DOI: 10.36959/926/550 | Volume 1 | Issue 1

Otolaryngology Research and Reviews

Review Article Open Access

Neuromodulation on Tinnitus Perception and Distress

***Sandra Bastos*[1,2] *and Tanit Ganz Sanchez*[1,3*]**

[1]*Instituto Ganz Sanchez, São Paulo, SP, Brazil*

[2]*Insper - Instituto de Pesquisa e Ensino, São Paulo, Brazil*

[3]*University of São Paulo School of Medicine, São Paulo, Brazil*

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 - TMS 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 complains, perception and distress.

Keywords

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

Abbreviations

AC: Auditory Cortex; LTA: Left Temporoparietal Area; rTMS: Repetitive Transcranial Magnetic Stimulation; tDCS: Transcranial Direct Current Stimulation; THI: Tinnitus Handicap Inventory; TMNMT: Tailor-Made Notched Music Training; TQ: Tinnitus Questionnaire; VAS: Visual Analogue Scale

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 2. 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-

***Corresponding author:** Tanit Ganz Sanchez, MD, PhD, Instituto Ganz Sanchez, São Paulo, SP, Brazil; University of São Paulo School of Medicine, Av. Padre Pereira de Andrade, 353, São Paulo - SP, 05469-000 Brazil, E-mail: tanitsanchez@gmail.com

Received: August 29, 2017; **Accepted:** November 02, 2017; **Published online:** November 04, 2017

Citation: Bastos S, Sanchez TG (2017) Neuromodulation on Tinnitus Perception and Distress. Otolaryngol Res Rev 1(1):39-48

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 complains 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 only on the 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.

Main author and year	Instrument	Stimulation (active)	Sample	Stimulation (time)	Stimulation (frequency)	Number of sessions (days)	Improvement (drop of scores - THI and/or VAS) (perception or distress)	Sustained effect
Randomized clinical trials								
Schecklmann, et al., 2015 [39]	TQ, DBQ, GÜF, VARL, MWT-B, ZVT	Temporal and frontal cortex	40	3 min, 20 sec	1 Hz, 200 pulses, 60% RMT	2	Tinnitus loudness reductions were scarce	Not mentioned
Wang, et al., 2015 [60]	THI, VAS	LTPC	21	Not mentioned	1 Hz, 1000 pulses, 110% RMT	10	THI: Drop of less than 20 points/ each group	< 4 weeks
Wang, et al., 2015 [60]	VAS	TPC	39	Not mentioned	1 Hz, 1000 pulses, 110% RMT	10	VAS: Drop of less than 2 points	< 4 weeks
Folmer, et al. 2015 [40]	TFI, THQ, HHQ, MHQ, VAS, THI, BDI II, STAI	AC	64	Not mentioned	1 Hz, 2000 pulses, 110% RMT	10	THI: Drop of 7 points	26th week
Park, et al., 2015 [48]	THI, VAS, BDI, STAI, PSQI	LAC, PFC	14	Not mentioned	1 Hz, 6000-12000 pulses, 110% RMT	not mentioned	THI and VAS: Drop of 10 points/ each	4 weeks
Hoekstra, et al., 2013 [37]	TQ, THI, VAS	Bilateral AC	50	Not mentioned	1 Hz, 2000 pulses, 110% RMT	5	No improvement	No follow up
Yang, et al., 2013 [46]	THI	Between left temporal and left parietal	36	Not mentioned	1 Hz, 2000 pulses, 110% RMT	10	THI: Drop of more than 30 points	Not mentioned
Barwood, et al., 2013 [38]	THI, Psychoacoustic measure of tinnitus	LAC	8	33 min	1 Hz, 2000 pulses, 110% RMT	10	THI: Drop of 7 or more points	One month
Anders, et al., 2010 [36]	TQ, THI, VAS	LAC	42	Not mentioned	1 Hz, 1500 pulses, 110% RMT	10	THI: Drop of 4 points TQ: Drop of 2 points on TQ modified by Goebel & Hiller score	26 weeks
Marcondes, et al., 2010 [41]	THI, VAS	LTPC	19	20 min	1 Hz - 1020 pulses - 110% RMT	5	Drop of less than 20 points on THI score, around 7 points	6 months
Yilmaz, et al., 2014 [61]	THI, VAS, Psychoacoustic measure of tinnitus	Not mentioned	60	30 min	1 Hz, pulses and RMT - not mentioned	10	Drop of 8 points on THI score	1 month
Randomized crossover clinical trials								
Lee, et al., 2013 [62]	THI, VAS	Between T3 and C3/T5 (EEG)	15	Not mentioned	1 Hz, 1200 pulses, 100% RMT	5	THI: Drop of 11 points	Immediate
Kim, et al., 2014 [44]	THI, VAS	TPC	40	10 min			Drop of 9 points on THI in ipsilateral group and 7 points in contralateral group	1 month
Piccirillo, et al., 2013 [45]	THI	LTPC	14	42.5 min	1 Hz, pulses not mentioned, 110% RMT	20	No improvement	None

