

Dorsolateral Prefrontal Cortex Transcranial Magnetic Stimulation and Electrode Implant for Intractable Tinnitus

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Key words

- Auditory
- Dorsolateral prefrontal cortex
- Electrode
- Frontal cortex
- Functional magnetic resonance imaging
- Neurostimulation
- Tinnitus
- Transcranial magnetic stimulation

Abbreviations and Acronyms

ACC: Anterior cingulate cortex
BOLD: Blood-oxygen-level dependence
BRL: Brain Research Laboratories
DLPFC: Dorsolateral prefrontal cortex
EEG: Electroencephalography
fMRI: Functional magnetic resonance imaging
IPG: Internal pulse generator
sLORETA: Standardized low-resolution brain electromagnetic tomography
tDCS: Transcranial direct current stimulation
TMS: Transcranial magnetic stimulation
VAS: Visual analog scale



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INTRODUCTION

Tinnitus is an elusive symptom affecting 10% to 15% of the population (2) for which no proven treatments exist (12). It severely impairs the quality of life in 2% to 3% of the population (2). Some forms of nonpulsatile tinnitus are considered to be an auditory phantom phenomenon (15) analogous to central neuropathic pain (26). Both pain and tinnitus share similarities in their clinical expression, pathophysiological mechanisms, and treatment approaches (9, 26, 36).

It has been demonstrated that both magnetic (10, 16, 18, 22) and electrical (9, 10, 35) stimula-

■ **OBJECTIVE:** Tinnitus is a distressing symptom that affects up to 15% of the population; no satisfactory treatment exists. We present a novel surgical approach for the treatment of intractable tinnitus based on electrical extradural stimulation of the dorsolateral prefrontal cortex via an electrode implant. Tinnitus can be considered an auditory phantom phenomenon similar to deafferentation pain in the somatosensory system. It is characterized by gamma-band activity in the frontal cortex that can be visualized with the use of electroencephalography, magnetoencephalography, and functional magnetic resonance imaging (fMRI).

■ **CASE DESCRIPTION:** Transcranial magnetic stimulation (TMS) is a noninvasive technique capable of modulating the ongoing activity of the human brain. When linked with a neuronavigation system, fMRI-guided frontal cortex TMS can be performed in a placebo-controlled way. If it is successful in suppressing tinnitus, this focal and temporary effect can be maintained in perpetuity by implanting a cortical electrode. A neuronavigation-based auditory fMRI-guided frontal cortex TMS session was performed in a patient experiencing intractable tinnitus, yielding 50% tinnitus suppression. Two extradural electrodes were subsequently implanted, also based on auditory fMRI-guided navigation. Postoperatively the tinnitus has improved by 66.67% and progressively continues to improve for more than one year.

■ **CONCLUSION:** Focal extradural electrical stimulation of the dorsolateral prefrontal cortex at the area of cortical plasticity is capable of suppressing contralateral tinnitus partially. TMS might be a possible method for noninvasive studies of surgical candidates for implantation of stimulating electrodes for tinnitus suppression.

tion via implanted electrodes of the primary and secondary auditory cortex in humans can benefit some patients who experience tinnitus. Studies in which the authors use magnetoencephalography have demonstrated that tinnitus is related to increased gamma-band activity in the contralateral auditory cortex (21, 43), and in a recent study in which the authors used electroencephalogram (EEG), they demonstrated that the amount of contralateral gamma-band activity actually correlates with the perceived intensity of the phantom sound (37).

Recently, research revealed that nonauditory brain areas are also involved in nonpulsatile tinnitus. In particular, the dorsolateral prefrontal cortex (DLPFC) seems to play a specific role in auditory processing and tinnitus. The DLPFC has a bilateral facilitatory effect on auditory memory storage and contains auditory memory cells (3).

