial nerve as part of retro-cochlear tumor surgery, tinnitus arose in 50% of the cases [7], while sectioning of the eighth cranial nerve in tinnitus patients did not provide relief of the tinnitus in 38–85% of cases [8] (reviewed by Kaltenbach

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[9]). In these cases, tinnitus cannot originate from the cochlea. Consequently, mechanisms in the central auditory system must be responsible for these forms of tinnitus.

In animals with induced hearing loss, spontaneous neural activity increases at several levels in the auditory pathway [10,11] and/or neural activity across neuronal populations may show an increase synchronicity [10,12]. Apparently, peripheral hearing loss can result in plastic changes in the balance of excitation and inhibition in the central auditory system. These findings suggest that, although tinnitus is associated with peripheral hearing loss, it appears not to originate from the cochlea. Rather, the central auditory system plays a key role in tinnitus.

If the central auditory system of tinnitus patients functions differently from that in normal-hearing subjects, it would be conceivable that the response to sound of the brain is also different in tinnitus. In this study we investigated the response of the auditory cortex (AC) and the inferior colliculus (IC) to monaural broadband stimulation. The response of the brain centers was measured using functional magnetic resonance imaging (fMRI).

Subjects and methods

Subjects

Ten patients with unilateral tinnitus and 12 subjects without tinnitus were recruited at the University Medical Center Groningen (UMCG), all with no neurological and psychiatric history. All subjects were investigated by an audiologist using standard pure tone audiometry (250–8000 Hz). The mean audiogram per subject group is shown in Figure 1. In the patient group, the tinnitus percept was assessed by matching the frequency with an external tone or noise band at the non-tinnitus side. Details of the subject characteristics are shown in Table I. The handedness of all subjects was assessed by using a translated version of the Edinburgh inventory [13]. Nine of the patients were right-handed and one was ambidextrous. Of the subjects without tinnitus, 10 were right-handed, 1 left-handed, and 1 ambidextrous. The study was approved by the local medical ethics committee and written informed consent was obtained for each participant.

MRI protocol

All imaging experiments were performed on a 3T MRI system (Philips Intera, Philips Medical Systems, Best, The Netherlands) with an eight-channel phased-array headcoil (SENSE headcoil).

A T1-weighted fast-field echo scan was acquired for anatomic orientation (TR 11.12 ms; TE 4.6 ms; flip-angle 15°; matrix $256 \times 256 \times 9$; voxel size $1.0 \times 1.0 \times 2.0$ mm^3). An imaging volume was positioned on this scan such that it contained the left and right cochlear nuclei (CN), superior olivary complex (SOC), inferior colliculi (IC), medial geniculate nuclei (MG), and both temporal lobes containing the auditory cortices (ACs). The volume was aligned to the brainstem on a mid-sagittal view. The data were acquired using coronal oriented slices. The functional scans consisted of 2179 ms single-shot

