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Primary and Secondary Auditory Cortex Stimulation for Intractable Tinnitus

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Key Words
Transcranial magnetic stimulation · Pure tone tinnitus · White noise tinnitus · Visual Analogue Scale

Abstract
Introduction: Recent research suggests tinnitus is a phantom phenomenon based on hyperactivity of the auditory system, which can be visualized by functional neuroimaging, and transiently modulated by transcranial magnetic stimulation (TMS). We present the results of the first implanted electrodes on the primary and secondary auditory cortex after a successful TMS suppression. ***Methods and Materials:*** Twelve patients underwent an auditory cortex implantation, 10 for unilateral and 2 for bilateral tinnitus, based on >50% suppression applying TMS. Results were analyzed for pure tone tinnitus and white noise tinnitus. ***Results:*** TMS results in 77% pure tone tinnitus and 67% white noise reduction. Electrical stimulation via an implanted electrode results in a mean of 97% pure tone tinnitus and 24% white noise suppression. Mean Visual Analogue Scale score decreases from 9.5 to 1.5 for pure tone and from 8.8 to 6.8 for white noise postoperatively. ***Discussion:*** Pure tone tinnitus might be the conscious percept of focal neuronal hyperactivity of the auditory cortex. Once visualized, this hyperactivity can be modulated by neurostimulation. ***Conclusion:*** The preliminary results of the first implantations suggest that patients with unilateral pure tone tinnitus are good surgical candidates for electrode implantation and permanent electrical stimulation of the auditory cortex, provided that the tinnitus is of recent origin and can be suppressed by TMS.

Introduction

Tinnitus is a symptom of high prevalence, similar in the USA and Europe: 10–15% of the population have prolonged tinnitus requiring medical evaluation. No effective treatment is available for long-term reduction of tinnitus in excess of placebo effects [1]. Medication such as clonazepam and antidepressants provide some benefit to some individuals, but can rarely suppress tinnitus entirely. Microvascular decompression of the auditory nerve can provide some relief in some selected individuals [2]. Tinnitus retraining therapy and various forms of masking can provide some relief in some patients with tinnitus [3].

Tinnitus has been widely considered a problem of the ear, but it is now recognized that many forms of tinnitus are phantom sensations similar to central neuropathic pain [4]. This means that the anatomical location of the physiological abnormality that causes the sensation of sounds when no sounds reach the ear is the central ner-

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vous system. In other words, there is evidence that some forms of tinnitus are caused by reorganization of the central nervous system through the expression of neural plasticity. More recently, evidence has been presented that this reorganization involves the auditory cortex, and that the intensity of the perceived tinnitus is related to the degree of cortical reorganization [5]. Studies in animal and human have also found evidence that tinnitus can be correlated with hyperactivity of the auditory system [6, 7]. This hyperactivity has been demonstrated both electrophysiologically and metabolically: EEG [8] and MEG [9] studies reveal a focal hyperactivity at the tinnitus frequency with surrounding hypoactivity due to lateral inhibition. PET studies in acute unilateral tinnitus sufferers reveal hyperactivity in the contralateral thalamus and auditory cortex [10], in the left auditory cortex [11] or in a right prefrontal-temporal network [12]. It has also been demonstrated that the extralemniscal nontonotopic system may be involved in some patients with tinnitus [13]. fMRI studies performed by us, using a 3T MRI unit, demonstrate that activation of both the cortical and subcortical auditory structures can be visualized by means of an fMRI block design which is combined with the clustered volume acquisition technique [14]. This paradigm can easily be used in patients with tumors and/or hearing disorders, and might visualize the cortical hyperactivity associated with tinnitus [15]. This visualized area can be used as a target for modulating associated abnormal neuronal activity, using neuronavigated magnetic and electrical stimulation [16].

In this paper we want to suggest that tinnitus is indeed a product of brain hyperactivity, that it can be clinically visualized using fMRI, and that it can be treated in selected patients by suppressing this hyperactivity by means of implanting electrodes on the primary and secondary auditory cortex. The results of the first 12 implanted patients will be presented, 12 on the secondary and 4 on the primary auditory cortex (all patients with intradural electrodes also have extradural electrodes implanted). Based on these data preliminary selection criteria are deduced for selecting surgical candidates.