The DLPFC also exerts early inhibitory modulation of input to the primary auditory cortex in humans (19) and has been found to be associated with auditory attention (1, 20, 41) resulting in top-down modulation of auditory processing (25). This finding was further confirmed by electrophysiological data indicating that tinnitus might occur as the result of a dysfunction in the top-down inhibitory processes (30). Interestingly, noninvasive neuromodulation such as transcranial direct current stimulation (tDCS) on the DLPFC can be used to successfully improve both tinnitus and distress that occurs as a result of tinnitus (38). Transcranial magnetic stimulation (TMS) that combines frontal and auditory stimulation yields results better than those obtained by auditory cortex stimulation alone, further demonstrating the involvement of DLPFC in tinnitus (17).

In this work we describe a novel treatment of severe tinnitus in a patient by using neurostimulation of the contralateral DLPFC. We believe that this is the first example of such treatment of tinnitus and the first frontal cortex implant ever performed for human disease.

CASE REPORT

History

A 57-year-old patient presented with a very disturbing high-pitched unilateral, left-sided, nonpulsatile tinnitus, which he scored 7 to 8 (of 10) for intensity and 9 to 10 (of 10) for distress on a visual analog scale (VAS). His tinnitus was treated conservatively with flu-anxol 0.5 mg plus melitracen 10 mg in the morning and clonazepam 2 mg at night. Phase-shift treatment was unsuccessful (23). Despite conservative treatments, his tinnitus distress worsened from grade II to grade III on the tinnitus questionnaire (14, 24, 39).

Audiologic Examination

Only hearing loss at high frequencies compatible with presbycusis was noted. Tinnitus matching revealed that the tinnitus intensity was 3 dB sensation level and the pitch matched 8000 Hz. Because the hearing loss matched the tinnitus pitch, the hearing loss was considered causal to the tinnitus.

Functional Magnetic Resonance Imaging

The patient was scanned on a 3T imager with a paradigm consisting of 50 seconds of tinnitus-matched sound, alternated with 50 seconds of nonstimulation. This alternation was repeated six times and also performed for nontinnitus-matched sound as a control. A T1-weighted structural image was acquired with the use of a 3D turbo fast echo sequence. Postprocessing was performed with SPM99 and consisted of realignment (to correct for bulk head motion), coregistration of the functional and structural scans, spatial smoothing, and statistical analysis to determine the significantly activated brain regions ($P < 0.05$ corrected for multiple comparisons). Functional magnetic resonance imaging (fMRI) of the frontal cortex demonstrated an asymmetry in activation strength and extent of

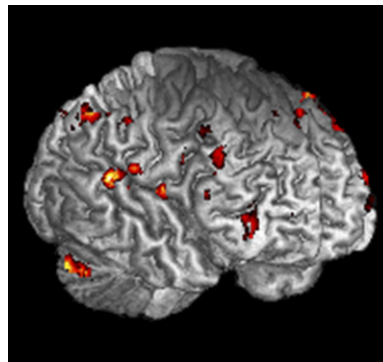


Figure 1. fMRI demonstrates an asymmetry in activation strength and extent of the DLPFC ($L < R$). BOLD signal elicited by tinnitus matched (for frequency = pitch) sound presentation.

area DLPFC ($L < R$; **Figure 1**). The noninvasive neuromodulation and the surgical implantation of electrodes on the frontal cortex were performed after approval from the ethical committee of the University Hospital of Antwerp, Belgium.

EEG

EEG recordings were obtained in a fully lighted room with the patient sitting upright on a small-but-comfortable chair. The actual recording lasted approximately 5 minutes. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2) in the standard 10–20 International placement referenced to linked ears and impedances were checked to remain below 5 k Ω . Data were collected with the patient's eyes closed (sampling rate = 1024 Hz, band passed 0.15–200 Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz, and subsequently transposed into Eureka! Software (13), then plotted and carefully inspected for manual artifact-rejection. All episodic artifacts, including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact, were removed from the stream of the EEG.

Average Fourier cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–45 Hz). In addition, the normative database of the Brain Research Laboratories (BRL)

of New York University was used. Exclusion criteria for the BRL database were known psychiatric or neurological illness, psychiatric history drug/alcohol abuse in a participant or any relative, actively taking psychotropic/central nervous system medications, or a history of head injury (with loss of consciousness) or seizures, headache, or physical disability.

