Neuromodulation on Tinnitus Perception and Distress

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Abstract

Background: Tinnitus is defined as a cortical phantom sound perception in the absence of an appropriate external stimulus. It has an estimated prevalence of 10% to 15% in the adult population and about 20% of them are distressed by it and even find the disorder life-changing. However, the best way to manage tinnitus perception and distress is unclear; in particular, it is unclear how neuromodulation might affect both these factors.

Purpose: To systematically review the effects of two neuromodulation techniques (Transcranial Magnetic Stimulation - rTMS and Transcranial Direct Current Stimulation - tDCS, as therapeutic options for tinnitus perception and distress relief; Research Design: Systematic review.

Data collection and analysis: We searched the PubMed database for publications between May 2014 and December 2014 using the following combinations of the words: Tinnitus and neuromodulation (57 papers), tinnitus and rTMS (69 papers), and tinnitus and tDCS (32 papers), ultimately identifying 158 papers.

Results: Only 3 trials comprising 102 tinnitus patients met our inclusion criteria. We did not find evidence that either technique is effective for managing tinnitus perception and distress. Conclusions: Tinnitus distress and perception are related. More research is needed to justify routine use of rTMS and tDCS as tinnitus therapies, especially regarding the lasting effects of tDCS. Hypothetically, the CN-NINM could improve both tinnitus complaints, perception and distress.

Keywords

Neuromodulation, Neuroplasticity, Transcranial magnetic stimulation, Transcranial direct current stimulation, Cranial-nerve non-invasive neuromodulation, Portable neuromodulation

Introduction

Tinnitus is defined as a cortical phantom sound perception in the absence of an appropriate external stimulus [1]. It has an estimated prevalence of 10% to 15% in the adult population. About 20% of them are distressed by it and even find the disorder life-changing [2,3]. The heterogeneity observed in tinnitus patients indicates that several different mechanisms are involved in the generation of the symptoms, which may explain why patients react and respond to treatments in such a variety of ways. It may be the case that any single treatment will not be effective for treating all tinnitus patients but that different treatments will be needed for each individual patient [4,5].

One of the mechanisms that usually trigger tinnitus is cochlear lesions, but it is unclear why patients retain perception and become annoyed by it [6]. Considering tinnitus as a consequence of cochlear lesions, a discrep-
ancy occurs between what the central auditory pathways expect to receive from the peripheral pathways and what they actually do. This leads to neuroplastic changes, such as instability in the central auditory circuitry, neuronal synchronization between the auditory and non-auditory systems, depolarization of specific thalamic nuclei and the limbic system [7], and excitability of the somatosensory system, dorsal column, and trigeminal system [8]. All these changes result in a reorganization of the central nervous system, including electrophysiological changes in order to adapt to a new situation and eventually compensate for the functional loss to recover homeostatic balance [9]. Hyperactivity in the central auditory system also occurs, causing tinnitus perception in the auditory cortex as a result [8].

Based on Hallam’s and Jastreboff’s models, tinnitus perception is maintained because patients involuntarily pay too much attention to the tinnitus signal [1,10] due to the abnormal synchrony between auditory responses and focus of attention [11].

The fixation of attention to tinnitus can partially explain tinnitus-related distress, depending on how the conscious and subconscious brain classifies tinnitus perception. If it is a neutral stimulus, it is likely to be blocked from reaching conscious perception (habituation, according to Hallam’s and Jastreboff’s models) and not spread to other systems in the brain [7]. Whenever it is classified as a non-neutral stimulus, it is likely that a negative emotional state will influence perception and lead to further distress due to the activation of multiple areas such as the dorsolateral pre-frontal cortex, anterior cingulate cortex, insula, amygdala, hippocampus, parahippocampus, striatum ventral, supplementary motor area, orbitofrontal cortex, posterior cingulate cortex, precuneus, and anterior frontal cortex [8,12]. This partially explains why some people are not bothered and others experience severe distress in response to tinnitus with similar psychoacoustic parameters [2,7]. These subjects experience reduced quality of life due to compromised sleep, concentration, social life, and emotional imbalance [12,13].

Nevertheless, the relation between tinnitus perception and distress still challenges the scientific community, and the search for the ideal management strategy would have to focus on the reduction of both tinnitus perception and its related distress [2].