Materials and Methods

Transcranial magnetic stimulation (TMS) was used as a selection criteria for implantation of an electrical stimulation device on the auditory cortex, in patients with intractable tinnitus. All patients underwent two TMS sessions on separate dates performed by a person not involved in the surgery (K.v.d.K.) in a placebo controlled way. If TMS resulted in a >50% tinnitus suppression on these two separate occasions, the patients were eligible for implantation.

Intracranial implantation of electrical pulse-delivering electrodes can be performed in 3 ways: (1) extradural secondary auditory cortex stimulation; (2) intradural intrasulcal grey matter stimulation of the primary auditory cortex, and (3) intradural intraparenchymatous white matter stimulation of the primary auditory cortex. We routinely implanted the electrode extradurally, using fMRI-guided neuronavigation. The initial fMRIs were performed with music as a stimulus. This method was quickly converted to frequency-specific fMRI as it was realized that this might improve the accuracy for finding the tinnitus generator in the auditory cortex. It furthermore evaded the problem of relative weaker activation associated with tinnitus as seen in fMRIs which use music (= all frequencies) as an evoking stimulus. The patient first underwent a tinnitus matching to determine the perceived pitch. This pitch (frequency) was subsequently presented in the fMRI to localize the area of the auditory cortex that generated the tinnitus. Only if no stability of tinnitus suppression could be obtained by extradural stimulation, the patient was offered an intradural approach, because of its more invasive character. The correct positioning of the electrodes can be verified by fusing the postoperative CT scan with the preoperative frequency-specific fMRI, demonstrating an overlap of the electrodes (on CT) on the area of hyperactivity (on the fMRI; fig. 1). This fusion is performed on the neuronavigation machine (Stealth, Medtronic, Denver, Colo., USA), which allows a dynamic progressive (split) fusion.

Surgical implantation was performed in a standardized way as described in a previous report [16]. In summary, a Lamitrode® 44 lead (Advanced Neuromodulation Systems, Inc., Tex., USA) was positioned on the dura in a neuronavigated way, using an auditory fMRI. For the intradural electrodes, a Lamitrode® 22 lead (Advanced Neuromodulation Systems) was used. They consist of a double paddle, each consisting of two poles electrodes. One paddle is positioned intradurally on the primary auditory cortex and the other paddle is positioned extradurally overlying the secondary auditory cortex. For the intradural approach, the Sylvian fissure was split and the Lamitrode 22 lead was placed with the electrodes on target under guidance of the neuronavigation. Then, the pressure of the parietal and temporal lobe kept the paddle in place. The second part of the paddle was positioned extradurally as mentioned before. The electrodes were connected to an internal pulse generator (IPG; Genesis; Advanced Neuromodulation Systems) once a stable suppression could be obtained during 1 week of external stimulation and the patient felt the stimulation was beneficial. The IPG was implanted subcutaneously in the abdomen.

Twelve patients were selected: 7 female and 5 male patients. Seven patients had left-sided, 3 right-sided and 2 bilateral tinnitus. Tinnitus duration ranged from 1 to 25 years (mean: 5.4 years) and follow-up from 3 to 28 months (mean: 13 months). All patients with unilateral tinnitus had a grade 3 or 4 tinnitus, according to Goebel and Hiller's Tinnitus Questionnaire [17]. The 2 patients with bilateral tinnitus presented with a grade 2 tinnitus. In 6 patients a pure tone tinnitus was present, in 10 patients a white noise or narrow band tinnitus was noted. Three patients with unilateral tinnitus were suffering from both white noise and pure tone tinnitus, and 1 patient with bilateral tinnitus was suffering from both white noise and pure tone tinnitus. For white noise (= narrow band noise in our patient population) the dominant pitch was analyzed with tinnitus matching. Details of patient data are presented in table 1.

