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REVIEW ARTICLE

Therapeutic impact of repetitive transcranial magnetic stimulation (rTMS) on tinnitus: a systematic review and meta-analysis

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Abstract In this study, we conducted a systematic literature review and meta-analysis on the effect of repetitive transcranial magnetic stimulation (rTMS) compared with sham in chronic tinnitus patients. We searched databases, from their onset up to August 2014, for randomized controlled trials (RCT) in English that assessed the effectiveness of rTMS for chronic tinnitus. RCTs were selected according to inclusion/exclusion criteria before data were extracted. For the meta-analysis weighted mean differences (and standard deviations) of Tinnitus Questionnaire (TQ) and Tinnitus Handicap Inventory (THI) scores were determined. Therapeutic success was defined as difference of at least 7 points in the THI score between baseline and the follow-up assessment after treatment. The odds ratio (OR) for this variable was assessed. Results from 15 RCTs were analyzed. The mean difference for TQ score at 1 week after intervention was 3.42. For THI, the data of mean difference score in two groups, 1 and 6 month after intervention, was 6.71 and 12.89, respectively. The all comparisons indicated a significant medium to large effect size in follow-up which is in favor of the rTMS. The pooled OR of therapeutic success of the studies which used THI at 1 month after intervention was 15.75. These data underscore the clinical effect of rTMS in the treatment of tinnitus. However, there is high variability of studies design and reported outcomes. Replication of data in multicenter trials with a large number of patients and long-term follow-up is needed before further conclusions can be drawn.

Keywords Tinnitus · Transcranial magnetic stimulation · Repetitive · Auditory cortex · Randomized clinical trials

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Introduction

Chronic tinnitus is experienced by 10–15 % of the adult population [1]. Of those people who experience chronic tinnitus, approximately 20 % consider it to be a "clinically significant" problem [2].

Currently, there is no specific pharmacological treatment available that provides a replicable, long-term alleviation of tinnitus. In recent years, several studies have been conducted that have examined the utility of repetitive transcranial magnetic stimulation (rTMS) for the treatment of tinnitus. TMS is a non-invasive intervention that involves delivering electromagnetic pulses through a coil that is in contact with the subject's scalp. These pulses produce intermittent magnetic fields in the strength range of 1 Tesla, and some of this energy is transmitted through the cranium, modulating the activity of the underlying neural tissue [3].

Studies in both animals [4–6] and humans [7, 8] have demonstrated that tinnitus can be associated with abnormal neural activity in central auditory pathways. This finding is supported by several functional imaging studies that have shown that people who experience tinnitus have increased

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activity in the auditory cortex compared with that in control subjects, even in the absence of external auditory stimuli [9].

George et al. [10] defined "fast" rTMS as having a stimulus frequency greater than 1 pulse per second (1 Hz). Fast rTMS is often used to treat depression by applying 10 or 20 pulses per second to the patient's left frontal lobe. Theoretically, this rate of stimulation increases neural activity beneath the coil and, over a series of TMS sessions, it helps to reduce patients' depression. In contrast, low-frequency rTMS (1 Hz or less) is known to reduce neural activity in the brain regions directly stimulated [11, 12] as well as in structurally connected remote brain regions [13].

Results from a number of studies in tinnitus patients demonstrate that rTMS treatment is effective for varying periods, with some results indicating that the treatment effect can extend beyond the stimulation period by 3–6 months [3]. Several rTMS studies have recently been conducted, with the aim of determining a stimulation protocol that increases the duration of tinnitus suppression. Several different parameters of rTMS and different study designs have been used, and the degree of improvement has varied across studies [14]. Paucity of treatment results and variation between studies has precluded physicians from achieving a comprehensive understanding of the therapeutic value of rTMS for tinnitus. Meng et al. [15] (May 2011) performed a recent systematic review to evaluate the benefits of rTMS as a treatment for tinnitus. Only five randomized controlled trials (RCT) [16–20] comprising of 233 participants met their inclusion criteria. Therefore, we conducted the current meta-analysis on the basis of systematic review of rTMS treatment results in tinnitus sufferers, with the aim of assessing effectiveness of rTMS for tinnitus suppression.

Materials and methods

Literature search

Using the Protocol A of PICO framework (Table 1) [21], we searched the following databases, from their onset up to August 2014, for randomized controlled trials in English that assessed the effectiveness of rTMS treatment for chronic tinnitus: MEDLINE, Google scholar, PubMed, Institute of Scientific Information (ISI), SCOPUS, EMBASE, Ovid, and the Cochrane Database of Systematic Reviews.

Three authors (S.R., J.M.M., H.T.) independently searched for the terms 'repetitive transcranial magnetic stimulations," "rTMS," "tinnitus," and "buzz." The reference lists of articles obtained through these searches were also reviewed in order to identify further reports that could be included in the systematic review. Additionally, we attempted to identify all unpublished literature on this topic by searching congress, dissertations and research projects, Ear Nose and Throat Disorders Group Trials Register, Clinical Trials.gov, and the Iranian Registry of Clinical Trials (IRCT). Abstracts were reviewed to identify articles appropriate for analysis, and references cited in these articles were cross-indexed to search for other articles appropriate for analysis. Patients that were included in more than one report were counted only once.