Advances in technology and emerging knowledge of the dysfunctional brain circuits underlying tinnitus have led to the use of some neuromodulation techniques as an attempt to change the brain’s neuronal activity in a more or less focal way. They can potentiate or inhibit the transmission of nerve signals of both auditory and non-auditory systems [12]. Thus, they can induce and modulate neuroplasticity, by altering pathologic and physiologic plasticity. Furthermore, they can potentially revert the central dysfunction that leads to the perception and distress seen in tinnitus patients [14,15].

Non-invasive transcranial neuromodulation techniques have been the subject of much research in the last decade. Although there are other neuromodulation techniques available, the goal of this article is to focus on the transcranial ones.

Transcranial Magnetic Stimulation (TMS) was introduced in 1985 by Barker, et al. as a non-invasive pain-free method to stimulate the human cortex [16,17] and has been found to be a promising noninvasive treatment for a variety of neuropsychiatric conditions [18-21], including tinnitus [22]. The number of applications continues to increase with a large number of ongoing clinical trials in a variety of diseases. A large industry-sponsored trial [23] and a multi-center trial in Germany [24] of rTMS in medication of refractory depression have been completed, and other appropriately controlled and sufficiently powered clinical trials of TMS are ongoing.

The initial studies on Transcranial Magnetic Stimulation (TMS) were prompted by the knowledge that repetitive stimulation of nerve pathways in animal models could induce changes in synaptic effectiveness [25].

Researches during the last 15 years in animal models significantly helped to understand some of the important biochemical mechanisms that underlie TMS [26]. As the stimulations pulses are repetitive, it is called repetitive Transcranial Magnetic Stimulation (rTMS) and it works based on the principle of electromagnetic induction of an electric field in the brain, capable of modulating cortical excitability in a frequency dependent manner, depolarizing neurons, and modulating cortical excitability, decreasing or increasing depending on the stimulation parameters [6,27,28]. High frequency rTMS (5 Hz or higher) has been shown to induce potentiation like effects, whereas low frequency rTMS (1 Hz) typically leads to depression like effects [29,30].

It is considered a safe treatment when in the short term use. The extent of action of the current density generated into the brain depends on many physical and biological parameters, such as the type and orientation of coil, the distance between the coil and the brain, the magnetic pulse waveform, the intensity, frequency, and pattern of stimulation, and the respective orientation into the brain of the current lines and the excitable neural elements [6,27]. On that account, the optimal parameters remain elusive and little is known about the electrophysiological mechanisms that underlie the beneficial effects and the exact nature of the neural effects induced.
by rTMS [31]. A deeper comprehension of these parameters could allow for longer lasting changes of cortical activity, enhancing its potential as a routine treatment [12]. Long-term follow-up to observe safety is still needed [22].

In Transcranial Direct Current Stimulation (tDCS), a relatively weak constant direct current is passed through the cerebral cortex via scalp electrode. Depending on the polarity of the stimulation, tDCS can increase or decrease cortical excitability in the brain regions to which it is applied [32].

Currently, tDCS is usually applied through two surface electrodes: The anode typically exerts an inhibitory effect on the local cerebral cortex, while the cathode induces excitation, with the current flowing constantly from the anode to the cathode. Some of the applied current is shunted through scalp tissue and only part of the applied current passes through the brain. At a cellular level, the applied external electric field modifies the transmembrane potential differences by forcing the displacement of intracellular ions, which cancel the generated intracellular field and thereby modify the spike firing probability [33]. The final effects of tDCS depend on parameters such as stimulation intensity, duration, polarity, and strength, as well as individual neural morphology, and the orientation of the somato-dendritic axes and neural pathways with respect to the applied electric field [32].

The objective of this paper is to systematically review the literature on the effects of Repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) on tinnitus clinical complaints of perception and distress/annoyance.

Data Collection and Analysis - Database Research

Those inclusion criteria were chosen during the literature search process as perceptions and distress points were usually seen as interest issues to look at in the studies. So the inclusion criteria studies for this systematic review were: 1) Double and single-blinded randomized controlled clinical trials studies and crossover randomized clinical trials studies of tinnitus studies using Transcranial Magnetic Stimulation or Tinnitus and Direct Current Transcranial Stimulation for evaluation on tinnitus perception and/or distress; 2) Published in the last 6 years (from January 2010 to January 2016); 3) The objectives of the studies must be related to the effects of rTMS or tDCS on tinnitus, in particular related to clinical complain of perception and/or distress/annoyance as the primary issue.

