

Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression

Clinical article

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Object. Tinnitus is a prevalent symptom, with clinical, pathophysiological, and treatment features analogous to pain. Noninvasive transcranial magnetic stimulation (TMS) and intracranial auditory cortex stimulation (ACS) via implanted electrodes into the primary or overlying the secondary auditory cortex have been developed to treat severe cases of intractable tinnitus.

Methods. A series of 43 patients who benefited transiently from 2 separate placebo-controlled TMS sessions underwent implantation of auditory cortex electrodes. Targeting was based on blood oxygen level–dependent activation evoked by tinnitus-matched sound, using functional MR imaging–guided neuronavigation.

Results. Thirty-seven percent of the patients responded to ACS with tonic stimulation. Of the 63% who were nonresponders, half benefited from burst stimulation. In total, 33% remained unaffected by the ACS. The average tinnitus reduction was 53% for the entire group. Burst stimulation was capable of suppressing tinnitus in more patients and was better than tonic stimulation, especially for noise-like tinnitus. For pure tone tinnitus, there were no differences between the 2 stimulation designs. The average pure tone tinnitus improvement was 71% versus 37% for noise-like tinnitus and 29% for a combination of both pure tone and noise-like tinnitus. Transcranial magnetic stimulation did not predict response to ACS, but in ACS responders, a correlation ($r = 0.38$) between the amount of TMS and ACS existed. A patient's sex, age, or tinnitus duration did not influence treatment outcome.

Conclusions. Intracranial ACS might become a valuable treatment option for severe intractable tinnitus. Better understanding of the pathophysiological mechanisms of tinnitus, predictive functional imaging tests, new stimulation designs, and other stimulation targets are needed to improve ACS results. (DOI: 10.3171/2010.11.JNS10197)

KEY WORDS • burst stimulation • tonic stimulation • transcranial magnetic stimulation • extradural electrode • neuromodulation • cortex • tinnitus

TINNITUS is a symptom with an incidence of approximately 1% and prevalence of 10%–15% in the Western world,^{1,24} for which no proven treatments exist.²⁰ It severely impairs the quality of life in 2%–3% of the population,¹ leading to insomnia,⁸ anxiety,^{3,60} and depression.^{3,19} The most common form of tinnitus, nonpulsatile tinnitus, is considered to be an auditory phantom phenomenon²⁶ analogous to central neuropathic pain.^{42,55} Both disorders have similar clinical features, pathophysiological mechanisms, and treatment approaches.^{9,42,55}

Abbreviations used in this paper: ACS = auditory cortex stimulation; BOLD = blood oxygen level–dependent; fMR = functional MR; IPG = internal pulse generator; MEG = magnetoencephalography; TMS = transcranial magnetic stimulation.

A pathophysiological model of tinnitus has been proposed both for pain and tinnitus, based on studies of consciousness suggesting that any conscious percept, including auditory consciousness, is related to gamma-band activity (generally 30–80 Hz),^{7,27} and thus also to nonpulsatile tinnitus.⁵⁸ At rest, the auditory thalamocortical columns oscillate at alpha frequencies (8–12 Hz). When there is hearing loss, alpha oscillations will decrease to theta frequencies (3–7 Hz), because there is less information to be processed.⁴ This increased theta activity results in an associated halo of faster gamma-band activity (30–80 Hz) at the lesion edge, due to decreased

This article contains some figures that are displayed in color online but in black and white in the print edition.

lateral inhibition mediated by γ -aminobutyric acid-A.^{35,36} This is called thalamocortical dysrhythmia.³⁶ Investigations conducted using MEG studies have demonstrated that tinnitus is indeed correlated to decreased alpha-band³⁸ and associated increased gamma-band activity in the contralateral auditory cortex.^{36,58} Furthermore, the amount of contralateral gamma-band activity correlates with the perceived intensity of the phantom sound.⁵⁶ It has also been shown that the auditory cortex BOLD signal on fMR imaging studies correlates with the gamma-band firing rate and local field potentials,^{46,47} suggesting that fMR imaging can be used as an indirect way of looking at the neural code of tinnitus.

It has been demonstrated that both TMS^{12,28,30,37} and electrical stimulation via electrodes^{11,12,17,22,50,52} implanted in the auditory cortex in humans can benefit patients suffering from tinnitus. It has also been shown on MEG studies that the electrical stimulation of the auditory cortex with implanted electrodes interferes with the proposed thalamocortical dysrhythmia model,⁵⁰ probably in the primary auditory cortex,²⁵ via functional connections that exist between the posterior lateral superior temporal gyrus and the primary auditory cortex.⁶

The rationale for ACS for tinnitus suppression can therefore be summarized in a 4-step model. 1) Tinnitus is related to synchronized gamma-band activity in the contralateral auditory cortex (Fig. 1A). 2) Synchronized gamma-band activity in the auditory cortex correlates with the BOLD signal on fMR imaging studies (Fig. 1B). 3) Transcranial magnetic stimulation can target this gamma hyperactivity and suppress tinnitus transiently. 4) If TMS is successful in tinnitus suppression, an fMR imaging-guided neuronavigated electrode implant could suppress tinnitus permanently (Fig. 1C and D).

