REVIEW
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Non-Invasive Neuromodulation for Tinnitus

Berthold Langguth
Department of Psychiatry, Psychotherapy, and Interdisciplinary Tinnitus Center, University of Regensburg, Regensburg, Germany

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Address for correspondence
Berthold Langguth, MD, PhD
Department of Psychiatry, Psychotherapy, and Interdisciplinary Tinnitus Center, University of Regensburg, Universitätsstr. 84, Regensburg 93053, Germany
Tel +49 941 941 2099
Fax +49 941 941 2025
E-mail Berthold.Langguth@medbo.de

Tinnitus is a prevalent disorder that has no cure currently. Within the last two decades, neuroscientific research has facilitated a better understanding of the pathophysiological mechanisms that underlie the generation and maintenance of tinnitus, and the brain and nerves have been identified as potential targets for its treatment using non-invasive brain stimulation methods. This article reviews studies on tinnitus patients using transcranial magnetic stimulation, transcranial electrical stimulation, such as transcranial direct current stimulation, alternating current stimulation, transcranial random noise stimulation as well as transcutaneous vagus nerve stimulation and bimodal combined auditory and somatosensory stimulation. Although none of these approaches has demonstrated effects that would justify its use in routine treatment, the studies have provided important insights into tinnitus pathophysiology. Moreover bimodal stimulation, which has only been developed recently, has shown promising results in pilot trials and is a candidate for further development into a valuable treatment procedure. **J Audiol Otol 2020;24(3):113-118**

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Introduction

With prevalence rates of 10–20%, tinnitus is prevalent [1,2]. Most patients with tinnitus are not severely impaired by the phantom sound, but approximately 2–3% of the total population experience severe tinnitus [3] that is frequently accompanied by frustration, annoyance, anxiety, depression, cognitive dysfunction, insomnia, stress, and emotional exhaustion. Consequently, tinnitus represents a major health burden and is of remarkable socioeconomic importance [4].

The available treatment options for tinnitus are limited. Cognitive-behavioral therapy may help in reducing tinnitus-related annoyance and handicap, but there is no established treatment with supporting evidence from randomized controlled studies for reducing tinnitus loudness. Thus, the need to develop better treatment options for tinnitus is urgent.

With the development of animal models of tinnitus and the advent of new brain imaging techniques within the last few decades, knowledge about the pathophysiology of tinnitus has increased. There is a consensus, among experts, that tinnitus is related to peripheral hearing loss. Typically, tinnitus is ipsilateral to hearing loss and their frequency ranges are congruent. Similar to phantom pain, which results from sensory deafferentation after limb amputation, tinnitus is assumed as a reaction of the brain to auditory deafferentation. After peripheral hearing loss due to partial damage of the hair cells in the inner ear, the neuronal input from the cochlea to the auditory cortex in the brain is reduced. Following this sensory deprivation, the corresponding neurons in the auditory cortex increase the firing rate and the synchronicity of their spontaneous activity. This mechanism has been described as thalamocortical level [5], which results from an alteration of the balance between excitation and inhibition, and is characterized by a specific pattern of neuronal oscillatory activity that can be detected by magneto- or electroencephalography.

Many patients with tinnitus have a normal or near-normal audiogram, and tinnitus does not develop in every person with hearing loss. Thus, non-auditory factors, in addition to auditory deafferentation, play roles in the development and progression of tinnitus. Neuronal networks, which are relevant for attention direction, salience attribution, emotional processing and memory function, are all involved in tinnitus pathophysiology. All of these networks are activated by the brain to compensate for missing auditory information. The mismatch between the expected auditory information and the impaired auditory input attributes salience to the auditory signal. This results in emotional co-activation and an effort to replace the missing auditory information with memorized auditory signals.

Thus, whether increased activity in the auditory cortex leads to tinnitus perception depends on the co-activation of the aforementioned non-auditory brain networks [6,7]. The co-activation of these non-auditory networks also determines personal aversiveness, loudness or accompanying symptoms such as sleep disorders, anxiety, panic and stress. Taken together, there is increasing consensus among experts, that tinnitus is a result of neuroplastic changes in auditory and non-auditory central nervous structures that occur as a consequence of peripheral deafferentation. Neural connections between the auditory and somatosensory systems located at the dorsal cochlear nucleus also have an impact on neuronal activity in the central auditory system and can play a role in tinnitus perception as well [8].

All these new insights have opened up new horizons for the development of therapies. First of all these insights led to the notion, that tinnitus is a treatable condition: if tinnitus is resulting from functional changes of neuronal activity, then there is no reason why tinnitus cannot be efficiently treated by neuromodulation or pharmacotherapy.