The exclusion criteria was: 1) Studies using double cone coin or circular coin or any specific wave burst that could interfere in the analysis of the results, since they use a different kind of stimulation. 2) Studies that did not have as objective to evaluate the effects of rTMS or tDCS on tinnitus perception and/or distress/annoyance.

A literature search was performed on PubMed database as it is a large reliable everyday database, using the terms “Tinnitus and Transcranial Magnetic Stimulation” and “Tinnitus and Direct Current Transcranial Stimulation”. A six-year filter (from January 2010 to January 2016) was employed and 254 articles were found. The retrieved titles and abstracts were then reviewed.

Among the 210 articles found with the words “Tinnitus and Transcranial Magnetic Stimulation”, 194 were excluded because they did not match the selection criteria. Finally, in this group, the sample was composed of 16 articles, and five of them were crossover studies.

Among the 44 articles found matching the words “Tinnitus and transcranial Direct Current Stimulation”, 35 were excluded because they did not match the inclusion criteria. Among the remaining 9 articles, three were crossover studies.

The total amount of tinnitus patients involved in all the TMS and tDCS studies was 717. Among them, 497 received rTMS and 220, tDCS.

The analysis considered the effects of each method on tinnitus perception (loudness or intensity) or distress (annoyance), considering the applied stimulation area, coin/electrodes, number of patients, current potential (frequency/amperage), number of sessions, duration of stimulation, and sustained effect over time.

Results

The results are presented according to specific topics. The findings obtained from rTMS and tDCS studies are separated and presented in descending order (from the most common to the least common findings), to aid understanding. Moreover, to avoid mixing results from slightly different methodologies, findings obtained from Randomized Clinical Trials (RCT) are separated from those obtained from Crossover Trials (CrT).

Regarding the sample group of articles, the search strategy selected 25 articles from January 2010 to January 2016. Seventeen (68%) articles were Randomized Clinical Trials (RCT) using a control/sham condition (11 rTMS, 6 tDCS), while 8 (32%) were Crossover Trials (CrT) (5 rTMS, 3 tDCS). The mean number of subjects was 31.06 ± 17.62 and only one study had less than 10 patients. A summary is provided in Table 1 and Table 2.

Regarding the target area of stimulation

A) For studies on rTMS, the 11 RCT trials mentioned...
Table 1: Overview of study parameters of rTMS studies.