Sufficient data support the first 3 steps; however, it is unknown whether TMS is predictive for cortex implants and what the results are in a larger study population. We therefore present our experience with 43 patients who underwent TMS of the auditory cortical area contralateral to the tinnitus side on 2 separate days and who subsequently received an electrode implant on the side contralateral to where the tinnitus was perceived (or on the right side in those with bilateral tinnitus).

Methods

This study includes 43 patients (24 female and 19 male patients) with intractable tinnitus in whom electrodes had been implanted. The mean age of the participants was 48.55 ± 12.68 years (mean values are given \pm SD), and the mean duration of their tinnitus was 6.83 ± 6.98 years. Twenty-nine patients had unilateral tinnitus, whereas 14 suffered from bilateral tinnitus. Twenty patients presented with pure tone tinnitus, 14 with narrow-band noise tinnitus, and 9 had a combination of pure tone and narrowband noise tinnitus. All participants presented with Grade 3–4 tinnitus; that is, severe tinnitus according to the questionnaire.²³ Grade 3 reflects severe tinnitus, and Grade 4 designates severe but psychologically decompensated tinnitus. The ethics committee of the University Hospital Antwerp, Belgium, approved the study.

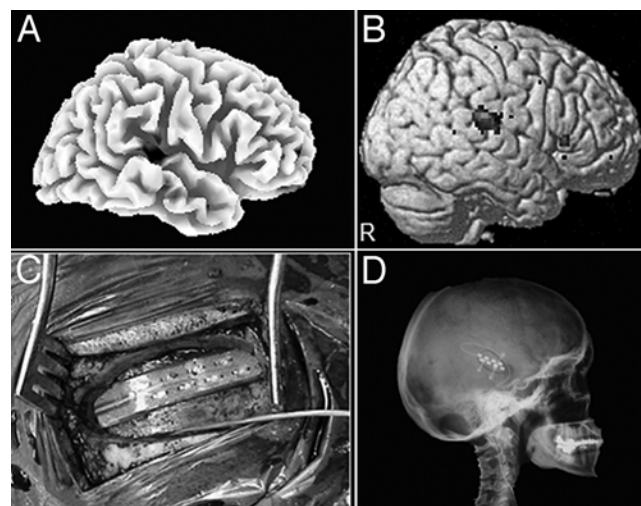


FIG. 1. **A:** Resting-state electroencephalography source localization demonstrating gamma (30–45 Hz) activity in the right auditory cortex in a patient with left-sided, 6000-Hz, pure tone tinnitus. **B:** A 3-T fMR image with BOLD activation evoked by tinnitus-matched sound presentation (6000 Hz) in the same patient in the right auditory cortex. **C:** Intraoperative photograph of the extradural electrode overlying the secondary auditory cortex. **D:** Postoperative radiographic image demonstrating location of the electrode.

In all patients, electrodes were implanted extradurally (Lamitrode 44 or Lamitrode 88; St. Jude Medical Neuromodulation Division) on a target over the secondary auditory cortex by using a previously described method.^{9,11,12} In summary, patients intractable to any treatment for their tinnitus undergo a TMS of the secondary auditory cortex both in burst and tonic mode, as previously described.^{14,15,40} We use a Super Rapid stimulator (Magstim, Inc.), which is capable of repetitive pulse modes/tonic stimulation of up to 50 Hz, as well as burst stimulation performed using a custom-made program capable of delivering burst stimuli (3–5 pulses at 50 Hz). If the TMS can ameliorate the tinnitus transiently in a placebo-controlled way in 2 separate sessions for a more than 20% tinnitus reduction, the patients are offered an implant of a Lamitrode 44 or Lamitrode 88 electrode on a predetermined area of the secondary auditory cortex. The target is selected by means of fMR imaging by using a method previously described.^{12,32,54} The frequency and intensity of the sound used as a stimulus to evoke a BOLD response is matched to the tinnitus perceived by the patient.

The electrode is implanted using a technique that has been previously described as well.^{9,11,12} The Lamitrode 44 lead has 8 individually programmable contacts embedded in it, with an electrode span of 28 mm and a 60-cm lead length. The paddle is configured using two 4-contact arrays with 1-mm lateral spacing. The contacts are 4.1 mm long and 2.5 mm wide, and longitudinal spacing measures 3 mm. The Lamitrode 88 has a similar configuration, but holds 16 contacts. A straight 6-cm-long incision is made overlying the auditory cortex, as determined by the fMR imaging-guided neuronavigation. The 6×2 -cm craniotomy and the location for the electrode placement are tailored in fMR imaging-based navigated fashion. After

bipolar coagulation of the dura mater to destroy sensory nerve endings, the lead, placed extradurally, is sutured to the dura and tunneled subcutaneously to the abdomen, where it is externalized.