Table 1 Developing a research question through the PICO format

Patient	Adults with chronic non-pulsating tinnitus
Intervention	rTMS
Comparison	Sham control group
Outcome	Impact of tinnitus measured by standard tinnitus-specific health-related quality of life instruments or other measure of tinnitus severity used by trial authors

Study selection

All studies selected were examined independently by the three authors. The inclusion criteria for the current meta-analysis were that the study (1) reported on rTMS in the management of tinnitus patients, (2) dealt with original data from a RCT in which tinnitus severity and quality of life were the outcome measure, (3) was performed with a randomized parallel design, including a sham control, (4) participants complained of persistent, distressing, subjective tinnitus of any etiology, and (5) participants and raters were both unaware of the treatment condition. We excluded studies, which assessed the impact of rTMS on pulsatile tinnitus or delusional auditory hallucinations, or if patients were receiving concurrent psychotherapeutic interventions. Additionally, percentage change in tinnitus intensity measures had to be either directly available or derivable from the data shown in the tables or figures of the publication. Due to the possibility that carry-over effects exist between trial stages of crossover studies, we did not include these studies.

Quality assessment

Using the Jadad scale (score range of 0–5), which includes evaluation criteria for randomization, blinding, and withdrawals and dropouts, relevant information was recorded to judge the methodological quality of each trial [22]. A high Jadad scale of a study means low biased study. The grading was done independently by two researchers (S.R., H.T.) and any disagreements were discussed until a consensus was reached. Quality score 3 or more was considered appropriate.

Data extraction and analysis

For initial data extraction, the following were extracted independently by two authors (J.M.M., H.T.) in a structured fashion, and then confirmed by one author (S.R.): (1) study design, (2) patient characteristics (age, tinnitus laterality, and tinnitus sound characteristics), (3) rTMS parameters (rTMS frequency, number of stimuli, stimulus intensity, target brain area, number of treatment sessions), and (4) primary outcomes that were patients' subjective assessment of tinnitus before and after treatment (change in overall severity of tinnitus and/or impact on quality of life). Patient questionnaires included the Tinnitus Handicap Inventory (THI), the Tinnitus Questionnaire (TQ), and the visual analog scale (VAS). The use of THI and TQ measures quality of life. A VAS scale could measure quality of life but could also measure severity, depending on the associated question. So these outcomes were not grouped together. Where possible, we considered "therapeutic success" as a secondary outcome. For the Tinnitus Handicap Inventory, it was defined as a reduction of seven points or more in the post-stimulation THI score [23]. For the Tinnitus Questionnaire, a minimum difference of five points was considered clinically important [24]. In cases of missing or incomplete information, data were extracted from the figures and tables as much as possible. Studies in which data were incomplete or ambiguous were discussed by the authors to ensure clarification.

Standardized measures of tinnitus

Tinnitus loudness (i.e., subjective intensity of tinnitus) is commonly measured using a VAS, but this scale varied between the studies examined. In most studies, tinnitus was rated on a 0 (no tinnitus) to 10 (severe, disabling tinnitus) VAS [18, 25–27]. In studies by Rossi et al. [28] and Smith et al. [29], tinnitus was rated on a 0–100 VAS, where 0 was wellness and 100 was the worst possible tinnitus-related discomfort. In one study [30], tinnitus loudness was assessed by a discrete VAS consisting of 11 steps (−5 to +5). The Tinnitus Magnitude Rating, which is similar to a VAS in that it attempts to measure the loudness of tinnitus using a scale of 0–100, was used in the study by Ghossaini et al. [17].

For tinnitus severity measurement, some studies used TQ or THI questionnaires. In the 52-question TQ [31], patients assigns a score between 0 (mild or no tinnitus) and 84 (very severe tinnitus) on the basis of experience with common complaints of tinnitus patients.

The THI [32] is a 25-question tool that is used to quantify the impact of tinnitus on daily living, and assigns a score between 0 (slight tinnitus) and 100 (catastrophic tinnitus).

Meta-analysis

Meta-analyses were conducted for outcome measures shared by at least three studies. From the systematic review data, a change in mean tinnitus intensity between two groups was calculated as the primary outcome. Additionally, we performed a meta-analysis on the results provided we thought them clinically relevant, and if no important clinical and methodological heterogeneity was found.

For continuous data, we calculated the mean difference. The main analysis was an examination of severity (subjective loudness) of tinnitus and its effect on quality of life. The statistical significance of the mean difference was evaluated using a Z test. For dichotomous data, we calculated the odds ratio. Weighting was performed using an inverse variance model. The odds ratio (OR) for binary variables was pooled using the Mantel–Haenszel method, along with their 95 % confidence intervals (CI).

Heterogeneity was assessed using I squared statistics and a p value of <0.1 was considered significant (i.e., showing heterogeneity) [33]. Heterogeneity approximates the percentage of the total variation (within and between studies) that is due to between-study variation. In the absence of heterogeneity, fixed and random effects models yield the same results. If the data were homogeneous we used a fixed-effect model, and if the data were heterogeneous we used a random-effect model.

The meta-analyses were performed using Review Manager (RevMan, version 5.3) from the Cochrane Collaboration (Oxford, UK).

Systematic review

After data extraction and meta-analysis, tinnitus outcomes that were not shared by other studies underwent systematic review.