<table>
<thead>
<tr>
<th>Main author and year</th>
<th>Instrument</th>
<th>Stimulation (active)</th>
<th>Sample Stimulation (time)</th>
<th>Stimulation (frequency)</th>
<th>Number of sessions (days)</th>
<th>Improvement (drop of scores - THI and/or VAS) (perception or distress)</th>
<th>Sustained effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized clinical trials</strong></td>
<td></td>
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</tr>
<tr>
<td>Schecklmann, et al., 2015 [39]</td>
<td>TQ, DBQ, GUF, VARL, MWT-B, ZVT</td>
<td>Temporal and frontal cortex</td>
<td>40</td>
<td>3 min, 20 sec</td>
<td>1 Hz, 200 pulses, 60% RMT</td>
<td>2</td>
<td>Tinnitus loudness reductions were scarce</td>
</tr>
<tr>
<td>Wang, et al., 2015 [60]</td>
<td>THI, VAS</td>
<td>LTPC</td>
<td>21</td>
<td>Not mentioned</td>
<td>1 Hz, 1000 pulses, 110% RMT</td>
<td>10</td>
<td>THI: Drop of less than 20 points/each group</td>
</tr>
<tr>
<td>Wang, et al., 2015 [60]</td>
<td>VAS</td>
<td>TPC</td>
<td>39</td>
<td>Not mentioned</td>
<td>1 Hz, 1000 pulses, 110% RMT</td>
<td>10</td>
<td>VAS: Drop of less than 2 points</td>
</tr>
<tr>
<td>Folmer, et al. 2015 [40]</td>
<td>TFI, THQ, HHQ, MHQ, VAS, THI, BDI II, STAI</td>
<td>AC</td>
<td>64</td>
<td>Not mentioned</td>
<td>1 Hz, 2000 pulses, 110% RMT</td>
<td>10</td>
<td>THI: Drop of 7 points</td>
</tr>
<tr>
<td>Park, et al., 2015 [48]</td>
<td>THI, VAS, BDI, STAI, PSQI</td>
<td>LAC, PFC</td>
<td>14</td>
<td>Not mentioned</td>
<td>1 Hz, 6000-12000 pulses, 110% RMT</td>
<td>not mentioned</td>
<td>THI and VAS: Drop of 10 points/each</td>
</tr>
<tr>
<td>Hoekstra, et al., 2013 [37]</td>
<td>TQ, THI, VAS</td>
<td>Bilateral AC</td>
<td>50</td>
<td>Not mentioned</td>
<td>1 Hz, 2000 pulses, 110% RMT</td>
<td>5</td>
<td>No improvement</td>
</tr>
<tr>
<td>Yang, et al., 2013 [46]</td>
<td>THI</td>
<td>Between left temporal and left parietal</td>
<td>36</td>
<td>Not mentioned</td>
<td>1 Hz, 2000 pulses, 110% RMT</td>
<td>10</td>
<td>THI: Drop of more than 30 points</td>
</tr>
<tr>
<td>Barwood, et al., 2013 [38]</td>
<td>THI, Psychoacoustic measure of tinnitus</td>
<td>LAC</td>
<td>8</td>
<td>33 min</td>
<td>1 Hz, 2000 pulses, 110% RMT</td>
<td>10</td>
<td>THI: Drop of 7 or more points</td>
</tr>
<tr>
<td>Anders, et al., 2010 [36]</td>
<td>TQ, THI, VAS</td>
<td>LAC</td>
<td>42</td>
<td>Not mentioned</td>
<td>1 Hz, 1500 pulses, 110% RMT</td>
<td>10</td>
<td>THI: Drop of 4 points TQ: Drop of 2 points on TQ modified by Goebel &amp; Hiller score</td>
</tr>
<tr>
<td>Marcondes, et al., 2010 [41]</td>
<td>THI, VAS</td>
<td>LTPC</td>
<td>19</td>
<td>20 min</td>
<td>1 Hz - 1020 pulses - 110% RMT</td>
<td>5</td>
<td>Drop of less than 20 points on THI score, around 7 points</td>
</tr>
<tr>
<td>Yilmaz, et al., 2014 [61]</td>
<td>THI, VAS, Psychoacoustic measure of tinnitus</td>
<td>Not mentioned</td>
<td>60</td>
<td>30 min</td>
<td>1 Hz, pulses and RMT - not mentioned</td>
<td>10</td>
<td>Drop of 8 points on THI score</td>
</tr>
<tr>
<td><strong>Randomized crossover clinical trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lee, et al., 2013 [62]</td>
<td>THI, VAS</td>
<td>Between T3 and C3/T5 (EEG)</td>
<td>15</td>
<td>Not mentioned</td>
<td>1 Hz, 1200 pulses, 100% RMT</td>
<td>5</td>
<td>THI: Drop of 11 points</td>
</tr>
<tr>
<td>Kim, et al., 2014 [44]</td>
<td>THI, VAS</td>
<td>TPC</td>
<td>40</td>
<td>10 min</td>
<td>1 Hz - pulses not mentioned, 110% RMT</td>
<td>20</td>
<td>No improvement</td>
</tr>
<tr>
<td>Piccirillo, et al., 2013 [45]</td>
<td>THI</td>
<td>LTPC</td>
<td>14</td>
<td>42.5 min</td>
<td>1 Hz, pulses not mentioned, 110% RMT</td>
<td>20</td>
<td>No improvement</td>
</tr>
</tbody>
</table>
Piccirillo, et al., 2011 [42]  THI  LTPC  14  42.5 min  1 Hz, pulses not mentioned, 110% RMT  10  No improvement  None
Mennemeier, et al., 2011 [43]  VARL, THQ, TSI  TPC  21  30 min  1 Hz, 1800 pulses, 110% RMT  5  VARL: 33% score drop  No follow up

**Legend:** AC: Auditory Cortex; BDI: Beck Depression Inventory; BDI II: Beck Depression Inventory II; DBQ: Depression Beck Questionnaire; GUF: German questionnaire for hyperacusis; HHQ: Hearing History Questionnaire; MWT-B: (verbal intelligence); PFC: Prefrontal Cortex; PSQI: Pittsburgh Sleep Quality Index; RI: Residual Inhibition; RMT: Resting Motor Threshold; STAI: State-Trait Anxiety Inventory; THI: Tinnitus Handicap Inventory; THQ: Tinnitus Handicap Questionnaire; TP: Temporal Cortex; TPC: Temporo Parietal Cortex; TSI: Tinnitus Severity Index; TQ: Tinnitus Questionnaire; VARL: Visual Analogue Ratings of Tinnitus Loudness; VAS: Visual Analog Scale and; ZVT: (General Processing Speed Free from Language Performance).