Secondly, brain structures gained increased focus as potential targets for treatment. The primary focus of neuromodulatory treatments was the auditory cortex, as it is involved in tinnitus pathophysiology and can be reached by non-invasive treatment approaches such as transcranial magnetic or electric stimulation. With the advancement in knowledge about involved brain networks in tinnitus, non-auditory structures were also identified as potential targets. Recently, cranial nerves were also considered as potential targets for tinnitus therapy. This article will describe the aforementioned approaches and conclude with perspectives on clinical practice and future research.

Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) uses magnetic fields for non-invasive brain stimulation. A coil that is connected to a stimulation machine is positioned over the subject's scalp. A strong electrical current in the coil produces a magnetic field that passes, largely undistorted, through the cranium and induces neuronal activity in superficial cortical areas [9]. The spatial extension of the generated magnetic field depends on the coil design. Figure-of-eight coils produce a more focused pattern of activation compared to round coils, but newer coil types, such as the double cone coil, can also activate deeper brain structures [10,11]. In repetitive TMS (rTMS), a large number of TMS pulses (typically between 100 and 3,000) are applied in a rhythmic pattern during one session. The effects of stimulation depend on the complex interaction of many factors. The most important factors are the activity of the stimulated area and the utilized frequency of rTMS. In the motor cortex, high-frequency rTMS (i.e. 5−20 Hz) typically leads to a transient increase in cortical excitability, whereas low-frequency rTMS (i.e. 1 Hz) typically reduces neural excitability [9].

rTMS has been used in tinnitus research in two different ways. First, single sessions of rTMS have been used to investigate the possible transient suppression of tinnitus perception by the modulation of activity in cortical areas. This has been demonstrated in the temporal and frontal cortices in a subgroup of patients [12]. The findings suggested that activity in the stimulated brain areas is relevant for tinnitus perception. Second, repeated sessions of low-frequency rTMS of the temporal cortex have been proposed as an innovative treatment strategy for tinnitus based on the assumption that it is related to increased neuronal activity in the auditory cortex [13]. This approach has been investigated in a large number of studies with somewhat conflicting results [14]. Comprehensive analyses of literature revealed possible therapeutic efficacy for the suppression of tinnitus symptoms, but the clinical effects are usually partial and temporary [15]. Moreover, the available studies vary in design, used stimulation parameters and inter-individual outcomes. Thus, a definitive conclusion on the efficacy of rTMS for the treatment of tinnitus is still not possible. A recent systematic analysis of the relationship between stimulation parameters and treatment outcomes revealed a higher success rate for lower stimulation intensities [14].

Over the years, many approaches have been tested to enhance the clinical effects, such as variation of the stimulation frequency, priming stimulation with high-frequency rTMS, theta-burst stimulation, additional stimulation of frontal brain areas, multisite stimulation, combining rTMS with auditory stimulation and individualizing rTMS. The latter approach aims to take the heterogeneity of tinnitus into account by performing a stimulation protocol tailored to the individual patient. A recent pilot study explored this [16], by delivering rTMS at various frequencies over the left and right dorsolateral prefrontal (DLPFC) or temporoparietal (TPC) cortex in a single test session to select the type of protocol to be applied for several days. Of 25 tested patients, an immediate effect on tinnitus perception was observed in 12, who received 9 further treatment sessions with a combined rTMS protocol over the most effective DLPFC and TPC targets found in the test sessions. In the remaining 13 patients, a standard combined protocol (20 Hz-rTMS over left DLPFC followed by 1 Hz-rTMS over the left TPC) was performed. The responders of the test sessions who received the individualized protocol had a higher benefit than those receiving the standard protocol. This result provides a basis for a "tailored" application of rTMS in tinnitus since the usual "standardized" rTMS protocols have shown significant, but only moderate, efficacy with high interindividual variability in treatment response.

To further the understanding of the mechanisms underlying the effects of rTMS, brain imaging has been performed before and after rTMS (for a review see Langguth, et al. [17]). Different neuroimaging methods have been used, including positron emission tomography (PET), single positron emission tomography (SPECT), electro- and magnetoencephalography (EEG and MEG), functional and structural magnetic resonance imaging, and magnetic spectroscopy. Most robust data come from structural magnetic resonance imaging: For temporal [18] and combined frontotemporal stimulation [19], clinical response to rTMS was related to specific structural baseline characteristics and structural alterations during stimulation. These results confirm the implication of non-auditory brain regions in the development of phantom sounds and suggest the dependence of therapeutic response to rTMS on the neuroplastic capabilities of specific brain regions.

