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Noninvasive and Invasive Neuromodulation for the Treatment of Tinnitus: An Overview

Sven Vanneste, Ma, Msc, PhD*†, Dirk De Ridder, MD, PhD*

Objective: Nonpulsatile tinnitus is an auditory phantom percept characterized as a tone, or a noise-like sound such as a hissing or buzzing sound or polyphonic, in the absence of any objective physical sound source. Although advances have been made in symptomatic pharmacologic and nonpharmacologic treatments, these treatments are unable to eliminate the tinnitus sensation in most patients. A novel approach using noninvasive and invasive neuromodulation has emerged as an interesting and promising modality for tinnitus relief.

Methodology: We review noninvasive neuromodulation techniques including transcranial magnetic stimulation, transcranial direct current stimulation, transcutaneous electrical nerve stimulation, and cortical neurofeedback, as well as invasive neuromodulation techniques including auditory cortex stimulation, dorsolateral prefrontal cortex stimulation, subcutaneous occipital nerve stimulation, and deep brain stimulation, as potential treatments of tinnitus.

Conclusion: Although the different techniques introduced revealed promising results, further research is needed to better understand how these techniques work and how the brain responds to neuromodulation. More sophisticated stimulation regimens and parameters should be developed to dynamically stimulate various regions at different frequencies and intensities, physiologically tailored to the patient's brain state in an attempt to maximize efficacy.

Keywords: C2, cortex, implantation, invasive, neuromodulation, noninvasive, tDCS, TENS, TMS, VNS

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INTRODUCTION

Tinnitus is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source (1). The American Tinnitus Association estimates that 50 million Americans perceive tinnitus and that 12 million of these people have chronic tinnitus that prompts them to seek medical attention. Up to two million have such a severe tinnitus that it becomes disabling, interfering with sleep and concentration, social interaction, and work, and results in major depressions. The Department of Veterans Affairs counted that about 400,000 veterans suffer from tinnitus through 2006 and reported in 2008 that just more than 93,000 returning Iraq veterans were affected. The math is unforgiving, considering that many of these military people are young. Tinnitus commonly gets a 10% disability rating, which translates to $1320 a year per individual. Fifty years of such payments for that 2008 group of 93,000 runs a little more than $6 billion.

The constant awareness of this phantom sound often causes a considerable amount of distress. Between 6% and 25% of the affected people report symptoms that are severely debilitating (2,3) and 2–4% of the whole tinnitus population suffers from the worst severity degree, in this group the condition leads to a noticeable decrease in the quality of life (4). Psychological complications such as lifestyle detriment, emotional difficulties, sleep deprivation, work hindrance, interference with social interaction, and decreased overall health have been attributed to tinnitus (5–8).

Although many advances have been made in symptomatic pharmacologic and nonpharmacologic treatments, these treatments are unable to eliminate the tinnitus sensation in most patients. In the majority of cases, the treatment goals are aimed at symptomatic relief. Over the last decade, a novel approach using noninvasive and invasive neuromodulation has emerged as an interesting and promising modality for tinnitus relief.

Here, we discuss the principles and mechanisms of noninvasive neuromodulation using transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcutaneous electric nerve stimulation (TENS), neurofeedback, and the principles and mechanisms of invasive neuromodulation using auditory cortex stimulation, dorsolateral prefrontal cortex (DLPFC) stimulation, subcutaneous occipital nerve stimulation, and deep brain stimulation (DBS). This article will discuss the targets for neuromodulation and the different methods that can be used, as well as the risks involved. It also will discuss how neuromodulation might be evolving within the field of tinnitus.

Address correspondence to: Sven Vanneste, Ma, Msc, PhD, Brai²n, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. Email: sven.vanneste@ua.ac.be; website: http://www.brai2n.com

* Brai²n & TRI, University Hospital Antwerp, Belgium; and

† Department of Translational Neuroscience, Faculty of Medicine, University of Antwerp, Belgium

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NEURAL MECHANISMS OF TINNITUS

Based on animal and functional imaging studies in humans, it is generally accepted that tinnitus is related to maladaptive plasticity due to damage to the auditory system. Most forms of tinnitus are attributable to reorganization and hyperactivity in the auditory central nervous system (3,9–11). Based on magnetoencephalography (MEG), thalamocortical dysrhythmia has been proposed as a pathophysiologic model for tinnitus generation (12). According to this pathophysiologic model, tinnitus is caused by an abnormal, spontaneous, and constant coupled theta–gamma band activity (theta: 4–7 Hz, gamma >30 Hz) generated as a consequence of hyperpolarization of specific thalamic nuclei. In physiologic circumstances, auditory stimuli increase thalamocortical rhythms from alpha to gamma band oscillations (13). In the deafferented state, however, the oscillation rate decreases to theta band activity (4–7 Hz) (14). As a result, γ-amino butyric acid type A mediated lateral inhibition is reduced, inducing a surrounding coupled gamma band activity known as the "edge effect." This edge or halo is suggested to be related to the positive symptoms (12,15). This theta–gamma coupling has been confirmed by recordings from electrodes overlying the secondary auditory cortex in a tinnitus patient and is only present at the area where the tinnitus is generated (16). Tinnitus has indeed been correlated to sustained high-frequency gamma band activity in temporal areas in humans in quantitative electroencephalographic (17) and MEG studies (12,15,18,19). Furthermore, the amount of gamma band activity on electroencephalography (EEG) correlates with the perceived contralateral phantom sound intensity (20). This is in agreement with a MEG study proposing that hemispheric dominance of tinnitus generation is determined by high-frequency activity around 55 Hz in presence of slow-wave activity in the contralateral auditory cortex (18).