### Table 2: Overview of study parameters of tDCS studies.

<table>
<thead>
<tr>
<th>Main author and year</th>
<th>Instrument</th>
<th>Sample</th>
<th>Time (minutes)</th>
<th>Intensity (mA)</th>
<th>Session (active + sham)</th>
<th>Improvement (perception or distress)</th>
<th>Sustained effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized clinical trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shekhawat, et al., 2013 [63]</td>
<td>CGI, VAS</td>
<td>LTPC</td>
<td>25</td>
<td>10, 15, and 20 with each current</td>
<td>1 and 2</td>
<td>6</td>
<td>Drop of 0.2 to 0.9 mean points on VAS</td>
</tr>
<tr>
<td>Forogh, et al., 2015 [64]</td>
<td>THI, VAS, CGI</td>
<td>LTPC</td>
<td>22</td>
<td>20</td>
<td>2</td>
<td>5</td>
<td>No improvement</td>
</tr>
<tr>
<td>Pal, et al., 2015 [65]</td>
<td>THI, STSS, HADS, VAS, CGI</td>
<td>Prefrontal cortex</td>
<td>42</td>
<td>20</td>
<td>2</td>
<td>5</td>
<td>No improvement</td>
</tr>
<tr>
<td>Shekhawat, et al., 2015 [58]</td>
<td>MML, VAS</td>
<td>LTPC</td>
<td>10</td>
<td>20</td>
<td>2</td>
<td>4</td>
<td>Drop of 1.2 point on VAS. No change in MML</td>
</tr>
<tr>
<td>Shekhawat, et al., 2013 [63]</td>
<td>TFI, MML, TCHO, TSNS, HADS, THQ, HHI, CGI, VAS</td>
<td>LTPC (followed by hearing aids for 6 months)</td>
<td>40</td>
<td>20</td>
<td>2</td>
<td>5</td>
<td>No improvement</td>
</tr>
<tr>
<td>Teismann, et al., 2014 [15]</td>
<td>THI, VAS, THQ, TQ</td>
<td>LAC (plus tailor made notched music training)</td>
<td>34</td>
<td>30</td>
<td>2</td>
<td>5</td>
<td>Drop only on THQ, but not on THI or VAS</td>
</tr>
<tr>
<td><strong>Randomized crossover clinical trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanneste, et al., 2011 [52]</td>
<td>VAS</td>
<td>RDLPFC</td>
<td>12</td>
<td>20</td>
<td>1.5</td>
<td>2</td>
<td>Drop of perception (41.67% on VAS) and distress (43.20% on VAS)</td>
</tr>
<tr>
<td>Garin, et al., 2011 [66]</td>
<td>VAS</td>
<td>LTPC</td>
<td>20</td>
<td>20</td>
<td>1</td>
<td>3</td>
<td>Significant drop of VAS score</td>
</tr>
<tr>
<td>Faber, et al., 2012 [67]</td>
<td>VAS, HADS</td>
<td>RDLPFC</td>
<td>15</td>
<td>20</td>
<td>1.5</td>
<td>6</td>
<td>Significant drop of VAS score. No changes in HADS scores</td>
</tr>
</tbody>
</table>

**Legend:** AC: Auditory Cortex; CGI: Clinical Global Improvement; DLPFC: Dorsolateral Prefrontal Cortex; HADS: Hospital Anxiety and Depression Scale; HHI: Hearing Handicap Inventory; LTPC: Left Temporoparietal Cortex; MML: Minimal Masking Level; RDLPFC: Right Dorsolateral Prefrontal Cortex; STSS: Subjective Tinnitus Severity Scale; TCHO: Tinnitus Case History Questionnaire; TFI: Tinnitus Functional Index; THI: Tinnitus Handicap Inventory; THQ: Tinnitus Handicap Questionnaire; TPC: Temporoparietal Cortex; TSI: Tinnitus Severity Numeric Scale; and VAS: Visual Analogue Scale.