Approximately 3 to 5 minutes of EEG was continuously recorded while the participant sat in a comfortable chair with his eyes closed in a quiet and dimly lit room. EEG data were acquired at the 19 standard leads prescribed by the 10–20 international system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) by the use of both earlobes as reference and enabling a 60-Hz notch filter to suppress power line contamination. The resistance of all electrodes was kept below 5 k Ω . Data of the BRL database were acquired by use of the 12-bit A/D BSA acquisition system (Neuroetrics, Inc., New York, New York, USA) and sampled at 100 Hz. For consistency, we subsequently up-sampled the BRL database to 128 Hz by using a natural cubic spline interpolation routine (13). We removed from all biological, instrumental, and environmental artifacts, paying particular attention to biological artifacts generated by the eyes, the heart, and the muscles of the neck, face, and jaw. EEG recordings were visually inspected on a high-resolution screen, and epochs containing visible artifacts were marked and ignored for ensuing analysis.

Standardized low-resolution brain electromagnetic tomography (sLORETA) (31) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the seven frequency bands. sLORETA computes electric neuronal activity as current density (A/m²) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size: 5 × 5 × 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by the digitized Montreal Neurological Institute probability atlas. To reduce confounds that have no regional specificity, such as total power intersubject variability, a global normalization of the sLORETA images was performed before statistical analyses.

The tomography sLORETA has received considerable validation from studies in which the authors combined LORETA with other more established localization meth-