Gamma band local field potentials from the auditory cortex correlate with the functional magnetic resonance imaging (fMRI) blood oxygen level dependence (BOLD) signal (21,22). The maximal gamma band activity recorded in a patient with an implanted electrode overlying the secondary auditory cortex colocalizes with the area of BOLD activation generated by tinnitus-frequency-specific sound presentation in the MRI scanner, suggesting that the BOLD area localizes the generator of the tinnitus accurately (16). It also appears that during tinnitus perception, gamma band activity in the area overlying the BOLD spot is coupled to more theta than more distantly from the BOLD area, suggesting that thalamocortical theta–gamma dysrhythmia is present only at the BOLD spot (16). It has been suggested that theta activity synchronizes large spatial domains and binds together specific assemblies by the appropriate timing of higher frequency localized oscillations (23–25) and that higher frequency gamma oscillations are confined to small neuronal spaces, whereas very large networks are recruited during slow oscillations (26). Connectivity data also demonstrated that theta connectivity is increased when the patient perceives tinnitus in comparison to when he perceives no tinnitus (16). This suggests that the theta activity might be the transfer wave required for coactivation of the tinnitus network (27,28) and that gamma activity encodes the tinnitus intensity (20). Postoperative analysis furthermore showed a decrease in gamma band activity in the stimulated secondary auditory cortex associated with a decrease in the perceived tinnitus intensity, demonstrating that this gamma band activity is indeed causally related to the perceived phantom sound intensity. This result, combined with the theta functional connectivity changes, confirms, by means of EEG, that fMRI-guided extradural stimulation interferes with thalamocortical dysrhythmia as previously demonstrated by MEG (29). It thus suggests that (thalamo)cortical theta–gamma dysrhythmia is a permanent (pathological) state of normally present temporary theta–gamma coupling required for normal physiologic sensory perception.

Tinnitus is not only related to auditory cortex hyperactivity. Non-auditory brain structures are also activated in tinnitus. Distress in tinnitus patients is related to increased beta activity in the dorsal part of the anterior cingulate cortex (ACC), and the amount of distress correlates with an alpha network consisting of the amygdala-ACC-insula-parahippocampus-DLPFC using source localization EEG (30). A MEG study further showed that long-range coupling between frontal, parietal, and cingulate brain areas in "alpha and gamma networks" is related to tinnitus distress (28). Due to the low spatial resolution of this MEG study (based on a coarse inverse solution), it cannot be deduced whether the frontal area also incorporates the anterior insula found in source localization EEG studies. The distress in tinnitus patients also correlates with an increase in incoming and outgoing connections in the gamma band in the DLPFC, the orbitofrontal cortex, and the parieto-occipital region (31).

Thus, the perception of tinnitus involves a large and complex interconnected network of neural structures, and tinnitus may result from a dysfunction in any part of this system. Therefore, modulation of any part of this network may interfere with the tinnitus percept or tinnitus distress.

NEUROMODULATION

The mechanism of neuromodulation for the relief of tinnitus is based on the modification of neuronal activity intimately involved in the neural circuits responsible for tinnitus processing and perception. In this way, it is believed that stimulation of the cerebral cortex either inhibits or interrupts and interferes with tinnitus signals that originate from the auditory central nervous system and other areas in the tinnitus network of the brain. We discuss noninvasive neuromodulation, TMS, tDCS, TENS, neurofeedback, and invasive neuromodulation techniques attempting to target different cortical areas using auditory cortex stimulation, DLPFC stimulation, subcutaneous occipital nerve stimulation, and DBS. The aim is to discuss the optimal target for neuromodulation as an entry port to the tinnitus network.

Noninvasive Neuromodulation for Tinnitus

Here, we consider four methods of brain neuromodulation that have been investigated for the treatment of tinnitus: TMS, tDCS, TENS, and neurofeedback.

TMS

TMS is a noninvasive tool provoking a strong impulse of magnetic field that induces an electrical current which can alter the neural activity at the applied area. This makes it possible to selectively and safely stimulate specific regions of the human brain. Typically, TMS in tinnitus is applied with a figure-eight coil (see Fig. 1a). Positron emission tomography scan studies have demonstrated that TMS not only modulates the directly stimulated cortical area, but it has an effect on remote areas functionally connected to the stimulated area (32,33). If the TMS stimulus is repeated over and over again in trains of stimulation, this is referred to as repetitive TMS (rTMS). A train of sTMS can modulate cortical excitability in a manner that lasts beyond the duration of the rTMS itself, i.e., it can induce a residual inhibition.