The following areas of stimulation: 1) The temporoparietal cortex (TPC, four articles), 2) The auditory cortex (AC, four articles), 3) The association of the prefrontal and auditory cortex (PFC plus AC, two articles). One article did not mention the area of stimulation. All five CrT articles on rTMS stated that the device was placed over the TPC.
Regarding the number of sessions of stimulation

A) Among the 16 trials on rTMS, eight specified the stimulation duration: 3 minutes and 20 seconds (1 article), 10 minutes (1 article), 20 minutes (1 article), 30 minutes (2 articles), 33 minutes (1 article), 42 minutes (1 article) and 42.5 minutes (1 article). Unfortunately, eight of them did not specify the duration of stimulation.

B) Among the 9 tDCS articles, the duration of stimulation was 20 minutes (7 articles), 30 minutes (1 article), and the last one applied tDCS for 10, 15, and 20 minutes in separate treatment groups.

Regarding the number of sessions of stimulation

A) rTMS was applied for 10 consecutive working days (8 articles), 5 days (5 articles), 20 consecutive working days (1 article), and for 2 days (1 article). The last article did not specify the number of sessions.

B) Among the 9 articles on tDCS, the stimulation was applied for 5 working days (4 articles), 6 days (2 articles), while 3 articles mentioned that the stimulation was performed for 2, 3, and 4 days each.

Regarding the instruments for outcome assessment before and after treatment, questionnaires and scales were used alone or in combination. There was no measurement of pitch, loudness, or Minimal Masking Level in such individuals. The Tinnitus Handicap Inventory (THI) was the most used questionnaire in studies on both techniques (16/25, 64%), being administered in 14/16 (87.5%) rTMS studies and 3/9 (33.33%) tDCS studies. The VAS was used in 18/25 (72%) studies on both techniques, being administered in 10/16 (62.5%) rTMS studies and 100% of tDCS studies. All other questionnaires used are displayed in Table 1 and Table 2.

Regarding the outcomes: THI scores dropped more than 7 points in 8 out of the 10 articles that used the THI to evaluate rTMS. The score dropped more than 30 points in one trial, and less than 4 points in another (Table 1). The VAS score dropped one or two points in the articles that specified the degree of tinnitus improvement in tDCS. The drop of THI scores varied from 0 to 30 points in rTMS articles. The VAS scores varied from 0 to 1.2 in tDCS articles. The duration of the sustained effect of rTMS varied from 0-26 weeks after active stimulation. The duration of the sustained effect for tDCS varied from 0-6 months (24 weeks) after active stimulation.

Discussion

The first study on the clinical indications for tinnitus treatment was published in 2003, in which a male patient who received a single session of high-frequency rTMS (10 Hz) applied to the temporal cortex experienced decreased tinnitus perception [34].

rTMS was later reported for tinnitus by other groups with heterogeneous results, which justifies the present doubts regarding the best cortical area, coil orientation, intensity, frequency, duration, and interval between sessions, as well as its effects on tinnitus perception and distress [35]. There remain doubts about how rTMS could produce longer-lasting structural and functional effects, as the clinical effects on tinnitus sensation are usually short [16]. As we have seen in this review, this result is observed regardless of the stimulation target or stimulation parameters.

In this review, the coil was placed over the temporal cortex [36-40], temporoparietal cortex [41-47] or left temporoparietal cortex [36,38,41,42,45-48], regardless of tinnitus laterality, which suggests that there is no uniformity in these results.

Some studies suggested that the rTMS effect might depend on the stimulation dose [34,49], tinnitus onset within 2 years [50,51] or the presence of normal hearing [41]. However, these arguments were not confirmed by other 40 studies that indicated that to date, rTMS reaches level C evidence (possible efficacy) for tinnitus [6].

In spite of the options for stimulation targets and coil placement strategies, the question that arises is whether the observed effects may be due to external unspecific factors and not from the actual stimulation. Indeed, some studies show that tinnitus reduction after real stimulation is similar to the one obtained after sham stimulation, suggesting that tinnitus suppression after rTMS could be entirely related to unspecific effects. On the other hand, this would further mean that the optimal target stimulation might depend on all parameters together, as well as the patient characteristics. The available data do
not demonstrate the superiority of one specific target or coil placement or any parameter itself. This suggests that tinnitus suppression by rTMS might depend on a complex interplay between the patient characteristics and stimulation parameters, such as stimulation frequency and coil placement, time and period of stimulation.