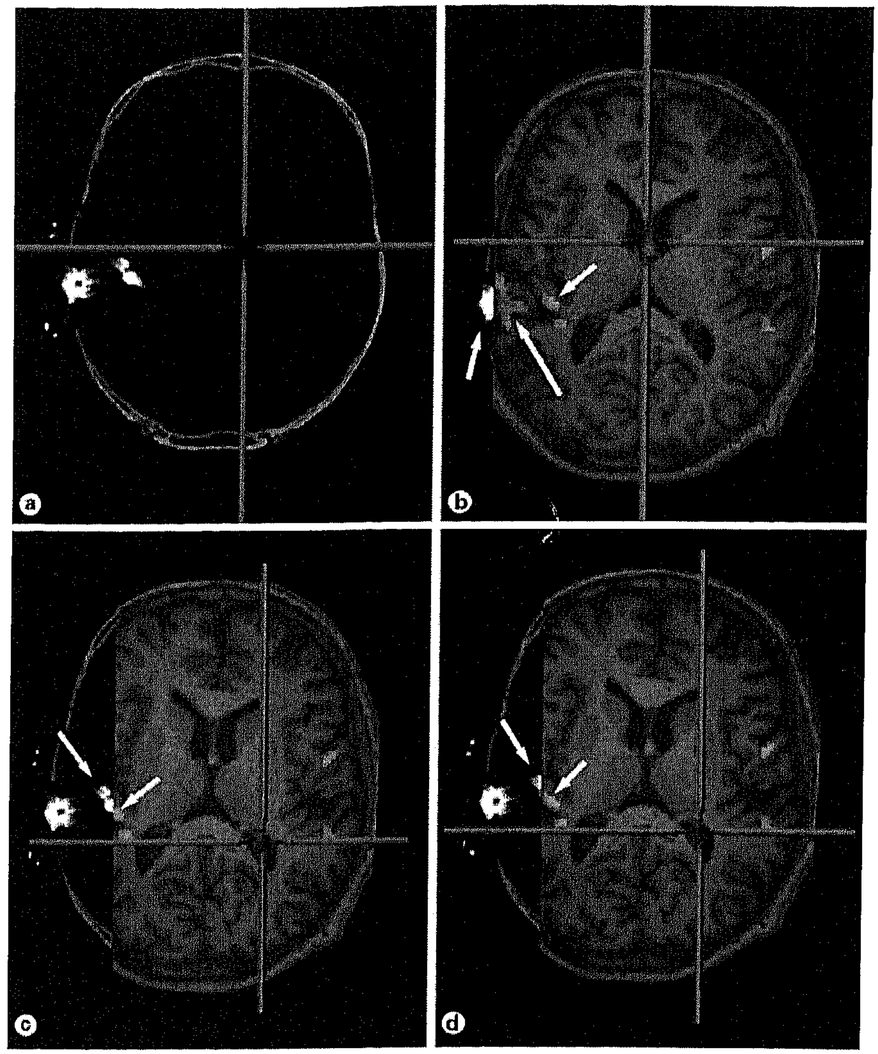

Fig. 1. Postoperative verification of correctness of electrode positioning. Patient 7, suffering from white noise tinnitus, but centered around 8,000 Hz. **a** Postoperative CT scan demonstrating the position of the Lamitrode 22 electrode, with one lead consisting of two poles on Heschl's gyrus, and one lead extradurally overlying the lateral superior temporal gyrus. **b** Fusion of preoperative fMRI, demonstrating two activation areas, one on Heschl's gyrus (short small arrow) and one on the lateral superior temporal gyrus (long small arrow). The extradural lead (large arrow) is correctly positioned. **c**, **d** Fusion images demonstrating the correct placement of the intradural lead of the electrode (large arrows), superposed on the activation area on Heschl's gyrus (small arrows).

Table 1. Characteristics of the 12 implanted patients

Patient	Age/sex	Tinnitus side	Follow-up months	Tinnitus duration, years	Tinnitus frequency	Tinnitus dB	VAS	Tinnitus grade	Hearing loss, dB	Tinnitus white noise	Tinnitus pure tone
1	32 F	L	28	1	4,000	80	10	4	cophosis	no	×
2	38 F	R	12	10	6,000	15	9	3	80	×	×
3	53 F	L	18	4	6,000	25	9	4	cophosis	×	×
4	40 M	L	8	5	7,000	5	7	3	90	×	no
5	40 F	L	21	2	6,000	75	9	4	85	×	×
6	49 F	L	17	1	4,000	45	10	4	90	×	no
7	62 M	R	5	3	8,000	5	8	4	30	×	no
8	40 F	L	8	3	16,000	25	10	4	80	×	no
9	51 F	L	2	5	1,000	20	9	4	cophosis	×	no
10	46 M	R	3	1	8,000	20	9	4	65	no	×
11	53 M	bilateral	11	5	16,000	10	8	2	20	×	no
12	43 M	bilateral	24	25	4,000	5	9	2	20	×	×