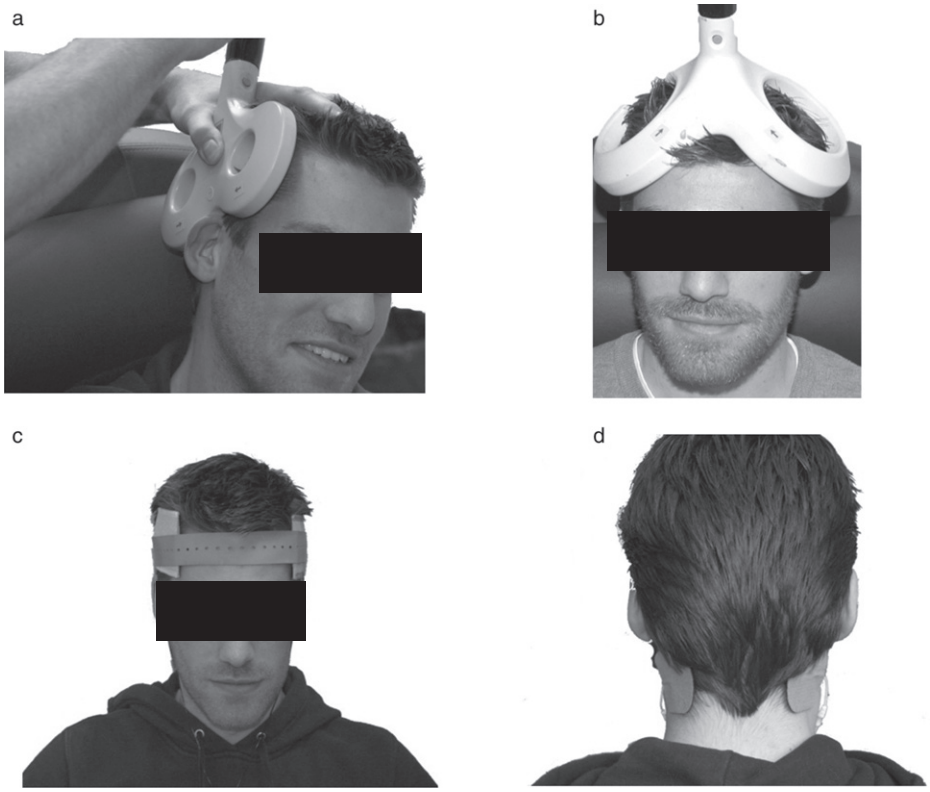

Figure 1. Noninvasive neuromodulation techniques: a. figure-eight coil TMS; b. double-cone coil TMS; c. bifrontal tDCS; and d. TENS stimulation of the C2 nerve. tDCS, transcranial direct current stimulation; TENS, transcutaneous electric nerve stimulation; TMS, transcranial magnetic stimulation.

In tinnitus research, different brain stimulation protocols are used to modulate cortical information. It is known that in the motor cortex, lower rTMS frequencies (i.e., 1 Hz) can usually suppress cortical excitability, while high rTMS frequencies (i.e., 5–20 Hz) lead to a transient increase in cortical excitability (34). Several studies have shown that trains of high-frequency rTMS applied at the temporoparietal area cause tinnitus suppression in about 50% of the participants (35–39). In addition, single sessions of low-frequency rTMS with coil navigated to individually determined areas in the temporoparietal cortex resulted in tinnitus reduction in six out of eight participants (40). As previous results were mostly obtained by tonic rTMS, recently burst rTMS has been developed as a new stimulation design that has a controllable, consistent, long-lasting, and powerful effect on the motor cortex (41). While, for example, 5-Hz rTMS in tonic mode consists of five tonic pulses per second, 5-Hz burst rTMS consists of five bursts per second, each burst consisting of five rapid rTMS pulses, e.g., at 50 Hz (see Fig. 2). Although this burst stimulation design was initially developed for the motor cortex stimulation, this also can be applied to the auditory cortex for tinnitus suppression (42,43). Tonic stimulation in these studies could mainly suppress pure tone tinnitus, whereas burst stimulation could temporarily suppress both pure tone and narrow-band tinnitus (42,43).

An increasing number of studies also demonstrated that repeated sessions (daily trains of 1200–2000 pulses for five to ten days) of low-frequency rTMS to the temporoparietal area can significantly improve tinnitus complaints (44–46). Some studies found that treatment effect is still detectable 6–12 months after treatment (47–49). The number of daily sessions may be an important factor regarding long-term effects in tinnitus patients (47). A case report further showed that rTMS may be used as a maintenance treatment to manage chronic tinnitus (50).

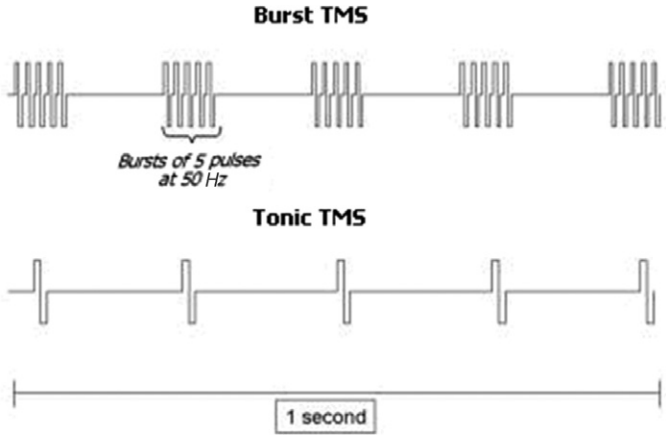

Figure 2. Tonic and burst TMS. TMS, transcranial magnetic stimulation.

It also has been shown that low-frequency rTMS of the temporoparietal area combined with high-frequency prefrontal rTMS improves tinnitus similarly to low-frequency rTMS of the temporoparietal area. However, after three months, a remarkable advantage was demonstrated for the combined prefrontal and temporal rTMS treatment (51). In addition, a recent study using a double-cone coil (see Fig. 1b), which has large angled windings to modulate deeper brain placed over the dorsal frontal cortex and to modulate the dorsal and subgenual ACC, revealed that 1 and 3 Hz of frontal TMS can improve both tinnitus transiently (52).

One limitation of most studies is related to the coil positioning. Most studies are not performed under neuronavigated control and were only defined by anatomic landmarks. Yet, recent studies for

TMS demonstrated that consistent results can be obtained with a probabilistic approach (i.e., nonneuronavigated) (53). Nevertheless, even if fMRI-guided stimulation might be accurate within the range of millimeters for targeting purposes, the area of modulation might still be as large as 3 cm (54), questioning the value of fMRI-guided TMS of, for example, the auditory cortex (37).

tDCS

tDCS is a noninvasive method of brain stimulation (see Fig. 1c). When tDCS is applied in humans, a relatively weak constant current (between 0.5 and 2 mA) is passed through the cerebral cortex via scalp electrodes. Depending on the polarity of the stimulation, tDCS can increase or decrease cortical excitability in the brain regions to which it is applied (55). Currently, tDCS is usually applied through two surface electrodes, one serving as the anode and the other as the cathode. Some of the applied current is shunted through scalp tissue and only a part of the applied current passes through the brain. Anodal tDCS typically has an excitatory effect on the underlying cerebral cortex by depolarizing neurons, while the opposite occurs under the cathode due to induced hyperpolarization. This effect of tDCS typically outlasts the stimulation by an hour or longer after a single treatment session of sufficiently long stimulation duration (56–59).