Although some authors consider it a promising therapy, others emphasize its limitations, the poor quality of rTMS studies with small samples and undefined selection criteria, and residual effects after treatment. Thus, there are many uncertainties about rTMS, especially regarding its long-term use in tinnitus patients [52]. This argument is corroborated by a systematic review that only found one study with a low risk of bias [22], and by the 2014 Guidelines for Tinnitus, which recommended that rTMS should not be routinely used for subjects who are bothered by tinnitus [53,54]. More recent studies [37,55] failed to show significant differences between groups receiving active and sham stimulations, and others have reported partial and temporary reductions of tinnitus with high individual variability [35,56-58]. A possible stumbling block slowing down research is that the stimulation protocols are based in the motor system, with no exact knowledge of the impact of rTMS on auditory cortical activity [35].

In agreement with a systematic review [22], we believe that further prospective, randomized; double blind, and placebo-controlled studies are required. Moreover, such studies should use uniform, validated, tinnitus-specific questionnaires and uniform measurement scales to evaluate outcomes. The measured parameters used should be the same, because the differences in measures between studies are probably one of the reasons for the large variability of results, which keeps the scientific community in doubt regarding the efficacy of rTMS. Longer-term follow-ups and longer periods of stimulation are necessary to assess the benefits and safety issues related to rTMS for tinnitus. On the other hand, because tinnitus patients are different from each other, the extent of involvement of the different areas of the brain might vary between patients, which will be a challenge for future investigators.

This review does not differ from other reviews about the cortical areas of stimulation for tinnitus sufferers. However, it is not clear how effective the transcranial technique is for reducing clinical symptoms, nor about the sustained effects. Among the various inconclusive findings: There were no robust changes on loudness parameters, the efficacy of tinnitus reduction declined over time, the drop in VAS scores was insignificant and the effect was not sustained, and the temporary decrease in THI scores was similar to placebo (Table 1). Thus, the routine clinical use of transcranial stimulation for tinnitus could raise expectations of relief that cannot be met. Only one article showed a drop of more than 30 points in THI scores, but no mention of the duration of this effect was found.

tDCS seems to transiently suppress tinnitus loudness and annoyance, perhaps by reducing abnormal cortical hyperactivity via inhibitory networks and competition due to the stimulation of the various cortical and subcortical regions underlying the different stimulation sites (e.g., the left temporoparietal area, dorsolateral prefrontal cortex, and auditory cortex). However, no study has shown that tDCS achieves long-lasting improvement. Similarly, the efficacy of tDCS in tinnitus could not be fully confirmed in a recent systematic review and meta-analysis because of the limited number of studies [58].

Regarding evidence of the sustained effect, studies have reported overnight relief and no significant long-term beneficial effects (Table 2). Thus, there remains a concern about the routine clinical use of this method for tinnitus sufferers.

A further point of discussion is the instruments used to analyze the results. The Tinnitus Handicap Inventory (THI) is useful for grading tinnitus severity and has been translated into many languages. It was the most commonly used questionnaire on both techniques (16/25, 64%), specifically, 14/16 (87.5%) rTMS studies and 3/9 (33.33%) tDCS studies (Table 2). A study [59] suggested that the minimal clinically significant change in THI score could be defined as a difference of 7 points, while a reduction higher than 17 points would be considered as an extremely relevant improvement. The Visual Analog Scale (VAS) is a well-known psychometric measure of subjective attitudes and characteristics in which patients specify their level of agreement to a statement by indicating a position along a continuous line between two endpoints. The advantage of the VAS is that it can be used to assess loudness, pitch, or any issue associated with tinnitus complaints. Some authors consider a treatment as effective when the VAS score decreases by 30-40% at the same time as any other questionnaire score reduces by 5 to 10 points. The lack of agreement about the best instrument to be used and the definite criteria of significant clinical improvement have likely complicated efficacy analyses [6].

In the near future, further research on transcranial techniques of neuromodulation may be helpful to clarify the present doubts and add to the available information.

**Conclusion**

This review does not suggest that repetitive Transcranial Magnetic Stimulation (rTMS) And Direct Current Transcranial Stimulation (tDCS) are effective treatment tools for...
tinnitus perception and distress, particularly because of disagreement regarding the optimal frequency and intensity, as well as short and long-term effects. In order to employ these techniques as tinnitus therapies, such parameters need to be better clarified and standardized, especially regarding the presence of long-lasting effects, before the routine use of transcranial stimulation can be justified.

Conflict of Interest Statement

There was no conflict of interest from any author in this paper.

References