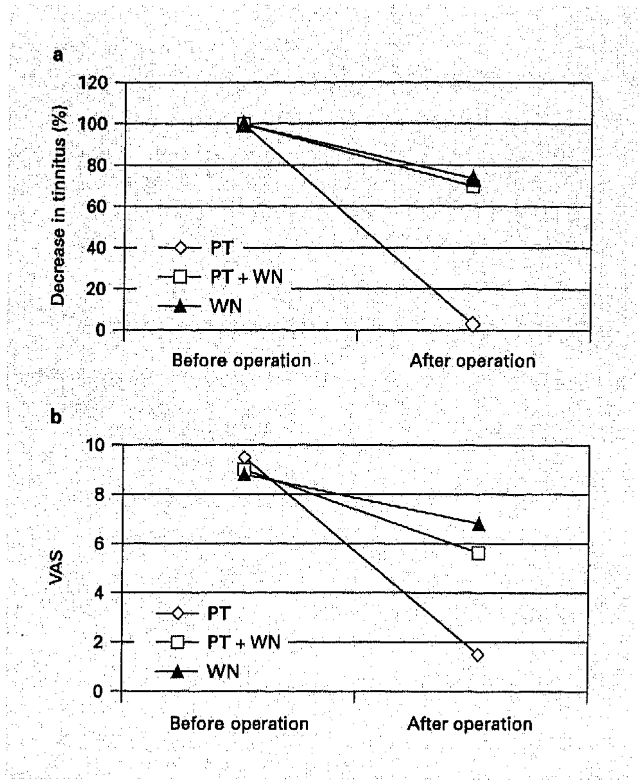

Fig. 2. a Percent tinnitus decrease after auditory cortex implantation, related to the type of tinnitus. **b** Pre- and postoperative VAS after auditory cortex implantation, related to the type of tinnitus. PT = Pure tone tinnitus; WN = white noise and narrow band noise.

Results

Results from preoperative TMS studies in the patients with tinnitus that had the character of white noise (some of whom also had associated pure tone tinnitus) showed an average tinnitus suppression of 69.5% (50–85%). In patients with pure tone tinnitus, the average suppression from TMS was 77% (70–90%; table 2).

Results from electrical stimulation through extradural implanted electrodes showed tinnitus suppression of 26.2% on average (0–50%) in the white noise group (with possible associated pure tone tinnitus) and 24% tinnitus suppression for the exclusive white noise group (0–50%), a nonsignificant difference (Mann-Whitney test: $U = 18.5$, n.s.). The average tinnitus suppression for the pure tone tinnitus group with extradural electrical stimulation was 97% (85–100%; table 2; fig. 2a), a highly significant difference with both the exclusive white noise group ($U = 25$, $p < 0.01$) and the white noise associated with pure tone tinnitus group ($U = 40$, $p < 0.01$).

The preoperative Visual Analogue Scale (VAS) decreased from 9.5 preoperatively to 1.5 postoperatively in patients with selective pure tone tinnitus (n = 2), from 8.8 to 6.8 in patients with selective white noise tinnitus (n = 5), and from 9 to 5.6 in patients with combined pure tone and white noise tinnitus (n = 3). Thus the tinnitus improvement as scored by VAS was 8 for pure tone tinnitus, 2 for white noise and 3.4 for patients with combined type

Table 2. Postoperative results

Patient	Best freq. TMS	Best freq. electr.	TMS suppression, %	ED supp. WN, %	ED supp. PT, %	ID supp. WN, %	ID supp. PT, %	Postoperative VAS	IPG implanted
1	40	80	90	n.a.	100	n.a.	n.a.	1	×
2	20	6	70	30	100	n.a.	n.a.	2	×
3	20	40	80	40	100	n.a.	n.a.	8	×
4	5	40	70	20	n.a.	n.a.	n.a.	6	×
5	5	40	70	20	100	30	100	7	×
6	20	60	50	40	n.a.	40	n.a.	8	×
7	10	6	70	0	n.a.	0	n.a.	8	no
8	20	6	60	10	n.a.	20	n.a.	8	no
9	20	40	85	50	n.a.	n.a.	n.a.	4	×
10	20	50	75	n.a.	85	n.a.	n.a.	2	×
11	10	0	65	0	n.a.	n.a.	n.a.	8	no
12	5	0	70	0	0	n.a.	n.a.	9	no