An initial tDCS study on a small sample was conducted, modulating the left temporoparietal cortex (38). It was shown that anodal tDCS of the left temporoparietal area with the cathode placed contralaterally at the supraorbital area resulted in a transient reduction of tinnitus, similar to 10-Hz TMS (38). However, no effect was found for cathodal tDCS of the left temporoparietal area with the anode on the contralateral supraorbital area. One possible reason might be that cathodal tDCS was too weak to unsettle ongoing activity. Therefore, it was proposed to use a longer and stronger modulation as an attempt to obtain significant suppression. This would be analogous to TMS, where a single session of high-frequency TMS induces an immediate change in tinnitus perception, while several sessions of low-frequency TMS are needed to induce prolonged decreases in tinnitus perception (47,60)

Several tDCS studies targeting the DLPFC demonstrated clinically beneficial results in treating major depression (61,62), as well as reducing impulsiveness (63) and increasing pain threshold (64,65). The DLPFC has a bilateral facilitatory effect on auditory memory storage and contains auditory memory cells (66). The DLPFC also exerts early inhibitory modulation of input to the primary auditory cortex in humans (67) and has been found to be associated with auditory attention (68), resulting in top-down modulation of auditory processing (69). This was further confirmed by electrophysiologic data, indicating that tinnitus occurs as the result of a dysfunction in the top-down inhibitory processes (70).

In a recent paper, it was demonstrated that bifrontal tDCS, placing the anodal electrode on the right DLPFC and the cathodal electrode on left DLPFC, also could suppress tinnitus and tinnitus-related distress (71).

TENS

Another method applying current to the nervous system used for tinnitus suppression is by TENS (72) (see Fig. 1d). TENS is a noninvasive, very safe method commonly used to reduce acute and chronic pain (73–75). For tinnitus, it was first shown that TENS of the median nerve could modulate the tinnitus percept in some patients (76). TENS was then applied to the temporomandibular joint, which had an inhibitory effect on 46% of tinnitus patients (72). Similar results were obtained in a large study of 500 tinnitus patients (77). In this study, TENS was applied to 20 arbitrarily selected points on the external pinna and tragus of each ear, which led to a 53% tinnitus improvement.

In a recent study, TENS was used to modulate the peripheral branches of the upper cervical nerve (i.e., C2) to modulate tinnitus. It is known that somatosensory stimulation of the C2 nerve might be especially relevant in combination with auditory cortex stimulation. C2 stimulation increases the inhibitory role of the dorsal cochlear nucleus on the central auditory nervous system (78,79). The dorsal cochlear nucleus receives auditory input from the VIIIth nerve (i.e., vestibulocochlear nerve) as well as from the somatosensory system, directly from the ipsilateral dorsal column and (spinal) trigeminal nuclei (80–82). The upper cervical nerve C2 projects to (spinal) trigeminal nuclei (83–85) and C2 electrical stimulation evokes large potentials in the dorsal cochlear nucleus (DCN). Stimulation of C2 produces a pattern of inhibition of the DCN principal cells (79), a hypothetical mechanism for suppressing tinnitus which is in accordance with animal studies (86,87). Two hundred forty tinnitus patients received both a real and a sham TENS treatment applied for 30 min (ten min of 6 Hz, followed by ten min of 40 Hz and ten min of sham) (88). Significant tinnitus suppression was found, but only 17.9% of the tinnitus patients responded to C2 TENS with a transient improvement of 42.92%. Six patients had a reduction of 100%.

In a recent study, it was shown that there is variability in responding to tDCS, TMS, and TENS (89). The results showed that TENS of the C2 nerve predicts bifrontal tDCS and auditory cortex TMS better than the opposite, and bifrontal tDCS predicts auditory TMS response and vice versa. Based on these results, it is argued that TENS only modulates the tinnitus brain circuit indirectly via the C2 nerve, activation of which modulates signal transmission in the dorsal cochlear nucleus, whereas TMS and tDCS have a dual working mechanism, a TENS like indirect mechanism via somatosensory influences mediated through the C2 and/or trigeminal nerve plus a direct brain modulating mechanism.

Neurofeedback

Neurofeedback acts by acquiring brain signals from a patient using EEG, fMRI, or near infrared spectroscopy (90). The relevant aspects of this signal are extracted and fed back to the participant in real time. As soon as the signal reaches a predefined target, the participant is rewarded (91). It is based on the seminal work of Miller (92), demonstrating that autonomic functions can be modified through operant conditioning. Based on this idea, Sterman and Friar showed that it is possible to use operant conditioning to increase sensorimotor EEG rhythms (93,94). This leads to a decrease of seizures in epileptic patients. Successful results also were obtained for attention-deficit hyperactive disorder by training alpha and decrease theta activity (95–97).

This principle also is applied for tinnitus. As mentioned, tinnitus patients have abnormal spontaneous brain activity revealing higher delta and theta bands and lower alpha power associated with increased gamma band activity in comparison to healthy subjects and that correlation between tinnitus-related distress and abnormal oscillatory activity patterns in the right temporal and left frontal areas (19).