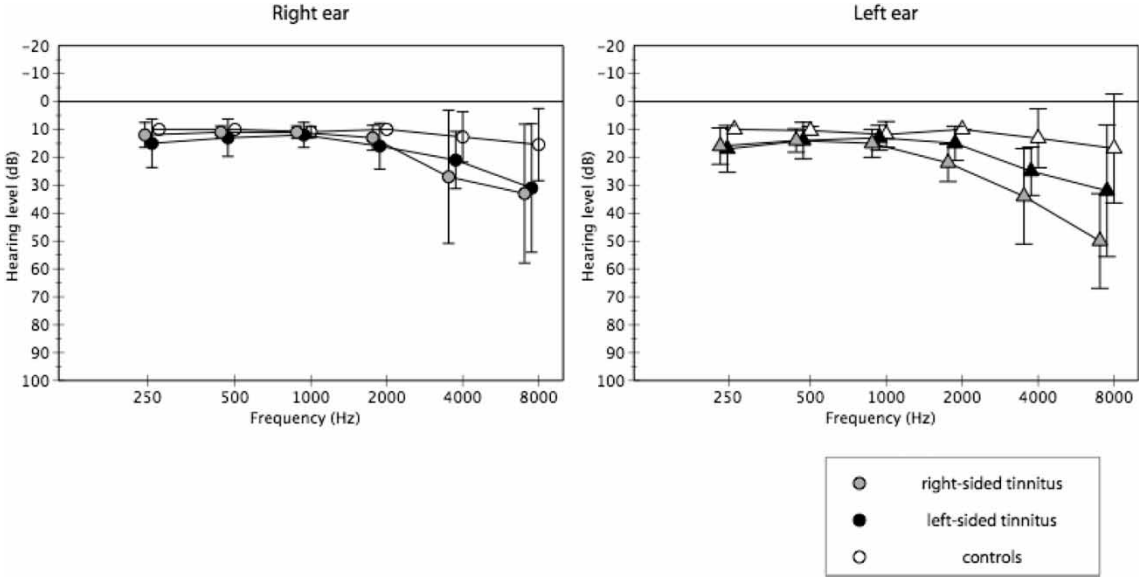

Figure 1. Subject group hearing thresholds. Hearing thresholds for controls and tinnitus patients were measured using pure tone audiometry. The error bars indicate the group standard deviation around the mean.

Table I. Subject characteristics.

Characteristics	Controls ($n=12$)	Left-sided tinnitus ($n=5$)	Right-sided tinnitus ($n=5$)
Age (years)			
Average	32.5	48.4	53.2
Range	24–59	37–61	30–67
Gender			
Male	6 (50%)	3 (60%)	2 (40%)
Tinnitus			
Average pitch (Hz)	–	8600	7800
Range (Hz)	–	6000–11 000	1000–14 000

$T2^*$-sensitive echo planar imaging (EPI) sequences with 41 slices 2 mm thick (TR 10 s; TE 22 ms; flip-angle 30°; matrix 128×128, field of view 224 mm, SENSE reduction factor 2.7). The influence of acoustic scanner noise was reduced by using a sparse sampling strategy [14] in which auditory stimuli were presented during a 7.8 s gap of scanner silence between two successive acquisitions. Three runs of 51 acquisitions were performed for each subject.

An additional 3D T1-weighted fast-field echo scan (TR 25 ms; TE 4.6 ms; flip-angle 30°; matrix $256 \times 256 \times 160$; voxel size $0.94 \times 0.94 \times 1.0$ mm^3) was acquired with the same orientation as the functional scans to serve as anatomic reference.

Stimulus and paradigm

Auditory stimuli were delivered by either an MR-compatible electrostatic audio system (S-001Mk2 and SRM-001, Stax Ltd, for the first patient and the first five control subjects) or by a an MR-compatible electrodynamic system (MR Confon GmbH [15]). These systems were driven by a PC set-up equipped with a digital-analog card (National Instruments 6052E, National Instruments Corporation, Austin, TX, USA), Labview (National Instruments Corporation) and Matlab 6.5 (The Mathworks Inc.), which generated dynamic rippled noise.

These rippled noise stimuli consist of temporally and spectrally modulated noise [16]. The stimuli had a frequency range of 125–8000 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%. The rippled noise stimuli were presented immediately when MR acquisition started and ended before the next acquisition. Each stimulus had a duration of 7.5 s.

Stimuli were presented at 0, 40, and 70 dB (SPL) at either the right or left ear. The stimuli were presented in a cyclic randomized order. Each stimulus condition (5 in total) was presented 10 times per functional run except for the 'silent' condition (i.e. 0 dB bilaterally), which was presented 11 times. Subjects were instructed to respond by left or right button presses with the right thumb whenever they perceived an audible stimulus in the left or right ear, respectively. This was done to monitor the subjects' attention to sound stimuli during acquisition.

Preprocessing

MR images were analyzed using Matlab 6.5 (The Mathworks Inc.) and SPM5 (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, London, UK). The functional images were realigned and spatially co-registered with the high-resolution anatomic image. Images were thresholded to omit voxels outside the brain.

Based on the high-resolution anatomic images, a customized normalization template was made by voxel-based morphometry methods using the anatomic data of the first 13 subjects. The functional images were spatially normalized to this template based on the gray matter segment of the anatomic image and were spatially smoothed with an isotropic 5 mm Gaussian kernel resulting in a voxel size of $2.0 \times 2.0 \times 2.0$ mm^3.

Regression analysis

A general linear model was set up to analyze the relative contribution of each sound condition to the measured response. The model included four covariates of interest (β_i), one constant factor to model the mean per session (Y_0), and a linear factor to correct for linear drift in the scanner signal. The model was applied to the data of all individual voxels and a significance level for each sound condition was determined separately by using T-test to visualize the localization, level, and extent of activation in individual subjects. The combined effect of all sound stimuli to the measured response was assessed by an F-test.