On the 3rd postoperative day, trial stimulations are started. All patients undergo a tonic stimulation^{10–12} at 40 Hz and a burst stimulation¹⁷ at 40 Hz consisting of 5 spikes with a 1-msec pulse width and a 1-msec interspike interval in a charge-balanced way; that is, at 40-Hz burst 500-Hz spike frequencies in random order. If no suppression can be obtained with these settings, a very labor-intensive trial and error programming session is initiated, in which we try multiple frequencies, multiple pulse widths, and multiple stimulation configurations (Fig. 2).

The tonic and burst stimuli are delivered by a commercially available rechargeable IPG (Eon; St. Jude Medical Neuromodulation Division) capable of delivering tonic and burst mode stimulation, using a custom-made software program.

The 43 patients were asked to rate their tinnitus intensity on a visual analog scale before (preoperative) and after (postoperative) tonic and burst stimulation. Because the stimulations do not generate sensory activation and thus cannot be perceived consciously, they can be performed in a placebo-controlled way. Unfortunately, placebo responses were not uniformly charted and can therefore not be provided.

The fMR imaging protocol was changed during the course of this retrospective study, from music presentation to presenting tinnitus-matched sound (Fig. 3), and the MR imaging machine was changed from a 1.5-T to a 3-T magnet (3-T MR imaging unit [INTERA; Philips Medical Systems]). The electrodes were changed from Lamitrode 44 to Lamitrode 88 to cover a larger anteroposterior area of the posterior part of the superior temporal gyrus, and burst stimulation was added once it became available.¹⁷ Therefore, the results have to be considered with care.

Results

Stimulation Protocol

In the period immediately following implantation, activating the electrode changes the tinnitus intensity within seconds, and the tinnitus intensity increases again within seconds when the electrode is deactivated. Because the patient does not feel the stimuli, this can be performed in a placebo-controlled way.¹⁶

Results from electrical stimulation delivered through extradurally implanted electrodes showed that a total of 29 patients (67.44%) responded to the stimulation if results from both tonic and burst stimulation were combined. On average, the stimulation with the implanted electrodes reduced the tinnitus by $53.2\% \pm 27.85\%$ in the participants. Thirteen of these patients (48.14%) who did not respond to tonic stimulation, did so to burst stimulation (Fig. 4), and the mean suppression effect was $51.30\% \pm 28.52\%$. Sixteen patients (37.21%) responded to tonic stimulation, yet 8 of these patients (50%) had a better suppression effect when they received burst instead of tonic stimulation. The mean suppression effect for this latter

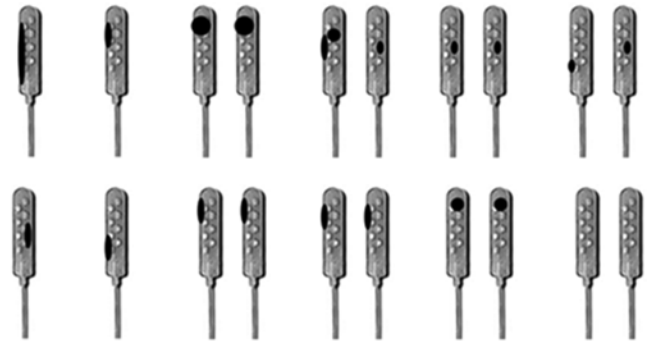


Fig. 2. Graphic depictions of electrodes showing multiple (12) trial and error programming attempts with different stimulation designs due to recurrence of tinnitus. Each electrode demonstrates the poles selected that yield maximal tinnitus suppression. When 2 electrodes are shown adjacent to each other, 2 stimulation settings are programmed to run concurrently.

group was $53.01\% \pm 31.78\%$ for burst stimulation, whereas it was $24.10\% \pm 11.63\%$ for tonic stimulation (Fig. 5). For patients who only responded to tonic stimulation, the suppression effect was $52.18\% \pm 28.91\%$ (Fig. 6). In total, 14 patients (32.56%) did not obtain a tinnitus suppression on either tonic or burst stimulation, although they experienced a tinnitus suppression effect of more than 20% on TMS. However, overall, a small but significant positive correlation (that is, a Pearson correlation) was revealed between the suppression effect due to TMS and the suppression effect due to cortical stimulation ($r = 0.38$, $p < 0.05$).

Comparison of the amount of suppression experienced by responders based on the stimulation protocol yielded no significant difference between the responses to tonic versus burst stimulation.

Univariate ANOVA revealed that tinnitus type (that is, pure tone, narrowband noise, or both) had a significant influence on the amount of suppression ($F = 7.79$, $p < 0.01$). A Bonferroni multiple comparison analysis demonstrated that pure tone tinnitus (mean $70.85\% \pm 29.44\%$) was better suppressed than both narrowband noise (mean $36.96\% \pm 24.80\%$) and the combination of pure tone with narrowband noise (mean $28.57\% \pm 26.98\%$) in the patients studied (Fig. 7). Furthermore, there was a significant effect obtained for the tinnitus side (unilateral or bilateral, $F = 4.07$; $p < 0.05$), demonstrating that unilateral tinnitus (mean $49.09\% \pm 28.99\%$) had better suppression than bilateral tinnitus (mean $44.80\% \pm 43.86\%$). No significant effect was obtained for the interaction of tinnitus type \times tinnitus side or for tinnitus duration. This was further confirmed with a Pearson correlation indicating that there was no correlation between tinnitus duration and the suppression effect of cortical stimulation. However, a negative correlation (Pearson correlation) was found between TMS suppression and tinnitus duration ($r = -0.37$, $p < 0.05$). No effect was found for patient sex or age on the amount of suppression due to cortical stimulation.