In two studies, tinnitus patients were trained to up-regulate the amplitude of their alpha activity and down-regulate the amplitude of beta activity (98,99). After 15 training sessions, a significant increase of alpha amplitudes and a decrease of beta amplitudes were demonstrated associated with a significant reduction in tinnitus-related distress. In a control group without tinnitus, no changes of alpha or beta amplitudes were revealed during the same training. In another study, it was attempted to normalize aberrant rhythms—mainly the enhanced delta power and reduced tau power (10-Hz recordings in the temporal regions)—within tinnitus patients (100). Simultaneous alteration of both frequency bands was strongly related to changes in tinnitus intensity. Comparing the neurofeedback treated patients with a group of patients

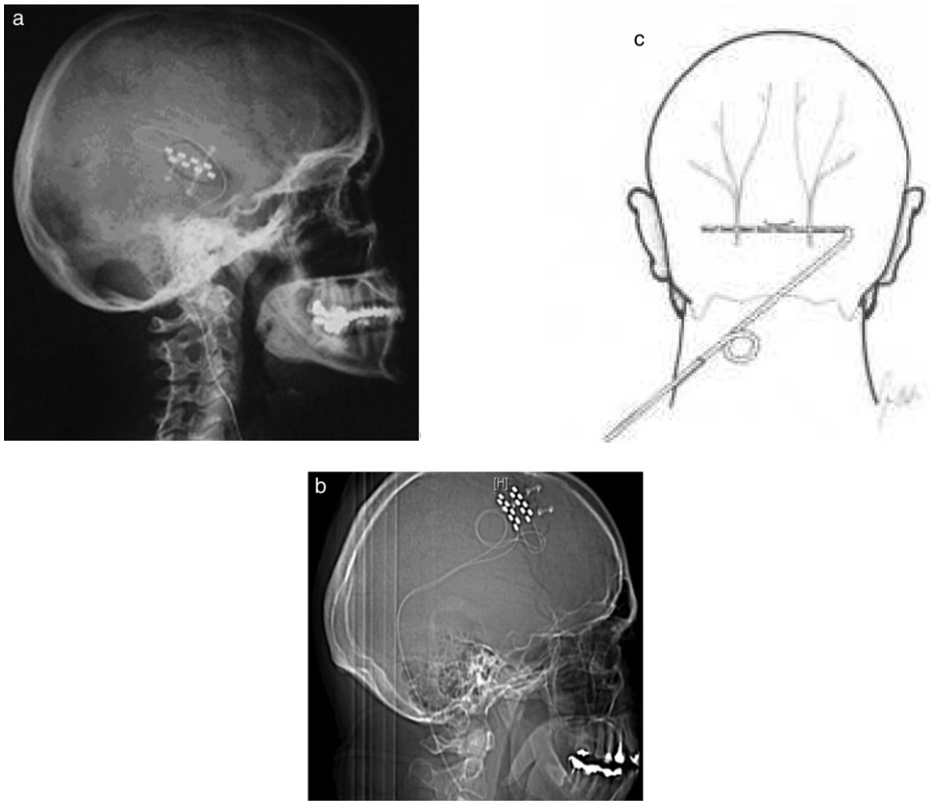

Figure 3. a. Auditory cortex stimulation; b. dorsolateral prefrontal cortex stimulation; and c. C2 stimulation.

trained with a frequency discrimination task, the tinnitus relief in the neurofeedback group was significantly stronger. In a second study by the same research group, modulation of delta power, alpha power, or the combination, i.e., a delta/alpha ratio, was applied in a tinnitus group at four fronto-central positions (91). A decrease of tinnitus-related distress was obtained without a significant difference between modulating delta power, alpha power, or the combination.

One small study was performed using real-time fMRI (rtfMRI) feedback in tinnitus patients (101). Six patients with chronic tinnitus were included. First, location of the individual auditory cortex was determined in a standard fMRI auditory block-design localizer. Then, participants were trained to voluntarily reduce the auditory activation (rtfMRI) with visual biofeedback of the current auditory activation. This reduced the subjective tinnitus in two of the six participants. It was suggested that optimized training protocols (frequency, duration, etc.) may further improve the results. The use of rtfMRI is however relatively new and findings (at least for tinnitus) remain equivocal. This may be due to the slow temporal resolution of the technique and the noise generated by the scanner, limiting its potential as a neurofeedback device. On the other hand, the increased spatial resolution might be beneficial.

Invasive Neuromodulation for Tinnitus

Four methods of neuromodulation have been investigated for the treatment of tinnitus: auditory cortex stimulation, DLPFC stimulation, subcutaneous occipital nerve stimulation, and DBS. Invasive auditory cortex stimulation, DLPFC stimulation, and subcutaneous occipital nerve stimulation could be considered permanent alternatives to TMS, tDCS, and TENS applications in the treatment of tinnitus.

Auditory Cortex Stimulation

If rTMS overlying the auditory cortex is successful in suppressing the tinnitus, an electrode can be placed extradurally overlying the secondary auditory cortical area to permanently modulate the hyperactivity on the same site as where the rTMS was successful (see Fig. 3) (102–105). The electrode is activated and powered by an internal pulse generator implanted subcutaneously in the abdomen. The stimulation parameters (frequency, amplitude, and pulse width) are selected postoperatively by trial and error programming to find the best parameters that yield maximal tinnitus control. Stimulation is not performed continuously as this could evoke epileptic seizures. Most often the stimulator is programmed in cycle mode, on for five sec and off for five sec. During this five sec, the tinnitus remains suppressed by a residual inhibition effect. In order to dramatically shorten programming, the programming also can be started at the poles that overlie the BOLD signal. This is performed by fusing the postoperative computerized tomography with the preoperative fMRI, with the fMRI processed with high thresholds so that only a couple of voxels remain (106). A second way to facilitate programming is based on electrophysiologic recordings from the implanted electrodes. A power to frequency analysis permits to find the poles exhibiting a theta peak, as signature of thalamocortical dysrhythmia (16).