Region of interest analysis

For each subject four large regions of interest (ROI) were drawn for the AC, and the IC, both left and right, based on anatomic atlases.

Within each ROI, the 10% of the voxels that responded most strongly according to the T-test per sound condition were selected and the coefficients from the linear regression (β_i) were averaged. A percent signal change (S_i) compared with the silence condition was calculated for each sound condition, based on the regression coefficients as indicated in equation (1).

$$S_i = 100 \cdot \frac{\beta_i}{Y_0} \quad (1)$$

For each subject we calculated this percent signal change for both the left and right AC and IC and determined if there were statistically significant differences ($p < 0.05$) between subject groups, between loudness levels and lateralization. This analysis was done by using a repeated measures ANOVA method within SPSS 13.

Results

ROI analysis

All measured responses were analyzed using repeated measures ANOVA with SPSS 13. In this analysis the loudness dependency, the lateralization and subject group were main effects that were tested. The loudness dependency was, for example, determined over both ears and all subject groups. The results were visualized using box-plots.

Auditory cortex

The box-plots in Figure 2 show the results of the measured responses in the left and right AC, for all subject groups. The responses to sound stimuli ranged from 0.1 to 3%.

A loudness dependency is clearly visible, i.e. a stimulus of 70 dB (SPL) yielded a statistically significant ($p < 0.05$) larger response than a stimulus of 40 dB (SPL). This loudness dependency was present for all three groups (controls, left-sided tinnitus, and right-sided tinnitus).

There was also a statistically significant ($p < 0.05$) lateralization; contralateral stimuli yielded larger responses than ipsilateral stimuli. This holds for all three groups (controls, left-sided tinnitus, and right-sided tinnitus).

There was, however, no statistically significant difference between the amplitudes of the responses of the subject groups for both left and right AC. The responses measured in the AC in controls did not differ significantly from those measured in the two patient groups (left-sided tinnitus and right-sided tinnitus).

Inferior colliculus

Figure 3 shows the results for the left and right IC, for all three subject groups. Compared with the AC, the measured responses in the IC were lower in magnitude, i.e. 0.15–1.5%, whereas the responses in the AC were up to 3%. In the control group, a similar staircase-like pattern as at cortical level is visible. It shows a loudness dependency, where

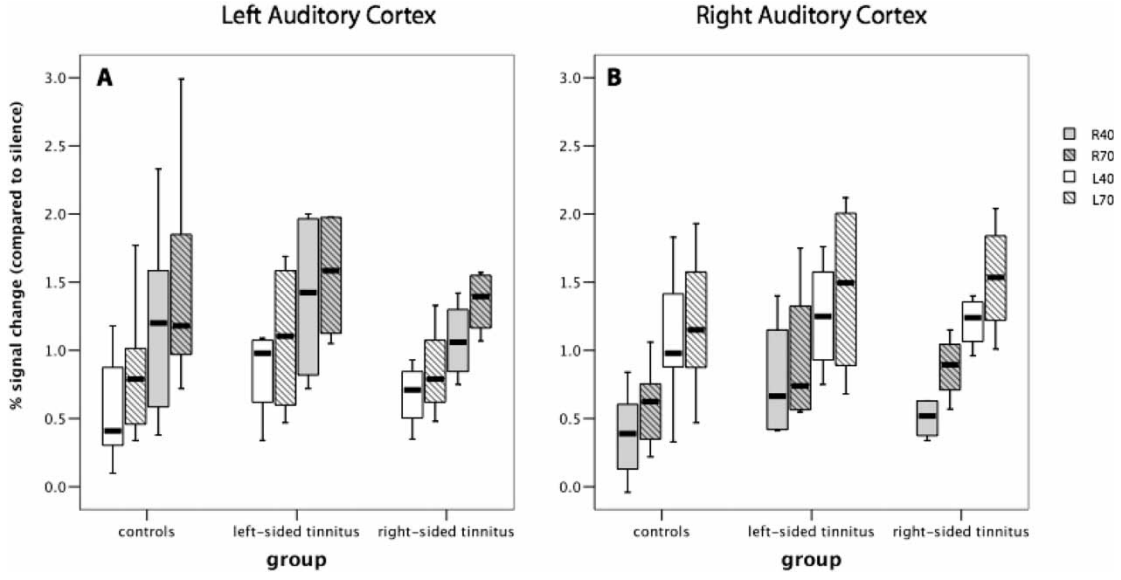

Figure 2. The percent signal change measured in the left (A) and right (B) auditory cortex for three subject groups shown as box-plots (showing smallest observation, 25th, 50th and 75th percentile, and largest observation). For each group, four responses are shown: responses to stimuli of 40 and 70 dB (SPL), respectively, presented at the left ear (L40 and L70) and the right ear (R40 and R70).