Furthermore, the type of stimulation (burst or tonic) did not depend on the tinnitus side. However, a likelihood ratio revealed that the type of stimulation was partially dependent on tinnitus type ($\chi^2_{\text{likelihood ratio}} = 5.04$, $p < 0.10$;

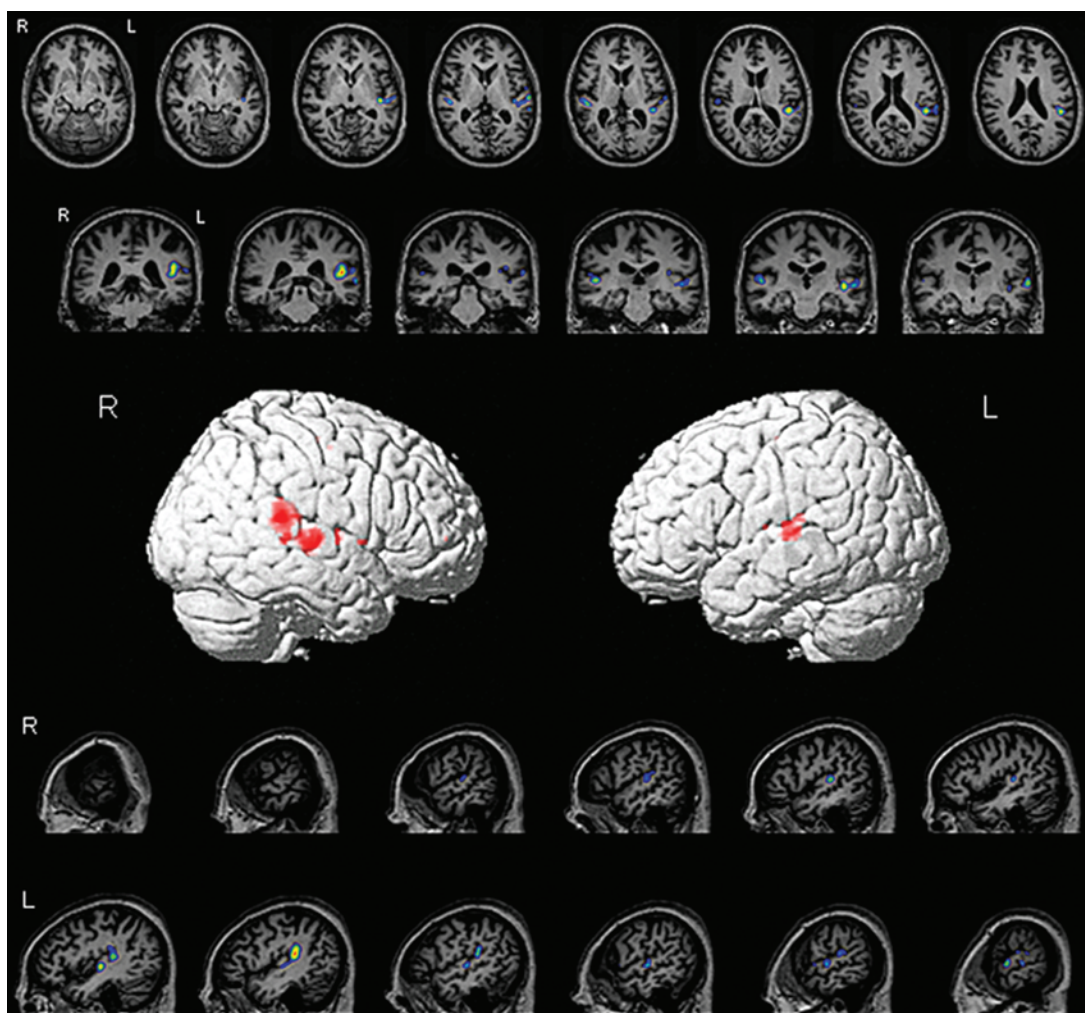


FIG. 3. A series of 3-T fMR images showing the BOLD response elicited by tinnitus-matched sound presentation in the MR imaging unit, with 3D, axial, coronal, and sagittal representations. Example of an fMR imaging session performed in a female patient with unilateral left-sided tinnitus at 5000 Hz (noise-like tinnitus).

see Table 1). More precisely, patients with the combination of pure tone and narrowband noise and with narrowband noise tinnitus responded more to burst stimulation in comparison with patients who had only pure tone tinnitus. Tinnitus duration and patient age and sex could not predict whether patients would respond to tonic or burst stimulation.