Initial results of auditory cortex stimulation via implanted electrodes using tonic stimulation demonstrated that patients with pure tone tinnitus, but not noise-like tinnitus, benefit from this treatment (102). It also was shown that in patients who present with a combination of pure tone tinnitus and a noise-like component both components had to improve in order to subjectively improve patient satisfaction. Even completely removing the pure tone, the component does not result in a subjective amelioration as long as the second noise-like component remains (102). Recently, a stimu-

lation design introduced in TMS called burst stimulation (41) has been applied in tinnitus patients with a cortical electrode overlying the auditory cortex, showing a significantly better suppression for narrow-band noise tinnitus with burst stimulation in comparison to tonic stimulation (107).

In an additional study, 43 patients with severe tinnitus according to the tinnitus questionnaire were implanted with a cortical electrode overlying the secondary auditory cortex (106). Although all patients reacted to TMS, only 67% patients did respond to cortical stimulation with a suppression effect of 51%. When comparing responders to cortical stimulation, only one-third of the patients respond to tonic stimulation, while an extra third of the population benefited from burst stimulation, resulting in a total response rate of two out of three patients. On average, a suppression effect of 38% was obtained for tonic stimulation and 51% for burst stimulation. From the 16 patients that respond to tonic stimulation, 50% of the patients responded significantly better to burst stimulation with a suppression effect of 53%, while for tonic stimulation only a suppression effect of 24% was obtained.

In the first period after the implantation, the tinnitus returns very quickly when the stimulator is turned off. After a couple of seconds, the sound starts to come back, so the residual inhibition is not very long. However, after years of stimulation, when the stimulator is switched off or the battery has become empty, it may take weeks before the tinnitus returns full scale. It might be that after many years of stimulation the tinnitus stays away for longer and longer periods of residual inhibition and finally forever, even without further stimulation.

DLPFC Stimulation

Interestingly, noninvasive neuromodulation such as tDCS on DLPFC can successfully improve tinnitus (71) (see Fig. 3). TMS combining frontal and auditory stimulation yields results better than those obtained by auditory cortex stimulation alone, further demonstrating the DLPFC involvement in tinnitus (51). In a recent case study, focal extradural electrical stimulation of the DLPFC at the area of fMRI BOLD activation with two lamitrode 44 electrodes yielded an improvement in tinnitus perception, with a stable and progressively further improving suppression of minimally 57%, with a follow-up for more than one year (108). More implants should be performed before any real conclusions can be drawn about the efficacy of the treatment.

Subcutaneous Occipital Nerve Stimulation

In extension to TENS, it is also possible to implant an electrode subcutaneously in the C2 dermatoma (see Fig. 3). Occipital nerve stimulation is being used successfully as a surgical treatment for primary headache syndromes with high success rates (109). Recently, occipital nerve stimulation was performed in a group of patients who met criteria for fibromyalgia, presenting with comorbid headache disorder (110). In this study, it was noted that not only did headaches improve, but so did the widespread bodily pain. Furthermore, associated mood and fatigue scales improved. In addition, pain trials with occipital nerve stimulation demonstrated an improvement of up to 35% (111). Preliminary analysis of occipital nerve stimulation for tinnitus suppression in six patients showed a mean suppression effect of 62.89% (De Ridder et al., unpublished data). These patients also had improvement for a placebo-controlled TENS stimulation.

DBS

The implantation of DBS in specific brain regions has become the basis of highly successful therapies that alleviate the symptoms of otherwise treatment-resistant disorders such as chronic pain (112–114), Parkinson's disease (115,116), tremor (117,118), and dystonia (119). DBS for tinnitus has not been performed but tinnitus has been evaluated in patients with movement disorders who presented with comorbid tinnitus. In a first study, seven patients with movement disorders who also reported to have tinnitus were implanted in the ventralis intermedius nucleus of the thalamus (120). Three of the seven patients reported reduced tinnitus loudness when DBS was turned on. Four patients tested in the clinic indicated that DBS of the ventralis intermedius nucleus of the thalamus caused a decrease in tinnitus loudness and in two patients with relatively prolonged residual inhibition. This suggests that DBS of nonauditory thalamic structures may provide tinnitus relief for some patients.

In a second study, six Parkinson patients who also suffered from tinnitus underwent an implantation of the subthalamic or ventralis intermedius nucleus of the thalamus (121). In five subjects where the DBS lead tip traversed the area of locus of the caudate neurons, tinnitus loudness in both ears was suppressed to a nadir of level 2 or lower on a zero to ten rating scale. In one subject where the DBS lead was outside the locus of the caudate neurons, tinnitus was not modulated. In three patients with preoperative and postoperative audiograms, hearing thresholds were unchanged by stimulating locus of the caudate neurons. It was suggested that the locus of the caudate neurons may be interrupting perceptual integration of phantom sensations generated in the central auditory system.

Clinical Impact of Other Treatments and Neuromodulation for Tinnitus

Currently, pharmacologic and nonpharmacologic treatments aim at symptomatic relief but do not eliminate the tinnitus percept in most patients, but do seem to exert a beneficial effect on the tinnitus distress.

None of the investigated drugs for tinnitus suppression have demonstrated replicable long-term reduction of tinnitus impact in the majority of patients in excess of placebo effects (122). Accordingly, there is no US Food and Drug Administration or European Medicines Agency approved drugs for the treatment of tinnitus. However, in spite of the lack of evidence, a large variety of different compounds are prescribed off-label. Therefore, it has been urged that more effective pharmacotherapies for this huge and still growing market are desperately needed and even a drug that produces only a small but significant effect would have an enormous therapeutic impact (122).