Best freq. TMS = Frequency at which transcranial magnetic stimulation yielded best tinnitus suppression; Best freq. electr. = frequency at which implanted electrical stimulation yielded best tinnitus suppression; ED supp. WN = suppression obtained with extradural electrode for white noise tinnitus; ED supp. PT = suppression obtained with extradural electrode for pure tone tinnitus; ID supp. WN = suppression obtained with intradural electrode for white noise tinnitus; ID supp. PT = suppression obtained with intradural electrode for pure tone tinnitus.

of tinnitus (fig. 2b). The 2 patients with bilateral tinnitus did not obtain any improvement.

The results from intradural electrodes showed that 2 of the 4 patients who had intradural electrodes implanted on the primary auditory cortex inserted in the Sylvian valley failed to improve. These 2 patients had not achieved any tinnitus suppression with an extradural electrode (0 and 10%; patient 7 and 8). In 2 other patients (patients 5 and 6), the purpose was to obtain stabilization of tinnitus suppression, as in both patients the electrodes had to be reprogrammed every 2 to 3 days. In both patients the intradural positioning resulted in a stabilized suppression of their tinnitus.

Discussion

A possible pathophysiological approach to intractable severe tinnitus can be based on the following rationale: (1) tinnitus is associated with auditory cortex reorganization and auditory cortex hyperactivity; (2) this reorganization and hyperactivity can be visualized by different neuroimaging techniques; (3) the visualized area of reorganization or hyperactivity can be used as a target for interventional modulation, using noninvasive TMS, and (4) if noninvasive TMS is successful in suppressing tinnitus, permanent electrical stimulation of the auditory cortex can be envisioned.

Group analysis of the fMRI data demonstrate that in both right- and left-sided unilateral tinnitus a weaker level of activity elicited by binaural music versus no music is seen in the contralateral auditory cortex as compared to the ipsilateral auditory cortex. In patients with bilateral tinnitus a difference in activity between left and right auditory cortex is not seen, but in comparison with normal hearing volunteers, the level of activity in the bilateral auditory cortex is generally weaker. Tinnitus is generated by a focal hyperactivity in the brain, already consuming more energy, rising the 'baseline fMRI level' at rest (no musical stimulation). When music is presented bilaterally, there will be less difference in oxygen consumption by the already hyperactive tinnitus-generating brain cells (at rest), and hence less differential fMRI activity, than the surrounding cells who are hypoactive due to lateral inhibition. The same will hold for the difference with the contralateral auditory cortex. The results of this study support the hypothesis that a weaker fMRI activation in tinnitus is caused by an increased neuronal activity at rest compared with the normal state [15].

Earlier studies have shown that TMS at rates of 10 Hz and higher is capable of only transiently suppressing tinnitus [18], whereas repetitive TMS at 1 Hz for 33 min daily (2,000 pulses) for 5 days has been shown to result in tinnitus suppression for longer periods [19]. A recent analysis of our first 114 TMS sessions performed in unilateral tinnitus demonstrated that TMS had a good effect (>80% transient suppression) in 28 of the patients studied (25%), a partial effect (21–80% suppression) in 32 (28%) and no effect (0–20% suppression) in 54 (47%). The amount of tinnitus suppression depended on the duration of the tinnitus: the longer the tinnitus exists, the less suppression that can be obtained by TMS [20]. Our studies furthermore indicate that the optimal stimulation frequency depends on the duration of the tinnitus, and tinnitus of recent origin is better suppressed by high-frequency stimulation (>10 Hz), chronic tinnitus by low-frequency stimulation (<10 Hz). This supports the findings of other studies that tinnitus that has been present for a long time is more difficult to suppress than tinnitus of short duration [2, 21, 22]. We also found that sham stimulation could suppress tinnitus (in 63% of our patients) but the mean tinnitus suppression in sham stimulation was significantly different from real stimulation, indicating that the TMS effect was a real effect and not mere placebo effect.