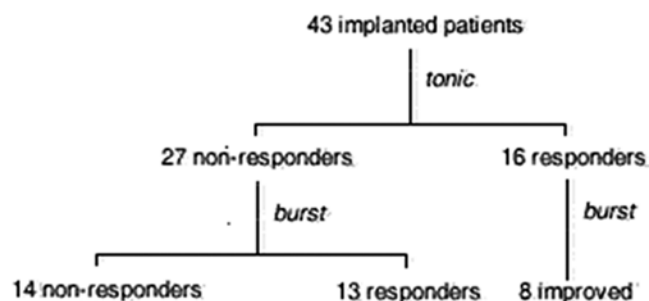


FIG. 4. Dendrogram showing responders and nonresponders to tonic or burst stimulation delivered through an extradurally implanted electrode.

Side Effects

Side effects are limited and do not occur at the stimulation parameters required for tinnitus suppression. Side effects may occur when high-frequency, high-intensity stimulation is used. Such side effects can consist of a feeling of being tipsy, problems finding words, dizziness, vertigo, and hearing perception changes (hearing perceived as being clearer, even for the patient's own voice),¹¹ and also altered spatial localization of the self (such as an out-of-body experience¹⁶ and altered spatial localization of external sounds). Stimulating the right auditory cortex at high intensity for left-sided tinnitus due to left-sided sensorineural hearing loss or deafness can induce the subjective experience that the patient can hear with his or her deaf ear and not the functional ear.¹⁰ Increasing the intensity first induces a perception of hearing in both ears, and at even higher intensities, the hearing is perceived only in the deaf ear.

If patients present with a feeling of aural pressure, successful tinnitus suppression by cortex stimulation also removes this feeling in all such patients, but the pressure

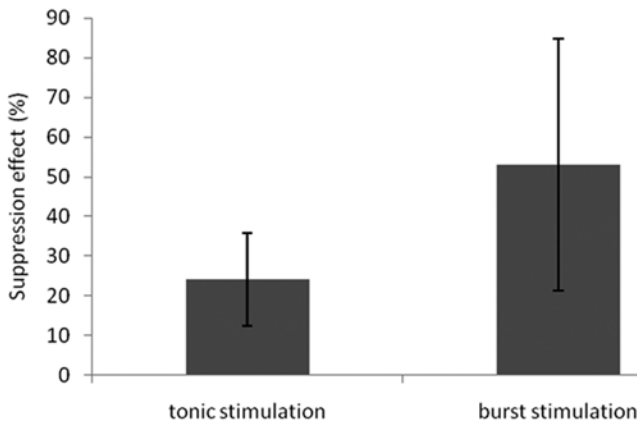


FIG. 5. Bar graph showing the amount of tinnitus suppression for responders to tonic stimulation and burst stimulation.

and the tinnitus do not always decrease with identical programming of the stimulation.

Complications Related to the Procedure

Complications specific for this approach are limited but can be severe. Epileptic seizures occurred in 3 of the 43 patients. In 2 patients, the epileptic seizures most likely occurred because of prolonged stimulation without enough stimulation-free intervals when the patient was still using an external stimulator, which cannot be programmed by the investigator but relies on patient cooperation. Since this occurred, the patients now only use programmable IPGs during the period of externalized stimulation. In a third patient, the epileptic seizure occurred during IPG programming in the hospital. It is probably wise, based on these data, not to include patients with epilepsy as candidates for this procedure.

Two major complications occurred with intradural implants. One of the 4 patients in whom the electrode was implanted directly on the surface of the primary auditory cortex¹⁰ developed postoperative intracranial bleeding in the superior temporal sulcus, at a distance from the sylvian fissure in which the electrode was inserted, with speech disturbances as a result, but a decrease in tinnitus occurred as well as a result of the bleeding. One of the 4 patients developed an intracranial abscess that required surgical evacuation, with removal of the electrode, with a good outcome but with worsening of the tinnitus. Thus, this treatment should be preferentially performed extradurally, because no serious complications were encountered in the last 30 patients, in whom the extradural technique was used.

Discussion

Advances in understanding of the pathophysiological mechanisms of tinnitus and in techniques for stimulation of specific structures in the brain as a treatment for tinnitus are not always the results of rigid, basic neuroscience. Retrospective analysis of clinical data such as those in this study can help to elucidate the strengths and weaknesses of electrical stimulation of the auditory cortex for intrac-

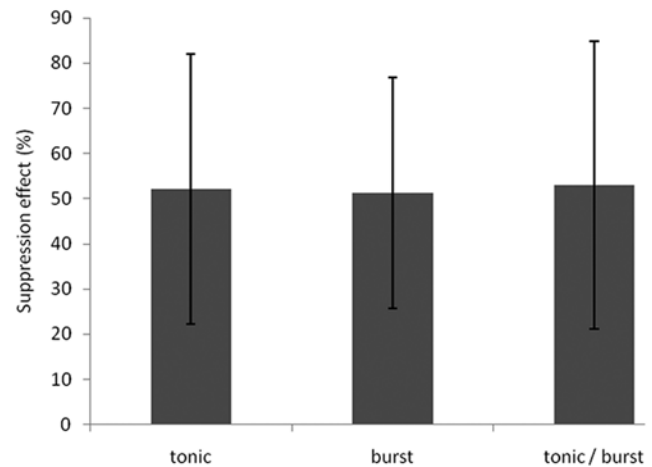


FIG. 6. Bar graph showing the amount of suppression for responders to tonic stimulation, burst stimulation after no response to tonic stimulation, and burst stimulation after response to tonic stimulation, respectively.

table severe tinnitus and provide critical information for future, more rigidly performed studies analyzing more detailed and specific clinical or scientific questions.