Results

Literature search and data extraction

Of 35 RCTs obtained in our search, sixteen were excluded from further examination for the following reasons: two were not intervention RCTs [34, 35], two due to design of the RCT [36, 37], six were systematic reviews or meta-analyses [15, 38–42], two were subsequent publications of an RCT already evaluated [26, 43], one was an intervention following surgery study [44], one had no English full text [45], one was non-relevant [46], and one was accessible only as a poster presentation [47]. In the article of Langguth et al. [48], results of two studies were published (We used two sub-references, '2014, study1' and '2014, study

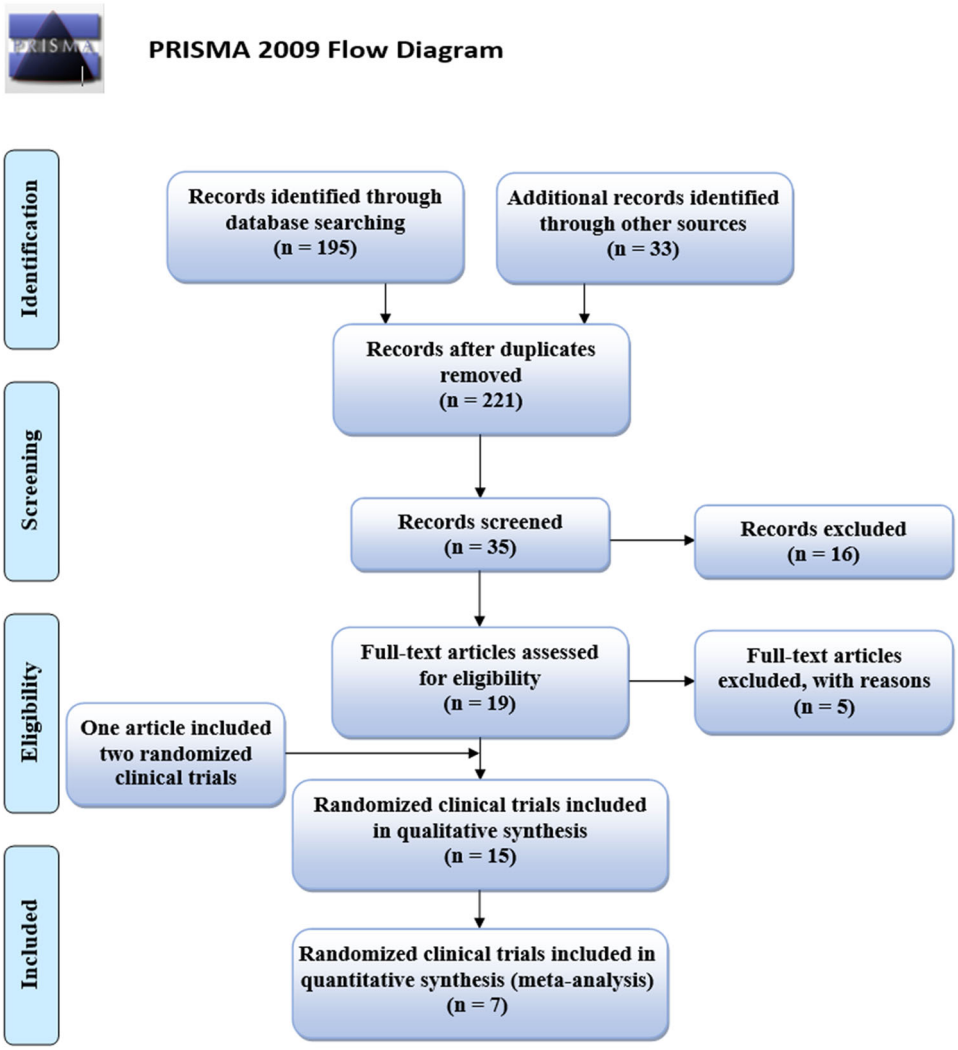

Fig. 1 Flow of information through the different phases of a systematic review. Details of the inclusion and exclusion process of the finally selected intervention randomized controlled trials in which at least one arm involved rTMS; shown in a PRISMA flow diagram

2'). Thus, nineteen articles encompassing twenty intervention RCTs were included (Fig. 1). The total number of participants corresponding to the 20 RCTs was 1014 subjects. The median number of participants per study was 43.5 (range 8–114).

Trial quality

In the twenty rTMS RCTs, the randomization method was described and appropriate in seven (35 %), described but inappropriate in four (20 %), and was not described in nine (45 %). Blinding using an appropriate method was reported in nine studies (45 %), blinding was reported but the method was inappropriate in eight (40 %), and blinding was not reported in three studies (15 %). Dropouts/withdrawals were described in eighteen (90 %). The median modified Jadad score for intervention RCTs was three (range 0–5). In general, according to the Jadad scale, 14 articles (15 RCTs) [16–20, 25–27, 48–53] were considered as high-quality studies (Jadad score 3–5), of which three articles [25, 48, 53] achieved the maximum quality score. Five studies [54–58], scored <3 in the Jadad scale and were categorized to be low-quality studies (Table 2).

Characteristics of included studies

Six trials evaluated were at risk of incomplete outcome reporting bias [16–18, 20, 48]. Drop-out rate of Anders et al. [16] study was 19.2 %. Drop-out rate of the other five trials [17, 18, 20, 48] ranged from 4.1 to 6.9 %, suggesting low risk bias. Table 3 summarizes the main characteristics of the fifteen trials that were included.