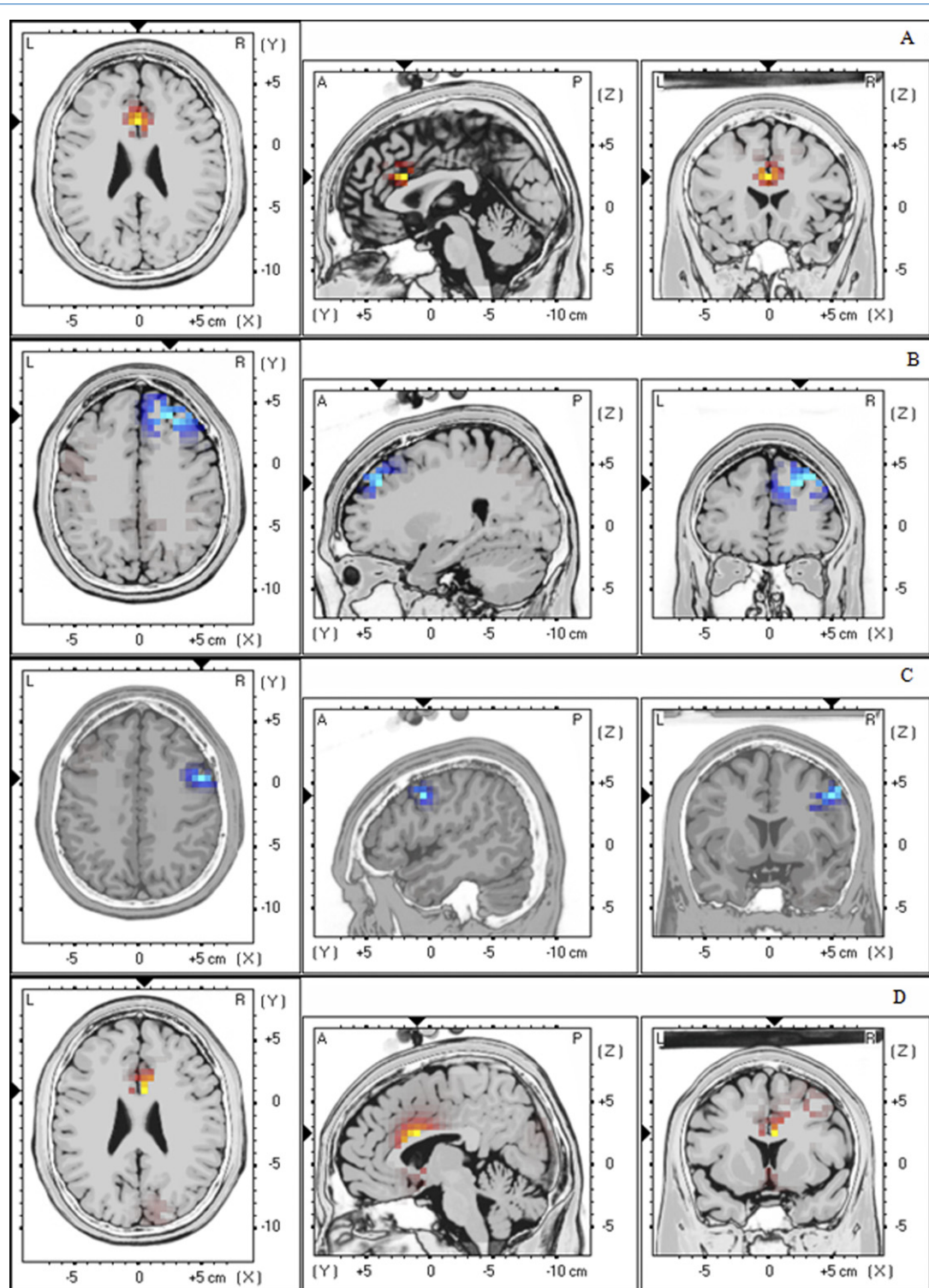


Figure 2. (A) Preoperative EEG source analysis (sLORETA) before treatment shows an increased activity in the ACC in comparison with an age-matched normative database of normal subjects. (B) Preoperative EEG source analysis after TMS of DLPFC reveals a reduced activation in the DLPFC in comparison with an age-matched normative database of normal subjects. (C) One year postoperative EEG source analysis during stimulation of DLPFC reveals a reduced activation in the DLPFC in comparison with an age-matched normative database of normal subjects. (D) One year postoperative EEG source analysis, after we turned off the stimulation, reveals a increased activation in the ACC in comparison with an age-matched normative database of normal subjects.

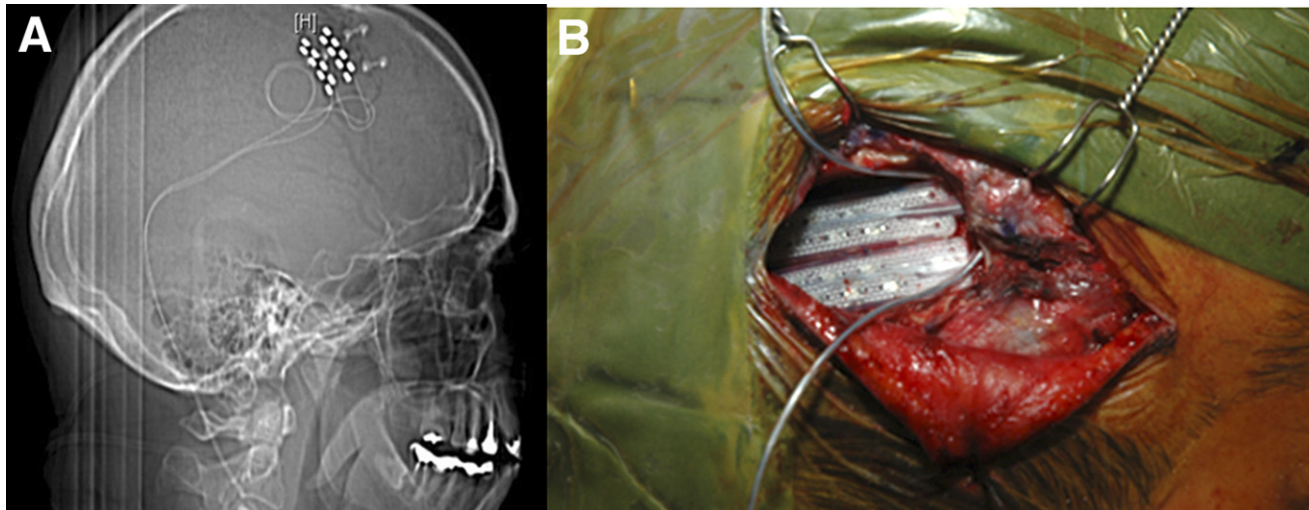


Figure 3. A postoperative radiograph (A) demonstrates the placement of the extradural (B) electrodes.