In this study, we focused on the possibility of using the results of TMS obtained while screening patients who might benefit from long-term stimulation from implanted electrodes. Unfortunately, we found that TMS is not a good predictor for who is going to benefit from an implant. However, some relevant preliminary conclusions can be drawn from analyzing the results of these first patients with implanted cortical stimulating electrodes.

Even though all patients who received implants had solid suppression of their tinnitus from TMS, as obtained at least twice in placebo-controlled tests, only 16 (37%) of 43 patients benefited from the implant when tonic stimulation was used. Because almost two-thirds of the patients obtained no relief (or < 20% relief), this can be considered a poor result. However, because the only patients receiving implants were those who responded twice in a placebo-controlled TMS on 2 separate days, it is not known whether performing the implant without TMS would worsen the results even more, or improve them.

Transcranial magnetic stimulation has some prognostic value if the patient's condition responds to the implant. We found a small but significant correlation between the amount of tinnitus suppression obtained with TMS and the amount obtained with the implant.

The stimulation design (burst vs tonic stimulation)

TABLE 1: Association between tinnitus types and type of stimulation

Stimulation Type	Tinnitus Type (%)			Total (%)
	Pure Tone	Narrowband Noise	Pure Tone & Narrowband Noise	
tonic	16.7	16.7	0	33.3
burst	16.7	29.2	20.8	66.7
total	45.8	33.3	20.8	100

significantly influences the number of patients who can be helped. Multiple reasons might exist for this effect. As mentioned in a previous study, tonic stimulation was not capable of suppressing noise-like tinnitus,¹¹ but only pure tone tinnitus. We found the same result in this larger sample of patients. However, based on data from burst TMS,^{14,15} it was suggested that changing the electrical stimulation design to the burst type could benefit patients presenting with noise-like tinnitus.¹⁷ Furthermore, it was also shown that, if a patient presents with both a pure tone and a noise-like component, both components had to be relieved to yield a substantial decrease in tinnitus-related distress.¹¹ Only suppression of the pure tone component, even if complete, did not benefit the patients. Indeed, using burst stimulation still permits us to obtain tinnitus reduction in almost half the patients (13 [48%] of 27) who initially do not respond to tonic stimulation (Fig. 4). Furthermore, 50% of patients who respond to tonic stimulation benefit more from burst than from tonic stimulation. In this group of responders to tonic stimulation, tinnitus suppression was 24% with tonic versus 53% for burst stimulation (Fig. 5). Therefore, adding burst stimulation to the armamentarium switches the treatment from a poor response rate to an acceptable, although far from ideal, suppression rate. A total of 2 of 3 (29 [67%] of 43) participants responded to stimulation via the implanted electrodes, with an average tinnitus reduction of 53%. Some participants in the study only responded to tonic stimulation; this subgroup of patients has a 52% suppression effect. According to these findings, both burst and tonic stimulation yield the same amount of suppression, yet more patients benefit from burst than from tonic stimulation. Thus, the question of when to apply burst or tonic stimulation arises. Tinnitus duration and the patient's age and sex could not predict whether patients would respond to tonic or burst stimulation. The only important factor seems to be the tinnitus character; that is, noise-like tinnitus responds better to burst stimulation, and pure tones respond equally well to burst and tonic stimulation, confirming our previously published data.¹⁷ A previous study of burst TMS demonstrated that women seem to respond better to this type of TMS than men,¹⁵ and this does not seem to hold for electrical stimulation via implanted electrodes.

The type of tinnitus has a significant influence on the degree of tinnitus suppression that can be obtained. Pure tone tinnitus was suppressed to a greater extent (71% tinnitus reduction) than noise-like tinnitus (37% reduction). The worst results (only 29% reduction; see Fig. 7) were obtained in individuals who had a combination of the pure tone and a noise-like tinnitus.

In a previous report on 12 patients, it was shown that those with bilateral tinnitus (2 patients) did not benefit from stimulation via implanted electrodes.¹¹ In the present larger study, these results do not seem to hold. Although there is a significant difference between unilateral and bilateral tinnitus, the minimal difference (49% vs 45% tinnitus suppression; Fig. 8) is not clinically relevant. It may sound surprising that the amount of suppression obtained in unilateral and bilateral tinnitus is essentially the same. All patients with bilateral tinnitus in the present study re-