An early investigation of rTMS in tinnitus sufferers by De Ridder et al. [52] used transcranial magnetic stimulation at 1, 3, 5, 10, and 20 Hz during one treatment session. The researchers delivered a relatively small numbers of pulses (200–300 maximum) during a single session for each subject, and they were delivered to the auditory cortex contralateral to the ear experiencing tinnitus. The amount of tinnitus suppression experienced by

Table 2 Quality assessment based on the Jadad scale

No.	Study	Study design[a]	Randomization (0/1/2)	Double blind (0/1/2)	Withdrawals and dropouts described (0/1)	Total Jadad score
1	Anders et al. [16]	Parallel group	2	2	0	4
2	Barwood et al. [49]	Parallel group	2	1	1	4
3	Bilici et al. [50]	Parallel group	1	2	1	4
4	Chung et al. [51]	Parallel group	1	1	1	3
5	De Ridder et al. [52]	Parallel group[b]	1	1	1	3
6	Ghossaini et al. [17]	Parallel group	1	2	1	4
7	Hoekstra et al. [25]	Parallel group	2	2	1	5
8	Khedr et al. [19]	Parallel group	2	0	1	3
9	Khedr et al. [54]	Parallel group	0	1	1	2
10	Langguth et al. [48][b]	Parallel group	2	2	1	5
11	Lee et al. [55]	Placebo-controlled trial	0	1	1	2
12	Lee et al. [56]	Placebo-controlled trial	0	1	1	2
13	Lorenz et al. [26]	Parallel group	1	1	1	3
14	Marcondes et al. [18]	Parallel group	1	2	1	4
15	Plewnia et al. [53]	Parallel group	2	2	1	5
16	Roland et al. [20]	Parallel group	1	2	1	4
17	Vanneste et al. [57]	Placebo-controlled trial	0	0	0	0
18	Vanneste et al. [27]	Parallel group	1	1	1	3
19	Yilmaz et al. [58]	Parallel group	1	0	1	2

[a] In the Jadad scale, 0, 1, or 2 points can be given for randomization (explicit statement that allocation was randomized and description of an adequate generation of the random sequence); 0, 1, or 2 points for double blinding (explicit statement that patients and evaluators were blinded and that treatments were indistinguishable); 0 or 1 point for the description of dropouts and withdrawals

[b] In this study, the researchers reported the results of two RCTs

subjects was 53 % (moderate efficacy of rTMS), and the duration of measured tinnitus suppression was often brief (a few seconds to a few minutes after the conclusion of the rTMS session). Since five different rTMS frequencies were delivered during a single session, it has almost the same limitations as a crossover study and its results should be used with caution.

Roland et al. [20] conducted a randomized, double-blind and placebo-controlled trial that considered the effectiveness of a Therapak device with non-navigated coil localization. The Therapak device generates monophasic electromagnetic pulses consisting of a complex waveform. The frequency is variable from 0.5 to 17 Hz, and contains components and harmonics ranging up to 2.5 MHz. The device was placed over the top of the neck and the mastoid process of each subject's ear, and they were treated for 1 week. The outcome measured was subjective response to treatment (tinnitus completely abolished, tinnitus improved, tinnitus unchanged, or tinnitus worse) after the trial. The authors found that 45 % of the subjects in the treatment group had a subjective improvement compared with only 9 % in the placebo group ($p = 0.01$).

Ghossaini et al. [17] evaluated the effectiveness of high-frequency pulsed electromagnetic energy using the Diapulse device in the treatment of chronic tinnitus. The Diapulse unit was set to deliver 27.12 MHz electromagnetic energy at a rate of 600 pulses per second during treatment sessions, and patients received 30-min treatments three times a week for 1 month. The authors concluded that there were no significant differences between the pre-treatment and post-treatment THI scores or the tinnitus rating scores in either subject group.

Although both Roland et al. [20] and Ghossaini et al. [17] studies have been included in the Cochrane review of Meng et al. [15], they are based on high-frequency pulsed electromagnetic stimulation, with very low energy and magnetic fields. The therapeutic effects of Pulsed electromagnetic energy therapy appear to depend more upon subtle interactions between the electric and magnetic field and biological tissue [59]. Therefore, the possible mechanisms of action are different from the effect of rTMS.

In two studies [27, 50], low and high frequencies of rTMS were delivered. In ten other trials, lower frequency (1 Hz) rTMS was delivered in an attempt to alleviate tinnitus. The investigators in all of these studies implemented protocols that used lower frequency rTMS (1 Hz) and delivered a greater number of pulses (900–2000) during one session. Also, subjects received rTMS on five to twenty successive days, instead of a single session, and the

Table 3 Characteristics of included randomized clinical trials

	Anders et al. [16]	Barwood et al. [49]	Bilici et al. [50]	Chung et al. [51]	De Ridder et al. [52]
No of participants[a] (dropout)	52 (10)	8 (0)	45	22 (0)	114 (0)
Mean age of participant (years)	48.1	42.7	40	52.9	Not stated
Mean duration of tinnitus (years)	8.9	1.7	>1	0.5–20	1 to >8
% bilateral tinnitus	64.3	100	51.1	22.7	7
% participants with normal hearing	100	50	45	36.4	Not stated
No. of treatment sessions	10	10	10	10	1
No. of stimuli per session	1500	2000	900	900	200 (each)
rTMS frequency (Hz)	1	1	1,10	1	1, 3, 5, 10, 20
Stimulus intensity (% of RMT)	110	110	110	80	90
Navigation	Yes	Yes	No	Yes	Only 10 cases
Target brain area	Left PAC	Left BA41	Left TP	Left TP	Contralateral AC
Duration of follow-up (months)	6	3	6	1	–
Outcome parameter[c]	THI, TQ, VAS-1, VAS-2	THI	THI, TSI	THI, TQ	No clear
Control of psychological factors	Yes	No	Yes	No	No
Conclusion by author	Significant	Significant	Significant	Significant	Reduce in 53 % pts