Passive auditory amplification with hearing aids seems to have only a marginal effect on the intensity of the tinnitus. In a recent study, the tinnitus percept was affected only weakly in a conventional amplification group and was not at all affected in a high-bandwidth amplification regimen (123). However, other studies do suggest that hearing aids can improve the clinical burden or the distress associated with the phantom sound percept in patients with hearing loss (124,125).

Active auditory amplification via sound therapy or masking was investigated in a recent Cochrane search, but it failed to show strong evidence of the efficacy of sound therapy in tinnitus management. This might be related either to weak study design or a lack of efficacy (124).

Adding psychological treatment to sound therapy, such as in tinnitus retraining therapy (126), could potentially be more efficacious than sound therapy alone (127).

Psychological treatments by itself, such as cognitive behavioral treatment, do not influence the subjective loudness of tinnitus either, nor does it improve the associated depression. However, it can induce a significant improvement in the quality of life (decrease

of global tinnitus severity), suggesting that cognitive behavioral therapy has an effect on the qualitative aspects of tinnitus and contributes positively to the management of tinnitus (128).

In view of the current status of other treatments for tinnitus, the emergence of noninvasive and invasive neuromodulation as potential treatment tools in tinnitus is promising. However, only the first steps have been taken and much more research is needed to further confirm and recognize the potentials these techniques might have in the treatment of tinnitus. Many studies only evaluate transient changes in tinnitus perception, without analysis of long-term effects. Other studies only evaluate improvement in tinnitus distress, without verifying the improvement in tinnitus intensity, and some studies demonstrate statistically significant improvements, with low effect sizes, revealing only marginal clinical relevance. At the moment, effect sizes and cost-effectiveness studies are needed to further explore the possibilities of neuromodulation as a treatment tool in routine clinical practice.

Noninvasive neuromodulation techniques introduced for the treatment of tinnitus are relatively easy to apply and carry few risks. Most research on neuromodulation in tinnitus is focusing on TMS. This shows that TMS has the potential for long-term tinnitus reduction in about 50% of the patients, but with moderate effect sizes. However, TMS is more expensive and more difficult to apply in comparison to tDCS and TENS, and it is quite a challenging technique requiring a trained technician to be present for the entire duration of the stimulation. TDCS and TENS have several advantages over TMS. As tDCS and TENS produce fewer artifacts such as acoustic noise and muscle twitching, they are more suitable for double-blind, sham-controlled studies and clinical applications of tinnitus research. The equipment for tDCS and TENS is compact and portable and less expensive. Seizure incidents have not been reported in tDCS and TENS studies, and the effects of a single tDCS session seem to last longer than those of rTMS, which makes it more suitable as a treatment tool. The use of tDCS and TENS should therefore be considered as complementary tools to rTMS. However, tDCS and TENS are limited with respect to the intensity of stimulation that can be applied and generally involve diffuse spread of electric current, while TMS is excellent in targeted brain stimulation. Presently not much is known for neurofeedback in tinnitus. Neurofeedback is a very safe method and patients actually train their own brain oscillations based on positive and negative feedback. No electrical or magnetic pulses are involved. However, this method also requires the presence of a trained technician, as artifacts might result in nonspecific feedback signals, resulting in training noise instead of real EEG signals.

Invasive neuromodulation requires neurosurgery and consequently carries a potentially higher risk of injury (and death). This method is quite expensive but might have major benefits as a prolonged duration of stimulation can be given, without patient effort, at extremely focalized targets, with easy placebo controls and very quickly. It might therefore induce the largest benefits as compared with noninvasive neuromodulation.

Future Directions

Although the different techniques introduced show promising results, other neuromodulation techniques such as transcranial alternating current stimulation and vagus nerve stimulation might also show benefit in the future.

In addition, new methodologies to analyze brain data might help to further explore the brain and help to target new brain areas or brain networks.

Transcranial Alternating Current Stimulation

Electrical stimulation of the human cortex has proven to be a useful method in neuroscience (129,130) and more specifically for the treatment of tinnitus. As already discussed, tDCS causes polarization and depolarization of the neuronal areas under the anode and cathode, respectively—thus modulating excitability of the cortex (131). tDCS mainly modulates gamma band activity (132), even at a distance (71), as bifrontal tDCS decreases gamma band activity in the auditory cortex associated with decreasing tinnitus. However, this modulation is brain state dependent. Theta tDCS during non-rapid eye movement (non-REM) and REM sleep has opposing effects: theta tDCS during non-REM sleep produces a global decrease in slow oscillatory activity conjoint with a local reduction of frontal slow EEG spindle power (8–12 Hz). In contrast, during REM sleep, theta tDCS appears to increase global gamma (25–45 Hz) activity (133).

A more recent application is trancranial alternating current stimulation (tACS) that also is potentially capable of interacting with rhythmic neuronal activity and has perceptual and behavioral consequences (134–137).

While tDCS modulating affects neural tissue via a sustained modulation of the membrane voltage of neurons, it is assumed that tACS most probably yields its effect via an up- and down-regulation of certain synapses as indicated above (138) and that tACS—like rTMS (139)—should be better suited to modulate functions that are closely related to brain oscillations at specific frequencies (140). However, preliminary results placing electrodes on the left and right auditory cortex modulating the individual alpha peak—as tinnitus is related to a decrease in alpha activity (19)—did not result in a reduction of tinnitus perception in tinnitus patients (Vanneste, unpublished data). It should be noted, however, that most probably tinnitus is not related to only one brain area or one EEG oscillation (19,20,30,141–143).

Vagus Nerve Stimulation

Several studies have reported that the severity of tinnitus is correlated with the degree of map reorganization in auditory cortex (70,144). Cortical stimulation of the auditory cortex can temporarily disrupt these auditory phantom sensations (16,106,145,146). In a recent animal study, it was demonstrated that reversing the brain changes responsible can eliminate the perceptual impairment in an animal model of noise-induced tinnitus (147). Exposure to intense noise degrades the frequency tuning of auditory cortex neurons and increases cortical synchronization. Repeatedly pairing tones with brief pulses of vagus nerve stimulation completely eliminated the physiologic and behavioral correlates of tinnitus in noise-exposed rats (147). These improvements persisted for weeks after the end of therapy. A possibility is to translate these findings in animals to humans for the treatment of tinnitus.