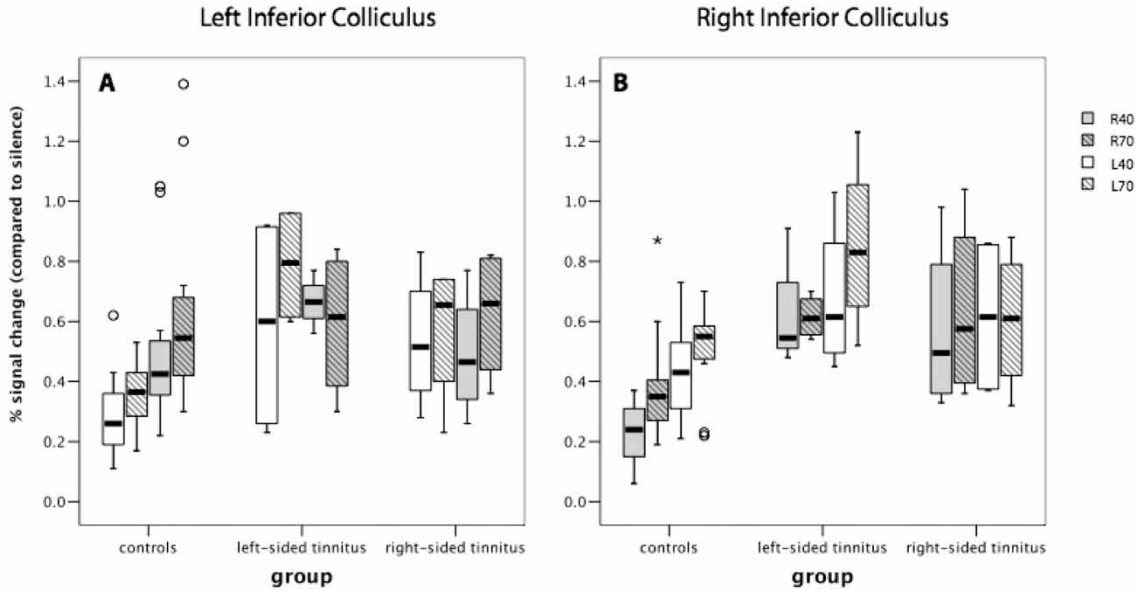

Figure 3. The percent signal change measured in the left (A) and right (B) inferior colliculus for three subject groups shown as box-plots, as in Figure 2. Outliers are depicted as separate points.

70 dB stimuli give a larger response than 40 dB stimuli. In this group there is also a clear lateralization towards the contralateral side, i.e. contralateral stimuli give larger responses than ipsilateral stimuli.

For the two patient groups, however, the responses in the IC differed significantly ($p < 0.05$) from the control group. Firstly, the median responses to the sound stimuli were larger in both patient groups (0.4–0.8%) when compared with the control group (0.2–0.6%), for each stimulus.

Also, the lateralization of the responses was disturbed in the patient groups. When a sound was presented at the side where the tinnitus was perceived, the fMRI response did increase with increasing loudness, but was elevated when compared with control subjects.

For a sound presented at the side opposite to the perceived tinnitus, the 40 and 70 dB stimuli gave the same amount of signal change (i.e. no increasing response with increasing loudness).

Discussion

In this study we investigated the response to broadband auditory stimuli in the AC and IC of normal-hearing subjects and tinnitus patients using fMRI. We used a sparse sampling paradigm [14] to minimize interaction between the auditory stimuli and the background scanner noise.

In the AC of all subject groups we found a lateralization effect, i.e. contralateral stimuli gave a larger response than ipsilateral stimuli. We also found a loudness dependency, i.e. stimuli of 70 dB (SPL) gave a larger response than stimuli of 40 dB (SPL). In the control group we found a functional asymmetry as described earlier [17]. The responses in the AC in the control group were higher in the left hemisphere than in the right hemisphere. In the patient groups this was not as clear due to the limited group size. No statistically significant group differences were observed in the AC: no tinnitus-related differences were observed.