	Ghossaini et al. [17]	Hoekstra et al. [25]	Khedr et al. [19]	Langguth et al. study 1 [48]	Langguth et al. study 2 [48][b]
No of participants[a] (dropout)	37 (2)	52 (0)	66 (0)	96 (5)	48 (0)
Mean age of participant (years)	59.5	52	41	47.5	50.4
Mean duration of tinnitus (years)	14.70	3.8	0.5–25	5.9	6.5
% bilateral tinnitus	54.1	60	22.2	47.7	25.5
% participants with normal hearing	No clear	No clear	80.3	No stated	No stated
No of treatment sessions	12	10	10	10	10
No of stimuli per session	600	900	1500	2000	2000
rTMS frequency (Hz)	27.12[b]	1	1, 10, 25	1	1
Stimulus intensity (% of RMT)	–	110	100	110	110
Navigation	Yes	Yes	Yes	Yes	No
Target brain area	Left TP	Bilateral PAC	Left TP	Left TP	Left T
Duration of follow-up (months)	–	6	4	3	3
Outcome parameter[c]	THI, TMR	THI, TQ, VAS	THI	TQ	TQ
Control of psychological factors	No	Yes	No	No	No
Conclusion by author	No significant	No significant	Significant	No significant	No significant

	Lorenz et al. [26]	Marcondes et al. [18]	Plewina et al. [53]	Roland et al. [20]	Vanneste and De Ridder [27]
No of participants[a] (dropout)	10 (0)	20 (1)	32 (0)	58 (4)	60 (0)
Mean age of participant (years)	49.8	>18	55.8	36–82	50.1
Mean duration of tinnitus (years)	1.8	>0.25	28	>1	8.3
% bilateral tinnitus	50	No stated	53.1	No stated	63.3
% participants with normal hearing	No stated	100	28.1	No stated	0
No. of treatment sessions	5	5	20	7	5
No. of stimuli per session	1000	1020	2400	–	900
rTMS frequency (Hz)	1	1	5	0.5–17	1, 10

Table 3 continued

	Lorenz et al. [26]	Marcondes et al. [18]	Plewina et al. [53]	Roland et al. [20]	Vanneste and De Ridder [27]
Stimulus intensity (% of RMT)	110	110	80 (of active motor threshold)	No stated	120
Navigation	No	No	Yes	No	Yes
Target brain area	Left PAC	Left TP	Bilateral cTBS	No stated	Left VLPC
Duration of follow-up (months)	–	6	3	–	1
Outcome parameter	VAS	THI, VAS-L	TQ	Subjective score	VAS
Control of psychological factors	No	Yes	No	No	No stated
Conclusion by author	Significant	Significant	No significant	Significant	Significant (for 10 Hz)

For Langguth 2014—study 2, we specified the data referring to one arm of the 2d RCT only (with left temporal rTMS)

AC Auditory Cortex, *PAC* Primary Auditory Cortex, *T* Temporal, *TP* Temporoparietal, *VLPC* Ventrolateral Prefrontal Cortex, *THI* Tinnitus Handicap Inventory, *TMR* Tinnitus Magnitude Rating, *TQ* Tinnitus questionnaire, *VAS* Visual Analog Scale, *VAS-L* Visual Analog Scale for loudness, *VAS-1* significance in life, *VAS-2* disruption with daily life

[a] Number of participants in rTMS and sham groups

[b] 27.12 MHz

duration of the follow-up periods in these studies was longer than the others discussed above (up to 6 months).

Most published studies (10 out of 15 trials analyzed here) reported that active rTMS had some degree of efficacy in reducing the loudness or severity of tinnitus. Anders et al. [16] claimed that their study yielded positive results, but the reported data revealed statistically insignificant improvement in tinnitus severity. Additionally, in the other five of the 15 trials analyzed, the authors concluded that active rTMS was no more effective than placebo.

Some studies compared the impact of low rate with high rate rTMS. We extracted the data from three trials for further analysis [19, 27, 50]. Bilici et al. [50] compared five groups (1 Hz, 10 Hz, 1 Hz +SSRI, SSRI, and sham group), and found that a 10-day rTMS treatment period was partially effective at both 1 and 10 Hz stimulation rates. Khedr et al. [19] compared the effect of different frequencies of rTMS (1, 10, 25 Hz) over a 2-week treatment period in 66 patients with chronic tinnitus. There was no significant difference between the responses to different frequencies of rTMS, in agreement with the Bilici study. Vanneste and De Ridder [27] studied the effect that TMS delivered to the left ventrolateral prefrontal cortex (VLPFC) had on the modulation of tinnitus loudness. The authors found that 10 Hz stimulation can modulate tinnitus loudness, whereas 1 Hz stimulation does not seem to exert the same effect.

Mean difference in tinnitus severity

It should be noted that we have analyzed questionnaires only. Several studies reported mean differences in TQ or THI to assess tinnitus severity at different times after intervention.

For TQ, the mean difference score between the TMS and sham groups evaluated 1 week after intervention was available for three trials [25, 48, 51]. One of these trials [48] included two studies. The mean difference in TQ score following active rTMS was 3.42 (95 % CI, 0.92–5.91). This comparison showed that active rTMS may be better than sham ($Z = 2.68$, $p = 0.007$) (Fig. 2).