Our results also demonstrate that sometimes an intradural approach might be more beneficial than extradural placement of stimulating electrodes. Some studies [23] indicate that plasticity is less pronounced in primary versus secondary (somatosensory) cortices and that may explain why we achieved better tinnitus suppression in some patients when the stimulating electrodes were repositioned on the primary auditory cortex providing lasting, stable tinnitus suppression.

Our data strongly suggest that white noise is difficult to suppress by auditory cortex stimulation, both by primary or by secondary cortex stimulation. In patients presenting with white noise and pure tone tinnitus, electrical neurostimulation induced a selective disappearance of the pure tone tinnitus while the white noise tinnitus remained unchanged. We do not have an explanation for that.

Only one patient with 8,000-Hz tinnitus has been improved with our stimulation. This could be explained by the stimulating electrode not being placed medially enough to affect the high frequency area of the auditory cortex. This explanation is most likely incorrect, as electrical stimulation devices have a current reach of only a couple of millimeters. It has been suggested [24] that the applied electrical current may modulate activity in neurons whose fibers connect the lateral superior temporal gyrus with the primary auditory cortex [25]. Why only one of our patients with tinnitus >8,000 Hz has a suppressive effect might be due to the fact that the patients presenting with tinnitus >8,000 Hz in our series also have a narrow band or bilateral tinnitus, and no pure tone tinnitus.

Our study also suggests that neurostimulation of the auditory cortex as a treatment is less effective for bilateral tinnitus than for unilateral tinnitus.

It is an important question whether TMS may be considered a valuable prognostic test for intracranial electrode placement. Good TMS suppression yields an impressive 97% pure tone tinnitus suppression with implantation and a poor 24% white noise reduction. (1) TMS seems to be able to modify tinnitus perception transiently. The amount of transient white noise tinnitus suppression with TMS (67%) seems better than with electrical stimulation (24%); (2) TMS seems to indicate whether subsequent surgical implantation will be beneficial in patients with pure tone tinnitus but it does not indicate whether that stimulation will provide stable and long-lasting tinnitus suppression. If the tinnitus recurs every time after 2–3 days, the patient is finally not helped. One solution might be repositioning the electrode on the primary auditory cortex, which was beneficial in the 2 patients described earlier; (3) TMS is different from intracranial electrical stimulation. One reason may be that it affects a larger area than electrical stimulation. This area of stimulation varies from 33 to 96 cm^2 [26], depending on the type of coil used, whereas electrical stimulation has a very limited area of direct impact, in the range of mm. TMS may therefore act in a different way from electrical stimulation which is an obstacle in the use of TMS as diagnostic test.

The fact that the tinnitus reappears after a certain time of stimulation in all our patients can be a result of habituation, (new) reorganization or perhaps a temporary placebo effect. Reprogramming of the stimulator can make it effective in suppressing the tinnitus again. Reorganization of the electrode array was always necessary, suggesting that other brain cells have to be stimulated in order to be effective.

Stimulation parameters required for clinical tinnitus suppression did not cause any noticeable side effects. In 2 patients (patients 1 and 7), increasing stimulation intensity beyond therapeutic levels induced a feeling of tipsiness. In 4 patients with severe hearing loss in their left ear (patients 4, 5, 6, 9) high-intensity, high-frequency electrical stimulation altered spatial localization of external sounds. Word finding problems could be observed in 2 patients (patients 2, 4), dizziness or vertigo in 6 (patients 1, 2, 4, 6, 8, 9). In 2 patients therapeutic stimulation altered hearing, which was described as being clearer, even their own voice (patients 4, 6). This might be related to a decrease of feeling of intra-aural pressure. The feeling of intra-aural pressure decreased in all patients who suffered from that (patients 4, 5, 6), but the electrode activation that affected the feeling of ear pressure was not always the same as that, which caused maximal reduction of tinnitus. In 2 patients, a short-lasting epileptic seizure was induced from prolonged stimulation without stimulation-free intervals. This occurred when the patient was still having an external stimulator, which cannot be programmed by the investigator, but relies on patient cooperation. With the IPG implanted no epileptic seizures were seen with current stimulation parameters: for high-frequency stimulation (>10 Hz) cycle mode is used, stimulating 5 s on, 5 s off. For low-frequency stimulation (<10 Hz) a cycle mode with the same parameters as for high-frequency stimulation or a cycle mode with 15 min on, 5 min off is chosen.