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; GÜF: German questionnaire for hyperacusis); HHQ: Hearing History Questionnaire; MWT-B: (verbal intelligence); PFC: Prefrontal Cortex; PSQI: Pittsburgh Sleep Quality Index; RI: Residual Inibition; RMT: Resting Motor Threshold; STAI: State-Trait Anxiety Inventory; THI: Tinnitus Handcap 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.

Main author and year	Instrument	Stimulation (anodal)	Sample	Time (minutes)	Intensity (mA)	Session (active + sham)	Improvement (perception or distress)	Sustained effect
Randomized clinical trials								
Shekhawat, et al., 2013 [63]	CGI, VAS	LTPC	25	10, 15, and 20 with each current	1 and 2	6	Drop of 0.2 to 0.9 mean points on VAS	Overnight relief
Forogh, et al., 2015 [64]	THI, VAS, CGI	LTPC	22	20	2	5	No improvement	None
Pal, et al., 2015 [65]	THI, STSS, HADS, VAS, CGI	Prefrontal cortex	42	20	2	5	No improvement	None
Shekhawat, et al., 2015 [58]	MML, VAS	LTPC	10	20	2	4	Drop of 1.2 point on VAS. No change in MML	Transient
Shekhawat, et al., 2013 [63]	TFI, MML, TCHQ, TSNS, HADS, THQ, HHI, CGI, VAS	LTPC (followed by hearing aids for 6 months)	40	20	2	5	No improvement	None
Teismann, et al., 2014 [15]	THI, VAS, THQ, TQ	LAC (plus tailor made notched music training)	34	30	2	5	Drop only on THQ, but not on THI or VAS	5 to 31 days
Randomized crossover clinical trials								
Vanneste, et al., 2011 [32]	VAS	RDLPFC	12	20	1.5	2	Drop of perception (41.67% on VAS) and distress (43.20% on VAS)	18 to 62 hours (mean = 24 h)
Garin, et al., 2011 [66]	VAS	LTPC	20	20	1	3	Significant drop of VAS score	< 1 hour
Faber, et al., 2012 [67]	VAS, HADS	RDLPFC	15	20	1.5	6	Significant drop of VAS score. No changes in HADS scores	Not mentioned

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; TCHQ: Tinnitus Case History Questionnaire; TFI: Tinnitus Functional Index; THI: Tinnitus Handicap Inventory; THQ: Tinnitus Handicap Questionnaire; TPC: Temporoparietal Cortex; TSNS: 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.

B) For studies on tDCS, the six RCT trials mentioned the following areas of stimulation: 1) The left temporoparietal cortex (LTPC, four articles; one of them was associated with hearing aids); 2) The prefrontal cortex (PFC, one article); 3) The left auditory cortex plus Tailor Made Notched Music Training, (LAC + TMNMT device, one article). The crossover trials involved stimulation to the Dorsolateral Prefrontal Cortex (DLPFC, two articles) and Left Temporoparietal Cortex (LTPC, one article).