For THI, the mean difference score between the TMS and sham groups evaluated 1 month after intervention was available in four studies [18, 25, 50, 51] and evaluated 6 months after invention was available in three studies [18, 25, 50]. One month after intervention the mean difference in THI score following active rTMS was 6.71 (95 % CI, 2.77–10.65), which indicates a therapeutic effect of active rTMS ($Z = 3.34$, $p = 0.0008$) (Fig. 3). Six months after intervention the mean difference in THI score following active rTMS was 12.89 (95 % CI, 6.57–19.22), which supports a long-term therapeutic effect of active rTMS ($Z = 3.99$, $p = 0.0001$) (Fig. 4). These results indicate a significant effect size at both 1 and 6 months following active rTMS intervention.

Comparison odds ratio of therapeutic success in participants with active rTMS versus sham

Of the studies that used THI to measure therapeutic outcome at 1 month after active rTMS intervention, the therapeutic success and odds ratio (OR) could be calculated in three [18, 49, 51] (Fig. 5). However, the 95 %

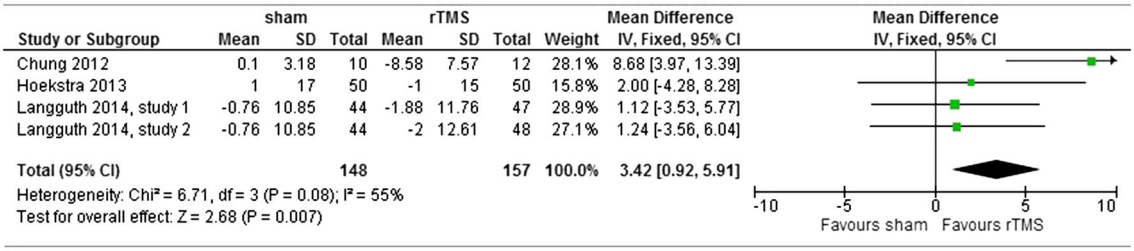

Fig. 2 Comparison of active rTMS with sham for mean change in Tinnitus Questionnaire 1 week after intervention. There was a significant improvement in Tinnitus Questionnaire, with 3.42-point reduction (95 % CI, 0.92–5.91; $p < 0.007$)

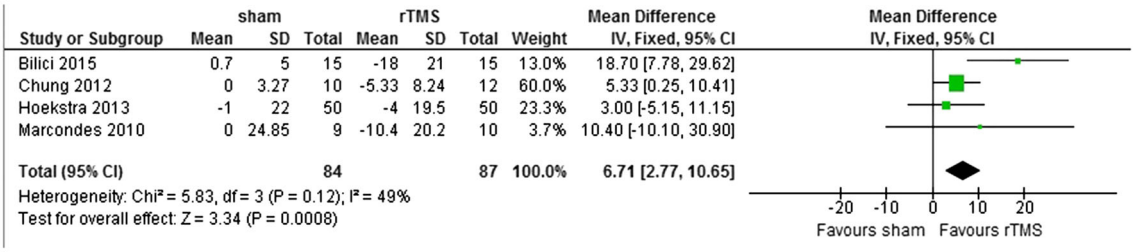

Fig. 3 Meta-analysis of active rTMS effects on Tinnitus Handicap Inventory 1 month after intervention. Mean summary difference across 4 studies demonstrated a 6.71 point reduction in tinnitus severity on the 100-point scale (95 % CI, 2.77–10.65; $p < 0.0008$). There was moderate heterogeneity between the studies ($I^2 = 49$ %)

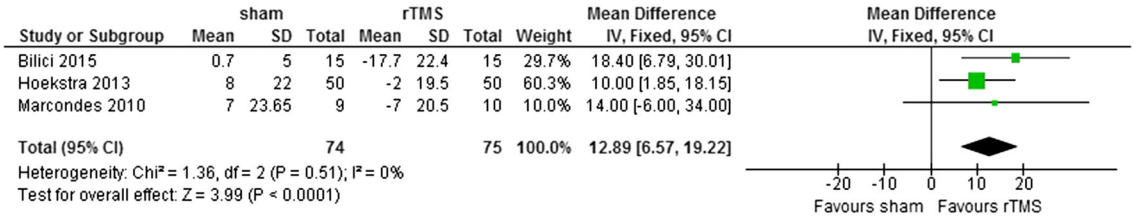

Fig. 4 Meta-analysis of active rTMS effects on Tinnitus Handicap Inventory 6 months after intervention. There was a significant improvement in Tinnitus Handicap Inventory with 12.89-point reduction (95 % CI, 6.57–19.22; $p < 0.0001$)