Transcranial Electrical Stimulation

Transcranial electrical stimulation (tES) can be applied as transcranial direct current stimulation (tDCS), transcranial alternating stimulation (tACS), or transcranial random noise stimulation (tRNS). In all forms, the stimulation is delivered by two electrodes that are connected to a battery-powered device. The electrodes are covered by wet sponges and placed over the areas of interest. It is possible to place one electrode over a specific brain area and the other electrode, as a reference electrode, over any body part or to place both electrodes over brain areas on the skull. tDCS, tACS, and tRNS differ by how the current is applied [20].

A constant current, an alternating current at a given frequency, and an alternating current at a random frequency is delivered in tDCS, tACS, and tRNS, respectively. All forms exert their effects on brain function by modulating the resting membrane potential of neurons in the brain.

Knowledge about the biological effects is predominantly available for tDCS, where anodal stimulation typically increases cortical excitability (long-term potentiation), whereas cathodal stimulation reduces cortical excitability. Recently, high-definition tDCS (HD-tDCS) has been developed [21]. HD-tDCS differs from tDCS by the use of smaller and more electrodes, enabling a more focal stimulation.

Within the last decade, tES has been used like rTMS in two different ways. Single sessions of tDCS, tACS and tRNS have been used to evaluate the involvement of specific brain networks in tinnitus pathophysiology and repeated sessions has been investigated as a potential therapeutic approach for tinnitus patients. Compared to rTMS, fewer clinical studies have been performed for tES and most of them have focused on the effects of single-session tDCS.

The targets for stimulation were the auditory, temporoparietal or the dorsolateral prefrontal cortex. Initial studies demonstrated transient tinnitus suppression following anodal, but not cathodal, tDCS over the temporoparietal cortex, but this effect could not be consistently reproduced in further studies (for a review see [22]). In a further pilot study, tACS (at the individual alpha frequency) and tRNS were applied bilaterally over the temporal cortices. This study revealed a transient suppression of tinnitus following tRNS, but not tACS [23].

Thus, the most promising approaches in single-session studies over the auditory cortex were left anodal tDCS and bilateral tRNS. Both approaches were tested as potential treatments in controlled studies, which applied repeated sessions, but the results were disappointing, as there was no superiority over sham stimulation [24] or a control treatment [25].

In addition to the studies focusing on temporal and temporoparietal areas, several studies have targeted the DLPFC, mostly by using a bifrontal electrode montage. A single session of bifrontal anode right/cathode left tDCS reduced tinnitus intensity or distress in approximately one-third of the patients, whereas anode left/cathode right tDCS had no effect [26]. In a further study, the same group investigated a possible increase in the efficacy of bifrontal tDCS, if the electrode polarity is informed by gamma connectivity in EEG measurements [27], but this was not the case.

The bifrontal tDCS protocol with anode right and cathode left was also investigated as a therapeutic approach with repeated sessions in uncontrolled pilot studies, which revealed promising preliminary effects [28,29]. tDCS has also been combined with different forms of auditory stimulation [30-32]. However, tDCS could neither enhance the therapeutic effects of hearing aids on tinnitus complaints [30] nor the effects of notched music training, a specific form of individualized auditory stimulation [31]

In summary, tDCS effects on tinnitus are minimal and inconsistent and largely depend on the method and montage used. Although there are findings from single-session studies indicating a potential for anodal left temporal tDCS and anodal right and cathodal left bifrontal tDCS, they were not confirmed by controlled trials involving multiple daily sessions.

Transcutaneous Vagal Nerve Stimulation

The combination of auditory and vagal stimulations had been first investigated in an animal model of tinnitus [33]. Based on the rationale that vagal stimulation makes the simultaneously presented sounds more salient, the combined treatment almost completely reversed neurophysiological and behavioral signs of tinnitus, which was not the case with auditory stimulation alone. In subsequent human pilot studies, the efficacy of the treatment could be confirmed [34], albeit the effects were less pronounced than in animals.

In these studies, vagus nerve stimulation was performed by implanting a neurostimulation device connected to an electrode located along the cervical branch of the vagus nerve. Recently, however, a noninvasive approach for stimulating the vagus nerve has been developed. The transcutaneous vagus nerve stimulation (tVNS) takes advantage of the afferent branch of the vagus nerve, which is located medially to the tragus at the entry of the acoustic meatus and innervates the external ear canal. For reliable electrical stimulation of the auricular branch of the vagal nerve, specific devices have been developed. Analogous to invasive VNS, stimulation of the vagus with tVNS is typically performed on the left side to minimize potential effects on cardiac rhythm [35]. In a first pilot study, the feasibility and safety of 6 months of tVNS were investigated in patients with tinnitus. The stimulation was well tolerated, but did not lead to a clinically significant improvement in tinnitus complaints [36]. In contrast, two small pilot studies involving the combination of tVNS and auditory stimulation have shown promising effects [37,38]. These findings are in line with the animal data [33], where the pairing of vagus nerve stimulation with tones was critical for the therapeutic effects, whereas vagal nerve stimulation alone had no effect.