The parameters used in the 16 rTMS trials are described in Table 1. Stimulation with 1 Hz frequency was used in 100% of the selected studies; the number of pulses varied from 200 to 12,000, at an intensity ranging from 60-110% of the patients' resting motor threshold intensity.

The intensity used in the tDCS articles ranged from 1-2 mA (Table 2). Five articles used 2 mA, two articles used 1.5 mA, one article used 1 mA and one article compared the results between 1 and 2 mA.

Regarding the duration 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 assessement 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, coin 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 pre-frontal 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

1. Jastreboff PJ (1990) Phantom auditory perception (tinnitus): Mechanisms of generation and perception. Neurosci Res 8: 221-254.
2. McKenna L, Handscomb L, Hoare DJ, et al. (2014) A scientific cognitive-behavioral model of tinnitus: novel conceptualizations of tinnitus distress. Front Neurol 5: 196.
3. Baguley D, McFerran D, Hall D (2013) Tinnitus. Lancet 382: 1600-1607.
4. Tyler R, Coelho C, Tao P, et al. (2008) Identifying tinnitus subgroups with cluster analysis. Am J Audiol 17: S176-S184.
5. De Ridder D, Vanneste S, Weisz N, et al. (2014) An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. Neurosci Biobehav Rev 44: 16-32.
6. Lefaucheur JP, André-Obadia N, Antal A, et al. (2014) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 125: 2150-2206.
7. De Ridder D, Vanneste S, Engineer ND, et al. (2014) Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation 17: 170-179.
8. Minen MT, Camprodon J, Nehme R, et al. (2014) The neuropsychiatry of tinnitus: a circuit-based approach to the causes and treatments available. J Neurol Neurosurg Psychiatry 85: 1138-1144.
9. Zhou X, Panizzutti R, de Villers-Sidani E, et al. (2011) Natural restoration of critical period plasticity in the juvenile and adult primary auditory cortex. J Neurosci 31: 5625-5634.
10. Hallam RS, Jakes SC, Hinchcliffe R (1998) Cognitive variables in tinnitus annoyance. Br J Clin Psychol 27: 213-222.
11. Low YF, Trenado C, Delb W, et al. (2007) The role of attention in the tinnitus decompensation: reinforcement of a large-scale neural decompensation measure. Conf Proc IEEE Eng Med Biol Soc 2007: 2485-2488.
12. Langguth B, Kleinjung T, Landgrebe M, et al. (2010) rTMS for the treatment of tinnitus: the role of neuronavigation for coil positioning. Neurophysiol Clin 40: 45-58.
13. Eggermont JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci 27: 676-682.
14. Kleinjung T, Steffens T, Landgrebe M, et al. (2011) Repetitive transcranial magnetic stimulation for tinnitus treatment: no enhancement by the dopamine and noradrenaline reuptake inhibitor bupropion. Brain Stimul 4: 65-70.
15. Teismann H, Wollbrink A, Okamoto H, et al. (2014) Combining transcranial direct current stimulation and tailor-made notched music training to decrease tinnitus-related distress-a pilot study. PLoS One 9: e89904.
16. Wassermann EM, Zimmermann T (2012) Transcranial magnetic brain stimulation: therapeutic promises and scientific gaps. Pharmacol Ther 133: 98-107.
17. Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1: 1106-1107.
18. Devlin JT, Watkins KE (2007) Stimulating language: insights from TMS. Brain 130: 610-622.
19. George MS, Nahas Z, Borckardt JJ, et al. (2007) Brain stimulation for the treatment of psychiatric disorders. Curr Opin Psychiatry 20: 250-254.
20. Aleman A, Sommer IE, Kahn RS (2007) Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: A meta-analysis. J Clin Psychiatry 68: 416-421.
21. Fregni F, Pascual-Leone A (2007) Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 3: 383-393.
22. Meng Z, Liu S, Zheng Y, et al. (2011) Repetitive transcranial magnetic stimulation for tinnitus. Cochrane Database Syst Rev CD007946.
23. O'Reardon JP, Solvason HB, Janicak PG, et al. (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62: 1208-1216.
24. Herwig U, Fallgatter AJ, Höppner J, et al. (2007) Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 191: 441-448.
25. Huang YZ, Edwards MJ, Rounis E, et al. (2005) Theta burst stimulation of the human motor cortex. Neuron 45: 201-206.
26. Rajan TS, Cuzzocrea S, Bruschetta D, et al. (2016) Repetitive Transcranial Magnetic Stimulation as a Novel Therapy in Animal Models of Traumatic Brain Injury. Methods Mol Biol 1462: 433-443.
27. Groppa S, Oliviero A, Eisen A, et al. (2012) A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 123: 858-882.
28. Rossi S, Hallett M, Rossini PM, et al. (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120: 2008-2039.
29. Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117: 2584-2596.
30. Thut G, Pascual-Leone A (2010) A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topogr 22: 219-232.
31. Fuggetta G, Noh NA (2013) A neurophysiological insight into the potential link between transcranial magnetic stimulation, thalamocortical dysrhythmia and neuropsychiatric disorders. Exp Neurol 245: 87-95.