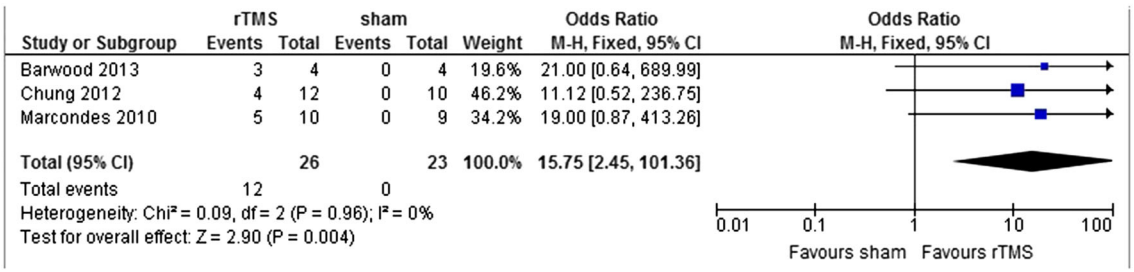

Fig. 5 Plot of odds ratios of therapeutic success in Tinnitus Handicap Inventory at 1 month after intervention. A *reference line* has been placed where OR = 1.0. Although the ORs for all studies are more than 1.0, the 95 % CI indicates that all studies were statistically insignificant. The overall OR is 15.75 (95 % CI, 2.45–101.36; $p < 0.004$) indicating a significant reduction in tinnitus might be expected with the use of active rTMS

CIs for all trials included 1.0; therefore, they were not significant. Of the three studies, one was statistically significant and two were not. The pooled odds ratio was 15.75 (95 % CI, 2.45–01.36), which showed a significant effect size ($Z = 2.90$, $p = 0.004$).

Discussion

Transcranial magnetic stimulation (TMS) is a non-invasive tool that can be used to modulate neural activity. TMS is often administered as a single pulse or as paired pulses, and

it ultimately affects activity of cortical neurons in the brain region beneath the coil. These kinds of stimulations are used for neurophysiological exploratory purposes. Repetitive TMS (rTMS) is the application of numerous TMS pulses to a subject's head during a single session [3]. Different TMS coil types are now available, and coil selection is influenced by both the neural target and whether the intended use is research or clinically based. The electric current and subsequent magnetic field generated by the coil are partly dependent on the design of the coil. Figure-eight coils are often used because they generate a focused pattern of activation, but other types are also used, such as double cone, round, or 4-leaf coils. Round coils are relatively powerful, whereas figure-eight coils achieve more focal stimulation with a maximal current at the intersection of the two round components [60].

Recent studies have examined the therapeutic utility of rTMS in the treatment of tinnitus. Given the relatively small number of subjects in most of these studies, as well as the broad range of outcome among them, we conducted a meta-analysis to estimate the benefit of rTMS for tinnitus.

Several key questions and procedural issues remain unresolved in clinical or research studies that have used rTMS for tinnitus, including small sample size, lack of adequate placebo condition, and various rTMS stimulation parameters and outcome measures used. These factors are discussed in the following sections.

Placebo (or ''sham'') procedures that have been used in TMS tinnitus studies include playing a recording of active stimulation while a non-active coil is held against the patient's head [18, 49, 50]; holding an active coil against the patient's head, but tilting the coil 45° or 90° to greatly reduce the delivered stimulus intensity [16, 26, 52, 57]; stimulating the subject's occipital lobe instead of the temporal lobe [19]; or using a placebo coil that seems identical to the active coil. There is variation among placebo coils that have been developed for different TMS systems, and their designs continue to change. Without a placebo condition, it is difficult to gage the true efficacy of TMS on tinnitus. Until placebo conditions are improved so that subjects cannot detect differences between active and ''sham'' rTMS, TMS studies will continue to be of limited value. All studies have the limitation that the medical personnel that deliver the stimulation are not blind to treatment condition. Stimulation of non-auditory brain areas as a control condition is also problematic, because tinnitus-related changes in brain activity are not restricted to the auditory cortex, and therefore this approach cannot be considered a sham condition. Angling the TMS coil is also not ideal, because a weak magnetic field may still affect brain tissue [61], as even fields as low as 1 milli-Tesla can alter brain activity [62].

Another concern surrounding the use of rTMS as a treatment for tinnitus is related to the rTMS stimulation parameters. Most studies that have used TMS to treat tinnitus deliver pulses between 80 and 120 % of the resting motor threshold (RMT). The percentage of RMT is used to gage or standardize the amount of electromagnetic energy delivered to each patient. However, Meeus et al. [63] concluded that stimulation intensity plays only a minor role in achieving higher tinnitus reduction. An increased stimulation intensity relative to the patient's motor threshold only accounts for 10 % of the therapeutic effect. Due to anatomic and functional differences of cortical areas in humans, it is likely that neuronal structures in different cortical areas are not similarly activated by TMS with the same stimulus intensities. There is not a direct relationship between motor cortex and sensory cortex excitability [64]. This should be considered in planning and execution of TMS studies of non-motor cortical areas. Also McConnell et al. [65] showed the variability of motor threshold with the distance to stimulated cortex. Until there is a greater degree of standardization, it will be difficult to determine the TMS intensity that is most effective in reducing the perception or severity of tinnitus.

An additional inconsistency that needs to be addressed if rTMS is to be used therapeutically for tinnitus is the scalp location where rTMS is delivered. The position of delivery remains variable across studies and controversial among tinnitus researchers. Plewnia et al. [66] conducted a positron emission tomography (PET) study to determine the most effective scalp location for application of rTMS. Their results indicated that the greatest amount of tinnitus suppression occurred when the rTMS coil was placed over patients' left temporal region. Based on the findings of Plewnia et al. [66], most researchers have decided to apply rTMS to the left temporal region exclusively, regardless of the location of the patient's tinnitus perception, though some studies have applied rTMS bilaterally [25, 53]. On the other hand, De Ridder et al. [52] hypothesized that neural activity in auditory cortex responsible for tinnitus generation is localized to the cerebral hemisphere contralateral to the patient's tinnitus perception, and therefore applied rTMS to the contralateral auditory cortex only. De Ridder et al. [67] found that in patients with lateralized tinnitus, fMRI activation produced by musical stimulation was lateralized toward the side of perceived tinnitus in the primary auditory cortex. According to the study of Khedr et al. [68], rTMS contralaterally to the side of the tinnitus has a greater beneficial effect on symptoms than ipsilateral rTMS and better suppression than left-sided stimulation. However, these results are obtained by non-placebo-controlled stimulation and future studies would be needed to decide this point unequivocally.