ods, such as fMRI (28, 40), structural MRI (44), and positron emission tomography (11, 32, 48). Furthermore, the validation of sLORETA has been determined by localization findings obtained from invasive, implanted depth electrodes, in which case there are several studies in epilepsy (46, 47) and cognitive event-related potentials (42). It is worth emphasizing those deep structures such as the anterior cingulate cortex (33) and mesial temporal lobes (45) can be correctly localized with these methods. A comparison was made between the patient- and age-matched subjects of the BRL for the sLORETA imaging.

tDCS was applied bifrontally (38) but did not improve the patient's tinnitus perception, nei-

ther the tinnitus intensity nor his associated distress. TMS was applied 10 months after the patient developed tinnitus. We used a Super Rapid stimulator (Magstim Inc, Wales, United Kingdom), which is capable of repetitive pulse modes of up to 50 Hz. This magnetic stimulator was connected to a frameless stereotactic system (Brainsight; Magstim Inc), which allowed exact localization of the target area, which was chosen from the results of the fMRI study. The magnetic stimulation was directed towards the area of maximal fMRI activity, contralateral (right-sided DLPFC cortex) to the left-sided tinnitus. Different frequencies and intensities were applied at different sites. Auditory cortex stimulation both on the left and right side was negative (maximal 15% transient improvement of the tin-

nitus), but frontal cortex stimulation improved tinnitus intensity by 50%, with a maximal improvement at the right DLPFC (intensity from 7/10 to 4/10 and distress from 9/10 to 3/10), which could be repeated on separate sessions.

The maximal effect was obtained with the use of a 5-Hz burst at a pulse rate of 20 pps and an intensity of 80% of the threshold for evoking a motor response. Moving the coil 1 cm away from target reduced the effect of the stimulation on the tinnitus. When the stimulating coil was further away from the target, the stimulation had little effect on the tinnitus, and sham stimuli had no effect on the tinnitus. Sham stimulation consisted of delivering identical stimuli but with the coil orthogonal to the surface of the head, generating a magnetic pulse parallel to the surface of the brain. In this way, the clicking sound of the coil and the sensory contact is nearly identical to real stimuli.

Preoperative EEG source analysis (sLORETA) showed an increased activity in the anterior cingulate cortex (ACC) in comparison with an age-matched normative database of normal subjects (Figure 2A). Preoperatively, an EEG with source localization analysis also was performed before and after frontal TMS in an attempt to objectify that tinnitus improvement was correlated with a reduction in DLPFC activity in the right DLPFC after DLPFC-burst TMS compared with a normative database. Gamma-band activity was decreased at the area of stimulation (Figure 2B). This TMS-related clinical improvement and associated reduction of DLPFC

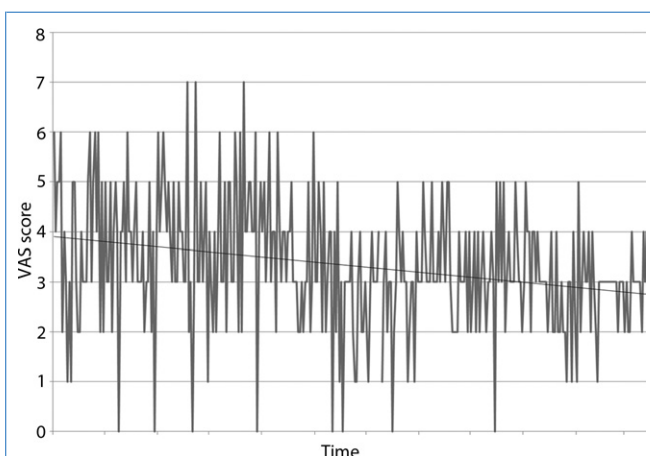
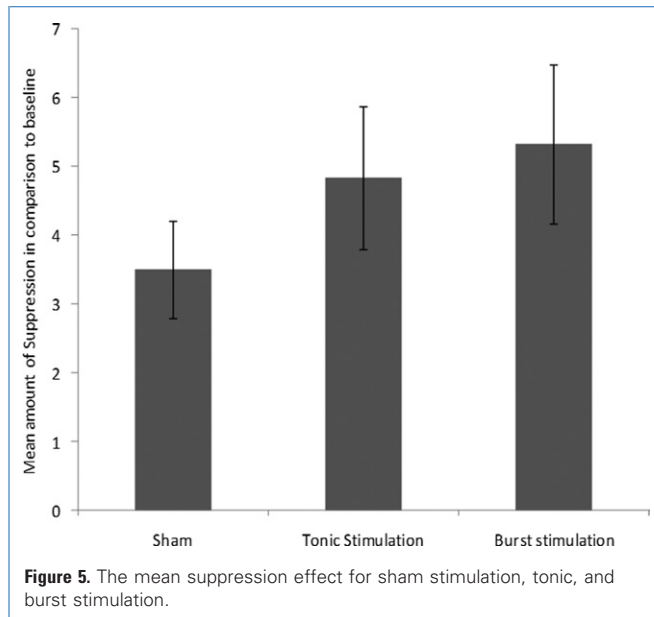