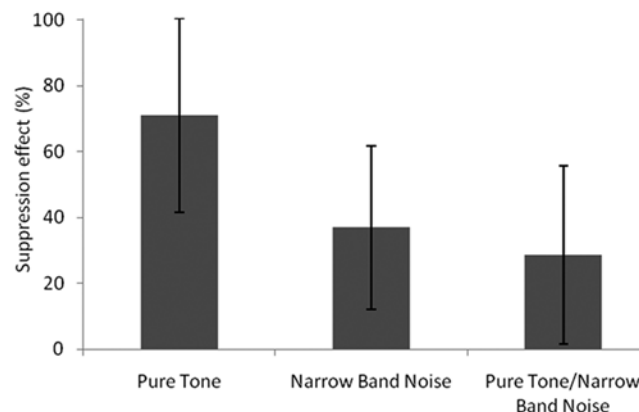


FIG. 7. Bar graph showing the amount of tinnitus suppression obtained in patients with electrode implants who responded to TMS after presenting with pure tone, narrowband noise, or combined pure tone and narrowband noise tinnitus, respectively.

ceived electrode implants on the right side, because this yielded the best results on preoperative tests performed using TMS.

No correlation was found between the amount of suppression obtained and the sex, age, or tinnitus duration in patients with implanted electrodes. Tinnitus duration is an important factor in the success rate in TMS studies, both in diagnostic single-session TMS and repetitive TMS as a treatment. The longer the tinnitus lasts prior to TMS application, the poorer the suppression rate,^{18,29,31,48} similar to what has been found for other tinnitus treatments such as microvascular decompressions.^{5,13,44,51} It is of interest to note that we found the same correlation in this study population between TMS suppression of tinnitus and the tinnitus duration, but did not find this when analyzing the data from the implanted electrodes for the same group of patients. This fact, combined with the fact that there are differences between men and women for responsiveness to burst TMS but not to electrical stimulation, and the fact that TMS suppression does not guarantee suppression with an implant suggest that TMS and electrical stimulation might not have the same neurobiological mechanism for modulating brain functioning.

There are thus consistent differences between the results of cortical stimulation performed using TMS and stimulation delivered through implanted electrodes, although both methods are supposed to induce similar electrical currents in the auditory cortex. The inability to produce the same benefit as TMS by using electrical current induced by electrodes placed on the dura mater over the auditory cortex is puzzling but cannot be explained yet.

In the period immediately following implantation, activating the electrode changes the tinnitus intensity within seconds, and the tinnitus intensity increases again within seconds when the electrode is deactivated. However, this might only be true in the immediate postoperative period. In the first patient in whom we implanted an electrode,¹² whose IPG stopped working because the battery was depleted after 5 years of stimulation, this was recognized by the recurrence of the high-pitched component of her tinnitus. It is unknown how long the IPG had

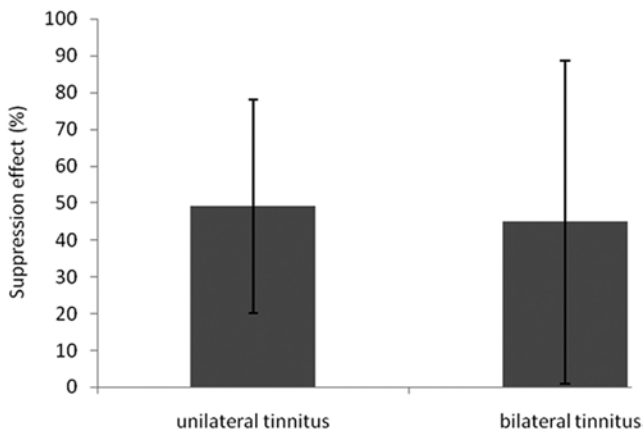


Fig. 8. Bar graph showing the amount of tinnitus suppression obtained in patients with electrode implants who responded to TMS after presenting with unilateral and bilateral tinnitus, respectively.

lacked battery power, but it took another 3 weeks for the low-pitched component of the tinnitus to reappear, suggesting that the residual inhibition becomes longer with long-term stimulation.

Failures of ACS

Although burst stimulation can increase the number of responders to ACS, there is still one-third of patients who do not show any improvement with the stimulation. What are the reasons for not obtaining a 100% response rate? Some conceivable reasons are as follows: 1) the electrode is incorrectly positioned; 2) the contralateral auditory cortex is not involved in tinnitus generation in all patients; 3) TMS is not prognostic of subsequent implant success; and 4) the stimulation design is not adapted.

Malpositioning of the electrode is possibly due to spatial resolution of the 3-T fMR images ($2 \times 2 \times 2 \text{ mm}^3$),⁵⁹ the neuronavigation system (0.3–2.6 mm),⁴⁹ and surgical inaccuracy (variable), which can add up to 5 mm or more. This can be evaluated by fusion of a postoperative CT scan with the preoperative fMR imaging study^{10,11} (Fig. 9) and subsequently corrected if necessary.