The responses measured in the IC showed a different pattern. On average these were lower in amplitude than those measured in the AC. The control group showed a response similar to that for the AC; there was both a lateralization effect and a loudness dependency. In tinnitus patients, the responses were significantly different from the control group. First, the response was significantly larger in both patient groups compared with the control group. Second, the loudness dependency was different in the IC opposite to the tinnitus percept. When a sound was presented at the tinnitus ear, the response was larger for a louder stimulus. However, when a sound was presented at the non-tinnitus ear, the response amplitude did not show a loudness dependency. Thus, we found a clear difference between tinnitus patients and normal-hearing controls regarding the response of the IC. Both the responses to stimulation of the tinnitus ear and stimulation of the non-tinnitus ear were different from that in normal-hearing controls.

In the literature various animal studies with noise-induced tinnitus report an increased spontaneous neural activity at the level of the (dorsal) cochlear nucleus [11] and the IC. Only a few studies describe the effect of auditory stimuli on the neural activity in

'tinnitus animals'. In chinchillas with induced noise trauma – and possibly tinnitus – Salvi et al. [18] have shown increased compound action potentials in the IC in response to an auditory stimulus. First, the slope of the amplitude level functions was steeper than normal after the noise trauma. Second, at frequencies below the induced hearing loss, the maximum response amplitude increased to threefold that of the normal response. Their explanation was a change in gain setting in the central auditory pathway. This gain setting can be up- or down-regulated to compensate for a decrease or increase of neural activity from the cochlea. Our data fit the findings of Salvi et al. [18] very well, since we also found increased responses to sound stimuli at the IC, in tinnitus patients compared with control subjects.

Melcher et al. [19] also performed fMRI on patients with unilateral tinnitus. In contrast to our results, they showed a decrease of the response in the IC contralateral to the tinnitus percept. Their explanation is twofold. First, if tinnitus is accompanied by increased neural activity in silence and if neural activity is bound to a maximum, the neural activity can be driven into saturation when presenting an additional auditory stimulus. When two stimulus conditions are compared (i.e. silence vs stimulus), a decreased level of activity can be found in areas in the brain linked with tinnitus compared with the unaffected areas. A second explanation was described as physiologic masking of the tinnitus-related activity. In this model, the neural activity related to tinnitus is decreased or masked by an external auditory stimulus. It is not possible to distinguish between these two explanations, since they predict the same fMRI result: a decreased response signal.

The results of Melcher et al [19] appear to contradict our results. However, the different findings may be due to differences in the experimental procedure. The MRI signal could be significantly influenced by the acoustic noise of the scanner. To minimize this effect, we used a sparse imaging strategy [14] with a repetition time (TR) of 10 s with 8 s of silence. However, Melcher et al. used a variable TR of $\sim$2 s with substantial noise produced by the scanner, which presumably affected the measured responses of the IC.

We show that in tinnitus patients, the IC produces an enlarged response. Possibly, the tinnitus subjects in the study by Melcher et al. [19] also show an enlarged response to the substantial scanner noise. This may have saturated the IC, resulting in only a small additional response when stimulated with sound from the headphones. Thus, our experiments and those by Melcher et al. are both consistent with the view that in tinnitus patients the IC is easily saturated.

Recently, Smits et al. [20] investigated the lateralization of activity in the auditory pathway of control subjects and patients with unilateral and bilateral tinnitus using fMRI. This was achieved by comparing the spatial extent of activation (i.e. number of voxels activated due to auditory stimuli) in the left hemisphere with the extent in the right hemisphere for nuclei of the auditory pathway. They found activation lateralized towards the tinnitus side in AC and IC of patients with right-sided tinnitus and the medial geniculate body of patients with left-sided tinnitus. In addition, controls showed a lateralization to the left AC. They interpret their results on patients with right-sided tinnitus as being in agreement with Melcher et al. [19], who showed a lower activation of the right IC in these patients. Similar to Melcher et al., Smits did not use a (sufficiently) sparse imaging paradigm. As explained above, this accounts for the observed effects.

The enhanced activity in the IC of tinnitus patients may be due to a change in the balance of excitation and inhibition. Reduced inhibition could explain the enhanced response, and may be responsible for the tinnitus our subjects experience. With this work we have succeeded in identifying a neural correlate of tinnitus measured with fMRI and locating it in the auditory pathway. Future work has to provide an insight into the response in the complete auditory pathway in tinnitus patients.

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