Looking for New Targets

Today, we increasingly recognize that nothing in the brain happens in isolation. Most events and phenomena are connected, caused by, and interacting with a huge number of other pieces of a complex universal puzzle (148). Since the late 1990s, development in our understanding of the physics of complex systems has led to the rise of network science (149). The modern theory of networks originated with the discovery of small-world networks and scale-free networks (150,151). Recently, it was found that the structural and functional brain also is a small-world network (152–154). The basic components of complex brain networks are nodes that are connected by edges (or lines). Interesting is that within the brain it seems that the network properties are scale invariant, meaning that both microscopic cellular networks and macroscopic networks derived from

different neuroimaging techniques demonstrate isomorphic properties such as modularity, the existence of hub nodes, hierarchy, centrality, and high efficiency of information transfer for nearly minimal wiring costs (154,155). Based on the new network science, it has to be possible to better delineate whether auditory cortex stimulation might be beneficial for an individual patient. However, using the same kind of research, it also should be possible to retrieve good alternative targets for neuromodulation (156). This requires a thorough analysis of resting-state data of an individual patient looking for the hubs in a scale-free network model of tinnitus. Once these methods become easily accessible, results of this promising technique of neuromodulation should improve.

Responders vs. Nonresponders

Not all patients respond to neuromodulation, and the question arises whether the functional state of the brain determines who will and who will not respond. Therefore, it might be interesting to look for biomarkers or endophenotypes that can predict which patients will respond or not to treatments. Preliminary data demonstrate that it is feasible to do these analyses in relatively simple ways. For example, it was shown for bifrontal tDCS for tinnitus that responders had higher gamma band activity in the right primary and secondary auditory cortex and right parahippocampus than nonresponders before tDCS treatment (157). It has been shown that gamma band activity in the auditory cortex is correlated with tinnitus loudness and that the anterior cingulate is involved in tinnitus distress. Patients who were undergoing bifrontal tDCS also demonstrated an increased functional connectivity in the gamma band between the right DLPFC and the right parahippocampus, as well as the right DLPFC and pregenual ACC. An analysis revealed that responders to bifrontal tDCS also experienced a larger suppression effect on TMS placed over the right temporal cortex (i.e., auditory cortex) than nonresponders. Responders to bifrontal tDCS seem to differ in resting-state brain activity compared with nonresponders in the right auditory cortex and parahippocampal area. They also have a different functional connectivity between DLPFC and the pregenual ACC and parahippocampal area. This kind of analysis might be worthwhile to pursue for other neuromodulation techniques.

In addition, brain-derived neurotrophic factor (BDNF) gene, which is one of many genes thought to influence synaptic plasticity in the adult brain, shows a common single nucleotide polymorphism (BDNF Val66Met) in the normal population that is associated with differences in hippocampal volume and memory (158). Altered hippocampal function and structure have been found in adults who carry the methionine (met) allele of the BDNF gene, and tinnitus is characterized by altered structural volume as measured by voxel-based morphometry (159). Furthermore, molecular studies elucidate the role of BDNF in neurogenesis and synapse formation, and the BDNF genotype also influences resting-state functional connectivity, i.e., functional connectivity at a system level (160), especially in situations requiring behavioral adaptation (161). It is thought that tinnitus-related plasticity changes in the inferior colliculus are mediated by BDNF (162), but in view of its effect on the hippocampus and the hippocampal changes documented in this study, it is tempting to speculate that depending on the BDNF polymorphism functional connectivity between the hippocampal area and the cortex is altered in some patients, and that this could hypothetically determine response to implanted electrodes. Thus, it could be of interest in the future to determine the BDNF polymorphisms in patients and correlate this to the response rate to the implants, the more so as the same Val66Met polymorphism also determines whether one responds to transcranial magnetic or tDCS (158), other well-known forms of neuromodulation.

Optimal Parameters

All of the above-mentioned neuromodulation designs except for neurofeedback are limited by the stimulation parameters being used. It has been shown for TMS and implanted electrodes that a burst stimulation design is superior to tonic stimulation for noise-like tinnitus (42,106,107). This suggests that neuromodulation should be further developed to improve magnetic or electrical communication with the brain. Many more stimulation designs can be developed, e.g., stochastic resonance stimulation, extreme high-frequency stimulation, adaptive stimulation, etc., which could all improve the obtained results of tinnitus neuromodulation. These techniques would ideally be driven by sensing methods in order to adapt the stimulation to the brain state. It has been clearly demonstrated that TMS neuromodulation is brain state dependent (163,164), thus adapting the stimulation to the underlying brain state, e.g., oscillations might be worthwhile in modulating the brain activity (165).

In Conclusion

The aim of the present paper is to give an overview of noninvasive and invasive neuromodulation techniques for the treatment of tinnitus. Techniques introduced were TMS, tDCS, TENS, neurofeedback, auditory cortex stimulation, DLPFC stimulation, subcutaneous occipital nerve stimulation, and DBS. Although the different techniques introduced revealed promising results, further research is needed to further explore these techniques to better understand how these techniques work and how the brain responds to neuromodulation. In addition, more sophisticated regimens and parameters of stimulation will probably be developed that may be able to dynamically stimulate various regions at different frequencies and intensities physiologically tailored to suit the brain state of each patient in an attempt to maximize efficacy.

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Drs. Vanneste and De Ridder both wrote this manuscript and approved the submitted version.

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