The contralateral secondary auditory cortex is the target for unilateral implants, and the right secondary auditory cortex is the target for patients with bilateral tinnitus. Based on some literature on repetitive TMS, it is possible that all the electrodes should have been implanted overlying the left auditory cortex.³⁷ This idea is derived from PET studies, which usually find increased metabolism in the left auditory cortex,^{33,34} irrespective of the side on which the tinnitus is perceived, and which also find that TMS on the left side can suppress this metabolic activity.³⁹ On the other hand, fMR imaging,^{32,34,41,54} electroencephalography,⁵⁶ and MEG^{45,58} studies suggest the auditory cortex involvement might be located contralaterally to the tinnitus side. This has led to criticism that implanting contralaterally might be implanting on the wrong side of the brain,²¹ which can be a reason to use TMS to verify whether the observed signal changes are causally related to the perceived tinnitus. As mentioned before, however, it is clear that TMS, even when performed twice and pla-

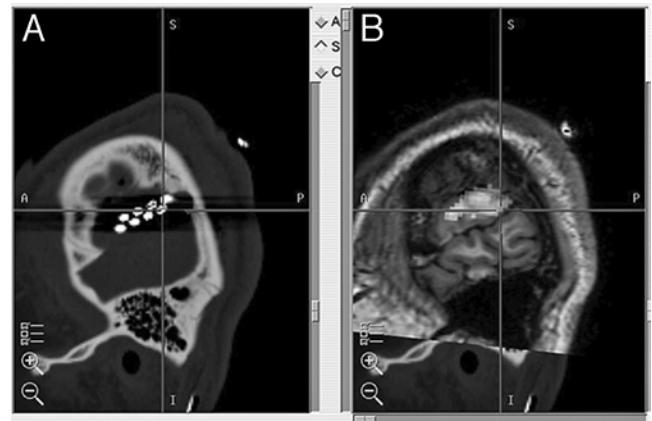


Fig. 9. **A:** Postoperative CT scan demonstrating positioning of electrode. **B:** Preoperative 3-T fMR image demonstrating the BOLD activation evoked by tinnitus-matched sound presentation. The images were fused in the Stealth Neuronavigation Station. The crosshairs are overlying the same anatomical location, demonstrating correct positioning of the electrode.

cebo controlled before every implant, is not a perfect predictor of success in subsequent implants.

The stimulation design might not be adapted. As has been shown, noise-like tinnitus does not seem to respond to tonic stimulation but does so to burst stimulation.¹⁷ If not for the development of burst stimulation, the results in this series of 43 patients would be very poor, with only 33% responding, because 48% of patients only responded when receiving burst stimulation. Based on this knowledge, it can be worthwhile to develop yet other stimulation designs that might be even more capable of modulating the tinnitus-related activity.

One way of finding out which patients might benefit is to analyze functional imaging data in responders and nonresponders and to look for differences in resting state or evoked activity patterns between each group. This could lead to the discovery of new anatomical neuromodulation targets in nonresponders. This is possible because, although this study focuses on the auditory system activity, this does not exclude other pathways that can modulate tinnitus-related auditory system hyperactivity. It has been shown that modulation of the somatosensory system by electrical transcutaneous stimulation of the median nerve⁴³ can influence tinnitus, as can modulation of the dorsolateral prefrontal cortex via transcranial direct current stimulation.⁵⁷ Furthermore, the visual system can modulate tinnitus intensity, as demonstrated by gaze-evoked tinnitus.² Electrical stimulation via deep brain stimulation in the ventralis intermedius nucleus can exert a tinnitus-modulating effect⁵³ as well. Thus, in the future, more studies in which neuromodulation is used for tinnitus can be expected, and due to the unpredictable response to auditory cortex implants, it is of great importance to find predictors or prognostic tests that will tell which patients with tinnitus might benefit from ACS.

Conclusions

This study confirms that brain stimulation can be a

valuable option for patients with severe intractable tinnitus. With proper selection of the patients, and preferably by extradural stimulation, this method is capable of suppressing tinnitus completely or partially in 67% of patients who experience suppression of their tinnitus from TMS, on the condition that burst stimulation is also applied. Using the results from TMS in the selection of patients for permanent implantation of electrodes placed for stimulation of the auditory cortex seems logical as a prognostic criterion. However, the results of this study indicate that, even in those in whom TMS produces good suppression of their tinnitus, 33% or more still are not likely to benefit with this operation. It is therefore essential to find out why not all patients benefit from ACS. The development of new stimulation designs and targets, as well as improved prognostic tests, is needed to improve results of this potentially promising technique.

Disclosure

The authors have not received any financial remuneration for this manuscript. The first author (D.D.R.) has submitted a patent application for the described technique and burst stimulation design. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: De Ridder. Acquisition of data: Vanneste, Sunaert. Analysis and interpretation of data: Vanneste. Drafting the article: Vanneste, De Ridder. Critically revising the article: Menovsky, van de Heyning, Møller. Reviewed final version of the manuscript and approved it for submission: Vanneste. Statistical analysis: Vanneste, Kovacs. Study supervision: De Ridder, Menovsky.

Acknowledgments

The authors thank the St. Jude Medical Neuromodulation Division and the Tinnitus Research Initiative for their educational grants.

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Manuscript submitted March 7, 2010.

Accepted November 15, 2010.

Please include this information when citing this paper: published online January 14, 2011; DOI: 10.3171/2010.11.JNS10197.

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