32. Vanneste S, De Ridder D (2011) Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. Eur J Neurosci 34: 605-614.

33. Ruffini G, Wendling F, Merlet I, et al. (2013) Transcranial current brain stimulation (tCS): models and technologies. IEEE Trans Neural Syst Rehabil Eng 21: 333-345.

34. Plewnia C, Reimold M, Najib A, et al. (2007) Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. J Neurol Neurosurg Psychiatry 78: 152-156.

35. Weisz N, Steidle L, Lorenz I (2012) Formerly known as inhibitory: effects of 1-Hz rTMS on auditory cortex are state-dependent. Eur J Neurosci 36: 2077-2087.

36. Anders M, Dvorakova J, Rathova L, et al. (2010) Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: A randomized, placebo controlled study. Neuro Endocrinol Lett 31: 238-249.

37. Hoekstra CE, Versnel H, Neggers SF, et al. (2013) Bilateral low-frequency repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: A randomised controlled trial. Audiol Neurootol 18: 362-373.

38. Barwood CH, Wilsonb WJ, Malicka AN, et al. (2013) The effect of rTMS on auditory processing in adults with chronic, bilateral tinnitus: A placebo-controlled pilot study. Brain Stimul 6: 752-759.

39. Schecklmann M, Lehner A, Gollmitzer J, et al. (2015) Repetitive transcranial magnetic stimulation induces oscillatory power changes in chronic tinnitus. Front Cell Neurosci 9: 421.

40. Folmer RL, Theodoroff SM, Casiana L, et al. (2015) Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg 141: 716-722.

41. Marcondes RA, Sanchez TG, Kii MA, et al. (2010) Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: A double-blind controlled, clinical and neuroimaging outcome study. Eur J Neurol 17: 38-44.

42. Piccirillo JF, Garcia KS, Nicklaus J, et al. (2011) Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus. Arch Otolaryngol Head Neck Surg 137: 221-228.

43. Mennemeier M, Chelette KC, Allen S, et al. (2011) Variable changes in PET activity before and after rTMS treatment for tinnitus. Laryngoscope 121: 815-822.

44. Kim BG, Kim DY, Kim SK, et al. (2014) Comparison of the outcomes of repetitive transcranial magnetic stimulation to the ipsilateral and contralateral auditory cortex in unilateral tinnitus. Electromagn Biol Med 33: 211-215.

45. Piccirillo JF, Kallogjeri D, Nicklaus J, et al. (2013) Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus: four-week stimulation trial. JAMA Otolaryngol Head Neck Surg 139: 388-395.