Figure 4. Further progressive improvement on average tinnitus intensity perception (VAS) for tinnitus for 356 days starting after implant activation.



activity provide further proof that cortical implantation might be a good option.

Electrode Implantation

Four months later, i.e., 2.5 years after the patient developed the tinnitus, two extradural eight-pole electrodes (Lamitrode 44; Saint Jude Medical Neurodivision, Plano, Texas, USA) were implanted for electrical stimulation of the DLPFC. The Lamitrode 44 lead comprises eight electrodes with a 28-mm electrode span and a 60-cm lead length, configured with two offset rows of four electrodes, each 4 mm × 2.5 mm with 3-mm spacing between the electrodes. An 8-cm incision was made overlying the DLPFC cortex, as determined by the fMRI-guided neu-

ronavigation. The 8 × 4-cm craniotomy (**Figure 3**) and the location for the electrode placement were tailored in the same navigated fashion. The lead, extradurally placed, was sutured to the dura after bipolar coagulation of the dura to prevent electrical activation of sensory endings in the dura resulting in painful stimulation. The lead was tunneled subcutaneously to the abdomen and connected to a 30-cm extension lead, which was externalized at the right lower flank. The extension wire was connected to a nonsterile internal pulse generator (IPG; EON, St. Jude Medical, Plano, Texas, USA).

Postoperative Course

The postoperative course was uneventful. One hour after completion of the operation

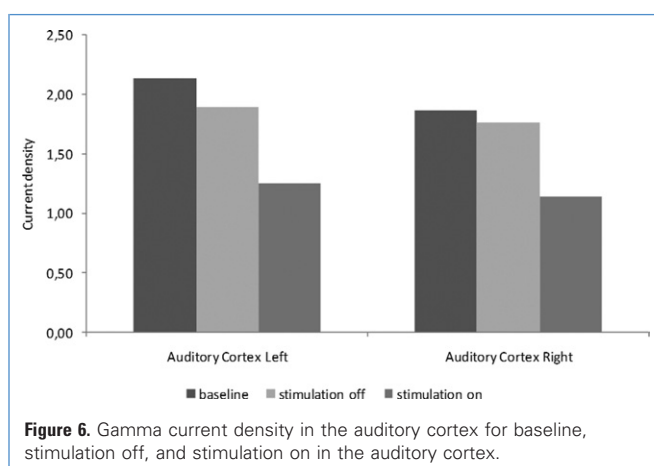
(with the IPG still in off mode), the patient woke up with the same tinnitus as before the operation. A postoperative radiograph demonstrated the placement of the electrodes (**Figure 3**). The patient was discharged home on the second postoperative day. When the IPG was activated two days later, the patient's high pitch tinnitus improved by 33% in a placebo-controlled fashion. The IPG was set to deliver impulses with duration of 0.5 milliseconds and a rate of 40 pps and 2.7 mA. The stimulation was off for 5 seconds and on for 5 seconds. After the patient was discharged from the hospital, the parameter settings were modified multiple times to allow better suppression of his tinnitus. This was performed on a trial-and-error basis in our attempt to find an electrode configuration and stimulation design that yielded best results.