Bi-modal and Multimodal Stimulation

Bi- or multimodal stimulation is presumably more effective for the induction of neuroplastic effects than unimodal stimulation, as the synchronicity of events is an important criterion for the induction of neuroplastic effects, as expressed by Donald Hebb several decades ago: “Neurons that fire together, wire together” [39]. Unimodal stimulation can induce activity-dependent neuroplastic changes, such as long-term potentiation or depression, whereas bimodal stimulation may additionally induce alterations of neuronal activity by the mechanisms of spike-timing-dependent plasticity. However, the experimental investigation of bimodal stimulation is more challenging because of the much larger parameter space.

Over the last few years, different approaches for bi- or multimodal stimulation have been proposed for the treatment of tinnitus. The combination of auditory and somatosensory stimulations has been investigated, in addition to the combination of vagal and auditory stimulations. The somatosensory stimulation was performed via the trigeminal nerve or the C2 afferents. The combination of auditory and somatosensory modulation is motivated by an increasing understanding of the relevance of the somatosensory system for tinnitus pathophysiology [8]. Many patients can modulate their tinnitus by face- or neck movements, and the suggested underlying mechanism is the interaction between somatosensory and auditory afferents at the level of the dorsal cochlear nucleus. This understanding, in turn, motivated two different approaches of combined somatosensory and auditory stimulation.

One approach aimed at the modulation of activity in the central auditory pathway by exerting an inhibitory effect on the dorsal cochlear nucleus. The somatosensory and auditory stimuli were presented at specific intervals, following descriptions of stimulus timing-dependent plasticity in the dorsal cochlear nucleus from basic neurophysiological studies in animals [40]. These findings were translated into a clinical pilot trial, involving 20 patients who underwent a 28-day application of a combination of sounds and transcutaneous electrical stimulation to the neck or the temporomandibular joint region. The bimodal treatment suppressed tinnitus loudness and intrusiveness, whereas the control condition (auditory stimulation alone) did not deliver either benefit [40].

In another approach, sounds are simultaneously applied with electrical stimulation of the tongue [41,42]. This approach is based on the idea that tinnitus is caused by auditory deafferentation and bimodal stimulation may compensate for the auditory deafferentation by stimulating the somatosensory system. The combined application of sounds and electrical stimulation to the tongue was investigated in two large trials (involving more than 500 patients) and the results have not been published yet [41,42].

Conclusion

Within the last decades, neuroscientific research has contributed to a better understanding of the pathophysiological mechanisms that underlie the development and progression of tinnitus and various neuromodulatory interventions have been developed.

Studies on rTMS, targeting the temporal, temporoparietal and the frontal cortices, are available. Some of these have demonstrated therapeutic suppression of tinnitus symptoms, but it was usually minimal, transient and only observed in a subgroup of patients. Thus, systematic meta-analyses are needed for further evaluation of the effectiveness of rTMS in chronic tinnitus.

Accordingly, the recent European guideline about the use of rTMS [15] recommended that repeated sessions of low-frequency rTMS of the temporoparietal cortex of the left hemisphere or contralateral to the affected ear have possible effects on tinnitus. Several questions on the use of rTMS in everyday practice remain, covering optimal treatment target(s) and protocol, and the role of individual susceptibility to auditory cortex stimulation, among others.

Different forms of transcranial electrical stimulation (tDCS, tACS, and tRNS), applied over the frontal and temporal cortex, have been investigated in tinnitus patients. Transient tinnitus suppression was observed for a subgroup of patients after single sessions of left frontal and temporal anodal tDCS as well as bitemporal tRNS, but none of these approaches provided any relevant clinical improvement when applied in repeated sessions.

Recently, promising findings were reported for bimodal stimulation approaches that paired auditory stimulation with vagal nerve stimulation or electric somatosensory stimulation of the tongue, face or neck.

Thus, two decades of research in non-invasive neuromodulatory interventions in tinnitus did not establish a routine clinical treatment for tinnitus. However, it provided important insights into the pathophysiology of tinnitus, especially on the relevance of non-auditory brain areas and the heterogeneity of tinnitus. The recently developed bimodal stimulation approaches have, so far, demonstrated promising pilot results. If these results can be confirmed in further systematic investigations, these approaches may become routine clinical treatments.

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Conflicts of interest

The author has no financial conflicts of interest.

ORCID iD

Berthold Langguth https://orcid.org/0000-0002-7066-510X

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