Conclusion

The present study supports the hypothesis that some kinds of tinnitus are auditory phantom phenomena and that pure tone tinnitus might be the conscious percept of focal neuronal hyperactivity of the primary and/or secondary auditory cortex. This hyperactivity can be visualized using fMRI. These MRI images can be used as a target for noninvasive or invasive neuromodulation.

The results of TMS suggest that cortex stimulation in some patients with chronic tinnitus yields poorer results than that in patients who have had tinnitus for a shorter time, and that the optimal stimulus parameters are different for patients who have had tinnitus for long and short periods.

The results of electrical stimulation through implanted electrodes suggest that patients with unilateral tinnitus of pure tone type with suppression on TMS may be good surgical candidates for electrode implantation.

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Comments

D. Alpini (Italy): The paper states that tinnitus is now recognized not as a problem of the ear but as a phantom sensation similar to central neuropathic pain in which the intensity of the perceived tinnitus is related to the degree of cortical reorganization due to the primary pathological event(s). Both the intensity of perceived tinnitus and the degree of cortical (and subcortical) reorganization in a specific subject may not be predicted on the basis of the primary pathological event. Perhaps the individual neural substrate of tinnitus could be linked to genetic hypothesis as formulated by Tyler et al. [1] in this issue.

The authors propose transcranial magnetic resonance as a preoperative study in order to use implanted electrodes to provide electrical stimulations of the auditory cortex.

Different results obtained in unilateral vs. bilateral tinnitus and different kind of stimulation depending on the duration of tinnitus underline, once again, that tinnitus perception is specific for each subject and that patients have to be selected accurately.

Cortical stimulation (electrical or magnetic) has been demonstrated to be effective for both tinnitus sensation and the functional activity of the brain. Weiler and Brill [2] have in fact shown that lessening of the tinnitus sensations was parallel to changes of EEG patterns after PMFT, especially in the frontal region of the brain.

Regarding the results of the invasive procedure proposed, they do not seem to be significantly different from those obtained by noninvasive repetitive transcranial magnetic stimulation, as reported by Kleinjung et al. [3].

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I. Kos, C. Degive (Switzerland): This study is based on the assumption that tinnitus can be visualized with the present techniques of imagery (fMRI, PET). The 12 tinnitus sufferers presented in this study are firstly selected according to their different levels of positive response to the transcranial magnetic stimulation. They are then grouped in separate categories established arbitrarily according to the type of tinnitus: white noise, pure tone and mixed. They consider them positive and significant in only 2 out of 12 patients. These were the only 2 pure tone tinnitus sufferers who obtained a significant relief with the electrical stimulation through extradural implanted electrodes. Although the results obtained are not a strong argument justifying invasive surgery, this study remains clinically appealing. It brings to the table interesting speculations such as the hypothesis that some forms of tinnitus are caused by a reorganization of the central nervous system.

P. and M. Jastreboff (USA): The search for a cure for tinnitus continues, and approaches which could eliminate tinnitus perception are sought after. The results presented by the authors are very interesting and offer better insight into the mechanisms of tinnitus and for potential development of a clinical method of its suppression. In spite of the invasiveness of the technique, it could be expected that many patients with significant tinnitus will be interested in it. The presented data indicate that the method appears to be effective only in a specific population of tinnitus patients, i.e. with tinnitus attenuation achievable by transcranial magnetic stimulation, and unilateral, pure tone tinnitus.

Many questions still remain to be answered before the method can be used in clinical practice, e.g. what is the duration of the effect, why is it necessary to reorganize the electrodes for the next set of stimulations to be effective, and how effective is the method on patients who do not show suppression when transcranial magnetic stimulation is used? The paper presents the first crucial step toward achieving suppression of tinnitus signal at the cortical level.

R. Tyler (USA), *W. Noble* (Australia), *C. Coelho* (Brazil): We believe this work is very important and has great potential. Dr. De Ridder and colleagues are certainly proceeding into potentially critical areas that could result in the ability to 'turn off' tinnitus. As they are aware, having a good control (some kind of sham stimulation) would make their case stronger. In addition, we recommend adding a tinnitus handicap scale with good resolution and sensitivity.