In general, the studies analyzed here delivered rTMS to temporal or temporoparietal cortical areas. However, the methods for coil localization varied across studies, ranging from highly sophisticated neuronavigation-based techniques to much simpler methods. Most trials used neuronavigation-guided coil localization based on different functional neuroimaging techniques, in order to target areas of tinnitus-related changes in brain activity [19, 25, 27, 48, 49, 51–53]. Five trials used a neuronavigation system in combination with structural imaging data, focusing on the primary auditory cortex [25, 27, 48, 49, 52]. Simpler techniques included coil localization according to the 10–20 EEG coordinate [19, 51, 53] and optimization techniques based on clinical effects [17, 18, 20, 26, 50].

Available clinical studies could not show superiority of neuronavigation-guided coil positioning compared to easier applicable strategies. Several explanations could account for this discrepancy. It has to be considered that the cortical area which is stimulated by TMS is about 2 × 3 cm large [69]. Therefore, the precision of a neuronavigation system may not be necessary since the correct target is still stimulated, if it is not more than 1 cm away from the hotspot of the coil. Langguth et al. [39] published an article in which other reasons for this phenomenon were assumed. They mentioned that the navigation might yield poorer results if studies did not identify the correct target and the therapeutic effects of rTMS may be mediated by changes in not directly stimulated areas via modulation of neuronal circuits. In this case, the necessary spatial accuracy for successful stimulation may depend on the size of the cortical target area of such a circuit. Also, the tinnitus suppressing effect of rTMS could be due to activation of the functional connections that exist between the secondary auditory cortex, which can be reached directly by the applied magnetic field, and primary auditory cortex [70]. Based on our knowledge of the physiological mechanisms of TMS, the exact position of the coil and also the exact orientation of the coil should matter. Further clinical and neurobiological research is needed before the questions about the optimal target and the usefulness of neuronavigation systems for coil placement can be answered.

An additional caveat is variation in outcome measures used in these investigations, making comparisons across studies difficult. Therefore, any claims of ''success'' should be interpreted with caution. The THI and the TQ were the major assessment methods used across studies, and THI and TQ may have different sensitivity and specificity in assessing tinnitus severity. However, two trials used both questionnaires. Anders et al. [16] showed that there was a significant reduction in both THI and TQ total score between real and sham TMS groups after short-term follow-up (2 weeks). In addition, the reduction of TQ in the TMS group persisted to week fourteen but only to week two in the sham group, whereas in the TMS group THI score worsened at week 6, yet was significantly reduced at week 26. In the study by Chung et al. [51], THI and TQ scores were significantly lower in patients that received active rTMS than those in the control group. However, after 1 month, THI and TQ scores were no longer significantly different from baseline value.

Together, the meta-analysis of the seven selected studies, which compared THI score between patients that received active rTMS and sham controls 1 and 6 months after intervention revealed that the mean summary difference was significant between the treatment groups ($p < 0.0008$ and $p < 0.0001$, respectively). In addition to confirming the findings of Meng et al. [15], this study showed long-term effects of rTMS on tinnitus.

Finally, it should be noted that the results of our study are interpreted with caution. In meta-analysis, three principal sources of heterogeneity can be distinguished. Variability in the participants, interventions, and outcomes studied may be described as clinical heterogeneity, and variability in study design and risk of bias may be described as methodological heterogeneity. Variability in the intervention effects being evaluated in the different studies is known as statistical heterogeneity, and is a consequence of clinical or methodological diversity, or both, among the studies [71]. Although we assessed statistical heterogeneity of the included studies by I^2 score, we could not evaluate other sources of heterogeneity. In this meta-analysis, patient baseline characteristics (such as age and duration of tinnitus) were different between patients from various studies. Also it should be noted that for TQ and THI comparisons, we included studies with various stimulation procedures (1, 10 Hz, theta burst, bilateral), which is methodologically questionable regarding the heterogeneity of this analysis.

Conclusions

In this study, we performed a meta-analysis on trials that examined the efficacy of rTMS on tinnitus, and in which the treatment outcomes were evaluated by the tinnitus questionnaire (TQ) and the tinnitus inventory handicap (THI). From our analysis of these trials, we observed moderate efficacy of low-frequency rTMS as a treatment for chronic tinnitus. The odds ratio of therapeutic success, defined by THI, is at least 15 times greater in the active rTMS group.

Although rTMS is a promising treatment for chronic tinnitus, our conclusions are based on a relatively small number of trials, which should be interpreted with caution. There were not many RCTs eligible for our meta-analysis, and the differences in study design, stimulation parameters,

and patient populations render a further comparison of the results difficult. Replication of data in multicenter trials with a large number of patients and long-term follow-up is needed before a firm conclusion can be drawn on short-term and long-term therapeutic benefits of rTMS.

Conflict of interest The authors declare no conflict of interest.

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