A follow-up took place for one year in which each morning the patient reported his tinnitus VAS. Results clearly show a further continuing slow decrease of the tinnitus intensity over time (**Figure 4**). One year postoperatively, an EEG with source localization analysis (sLORETA) shows a reduction of DLPFC activity in the right DLPFC during stimulation in comparison with a normative database. Gamma-band activity was decreased at the area of stimulation (**Figure 2C**). After we turned off the stimulation, we found increased activation in the ACC in comparison with an age-matched normative database of normal subjects (**Figure 2D**).

To further explore the effect of DLPFC cortical stimulation, we conducted a three-week evaluation during which the patient had three stimulation protocols, namely sham stimulation, tonic, and burst stimulation. The patient received each stimulation twice, which was randomized to avoid an order effect. **Figure 5** clearly shows that the burst stimulation had a better suppression effect than tonic and sham stimulation and that tonic stimulation had a better suppression effect than sham stimulation. **Figure 6** further demonstrates that the gamma current density in the auditory cortex decreases during stimulation on in comparison with baseline and stimulation off.

DISCUSSION

The relationship between the auditory cortex and tinnitus is well studied. Recently it has become clear that nonauditory areas also are involved in tinnitus. For an auditory stimulus to be



consciously perceived, activation of the primary auditory cortex is a prerequisite but not sufficient (4, 7). There is a sound level-dependent activation of the primary auditory cortex in humans as investigated with EEG and fMRI (27, 28), with an increasing primary auditory cortex activation for increasing loudness, similarly to what has been described in the somatosensory system, both in humans (5, 29) and on single-cell level in primates (8). Tinnitus intensity has been related to gamma-band activity in the auditory cortex (37). One could therefore postulate that the gamma oscillations, which are present in primary auditory cortex in tinnitus, are not related to conscious perception of tinnitus but only code the intensity of the perceived phantom sound. This is similar to what has been demonstrated at a single-cell level for somatosensory stimuli in the primary somatosensory cortex: stimulus intensity is coded in the primary somatosensory cortex, the conscious percept perse in the prefrontal cortex (8).

Patients in vegetative state, who do not have conscious auditory percepts, still activate the primary auditory cortex on sound presentation, but there is no functional connectivity to frontal areas in these patients (4), suggesting that isolated primary auditory cortex activation does not result in auditory consciousness. This finding is analogous to what has been suggested for the visual (6) and somatosensory (8) system. The global workspace model suggests that conscious perception of sensory events requires sensory cortex activation embedded in a larger cortical network, called the global workspace, extending beyond the primary sensory regions, including prefrontal, parietal and cingulate cortices (7). In patient with tinnitus, differences in long-range coupling between auditory cortex and frontal, parietal, and cingulate brain areas have been shown in comparison with control patients (34), suggesting that the tinnitus percept could be an emergent network property rather than an event limited to the auditory cortex.

It has recently been shown that TMS of the frontal cortex associated with the auditory cortex yields better tinnitus suppression than TMS of the auditory cortex alone (17), and tDCS limited to the DLPFC is capable of improving both tinnitus intensity and tinnitus distress (38).

On the basis of these basic neuroscientific and preliminary clinical data, TMS was performed targeting the area of blood-oxygen-level dependent (BOLD) activation in the DLPFC contralateral to side on which the tinnitus was perceived (Figure 1). The area that selectively acti-

vated with presentation of the tinnitus-matched sound was chosen as target for neuronavigated TMS. Because the patient perceived a transient amelioration of the tinnitus intensity on repeated placebo-controlled TMS sessions, two electrodes were implanted extradurally overlying the same area of BOLD activation elicited by tinnitus matched sound presentation in the scanner (Figure 3). The improvement of the patient's symptoms suggests that the DLPFC could indeed be a target for neuromodulation for this elusive symptom, although full suppression of the auditory phantom percept was not achieved.

CONCLUSION

Focal extradural electrical stimulation of the dorsolateral prefrontal cortex at the area of fMRI BOLD activation can modulate tinnitus perception. TMS can potentially be used to select surgical candidates for implantation of stimulating electrodes for tinnitus suppression.

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