46. Yang H, Xiong H, Yu R, et al. (2013) The characteristic and changes of the event-related potentials (ERP) and brain topographic maps before and after treatment with rTMS in subjective tinnitus patients. PLoS One 8: e70831.

47. Wang H, Li B, Wu H, et al. (2016) Combination of gaps in noise detection and visual analog scale for measuring tinnitus components in patients treated with repetitive transcranial magnetic stimulation. Auris Nasus Larynx 43: 254-258.

48. Park JH, Noh TS, Lee JH, et al. (2015) Difference in tinnitus treatment outcome according to the pulse number of repetitive transcranial magnetic stimulation. Otol Neurotol 36: 1450-1456.

49. Rossi S, De Capua A, Ulivelli M, et al. (2007) Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: a randomised, crossover, double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 78: 857-863.

50. Kleinjung T, Steffens T, Londero A, et al. (2007) Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects. Prog Brain Res 166: 359-367.

51. Khedr EM, Rothwell JC, Ahmed MA, et al. (2008) Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. J Neurol Neurosurg Psychiatry 79: 212-215.

52. Lefaucheur JP, André-Obadia N, Poulet E, et al. (2011) French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications. Neurophysiol Clin 41: 221-295.

53. Tunkel DE, Bauer CA, Sun GH, et al. (2014) Clinical practice guideline: Tinnitus. Otolaryngol Head Neck Surg 151: S1-S40.

54. Tunkel DE, Bauer CA, Sun GH, et al. (2014) Clinical practice guideline: Tinnitus executive summary. Otolaryngol Head Neck Surg 151: 533-541.

55. Langguth B, Landgrebe M, Frank E, et al. (2014) Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. World J Biol Psychiatry 15: 276-285.

56. Londero A, Langguth B, De Ridder D, et al. (2006) Repetitive transcranial magnetic stimulation (rTMS): a new therapeutic approach in subjective tinnitus? Neurophysiol Clin 36: 145-155.

57. Burger J, Frank E, Kreuzer P, et al. (2011) Transcranial magnetic stimulation for the treatment of tinnitus: 4 year follow-up in treatment responders-a retrospective analysis. Brain Stimul 4: 222-227.

58. Shekhawat GS, Stinear CM, Searchfield GD (2015) Modulation of perception or emotion? A scoping review of tinnitus neuromodulation using transcranial direct current stimulation. Neurorehabil Neural Repair 29: 837-846.

59. Zeman F, Koller M, Figueiredo R, et al. (2011) Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? Otolaryngol Head Neck Surg 145: 282-287.

60. Wang H, Li B, Feng Y, et al. (2015) A Pilot Study of EEG Source Analysis Based Repetitive Transcranial Magnetic Stimulation for the Treatment of Tinnitus. PLoS One 10: e0139622.

61. Yilmaz M, Yener MH, Turgut NF, et al. (2014) Effectiveness of transcranial magnetic stimulation application in treatment of tinnitus. J Craniofac Surg 25: 1315-1318.

62. Lee HY, Yoo SD, Ryu EW, et al. (2013) Short term effects of repetitive transcranial magnetic stimulation in patients with catastrophic intractable tinnitus: preliminary report. Clin Exp Otorhinolaryngol 6: 63-67.

63. Shekhawat GS, Stinear CM, Searchfield GD (2013) Transcranial direct current stimulation intensity and duration effects on tinnitus suppression. Neurorehabil Neural Repair 27: 164-172.

64. Forogh B, Mirshaki Z, Raissi GR, et al. (2016) Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: A pilot randomized controlled trial. Neurol Sci 37: 253-259.

65. Pal N, Maire R, Stephan MA, et al. (2015) Transcranial Direct Current Stimulation for the Treatment of Chronic Tinnitus: A Randomized Controlled Study. Brain Stimul 8: 1101-1107.

66. Garin P, Gilain C, Van Damme JP, et al. (2011) Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation. J Neurol 258: 1940-1948.

67. Faber M, Vanneste S, Fregni F, et al. (2012) Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex. Brain Stimul 5: 492-498.