Repetitive Transcranial Magnetic Stimulation on Chronic Tinnitus: A Systematic Review and Meta-Analysis

Zhengrong Liang  
Jinan University First Affiliated Hospital

Gui Cheng  
Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Lingfei Huang  
Jinan University First Affiliated Hospital

Tao Zhang  
Jinan University First Affiliated Hospital

Haidi Yang  
Third Affiliated Hospital of Sun Yat-Sen University Department of Otorhinolaryngology Head and Neck Surgery

Haiying Jia  
Jinan University First Affiliated Hospital

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Abstract

Background: Although the clinical efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in the treatment of chronic tinnitus have been frequently examined, the results remain contradictory. Therefore, we performed a systematic review and meta-analysed clinical trials examining the effects of rTMS to evaluate its clinical efficacy and safety.

Methods: Studies of rTMS for chronic tinnitus were retrieved from PubMed, Embase, and Cochrane Library through April 2020. Review Manager 5.3 software was employed for data synthesis, and Stata 13.0 software was used for analyses of publication bias and sensitivity.

Results: Twenty-nine randomized studies involving 1,228 chronic tinnitus patients were included. Compared with sham-rTMS, rTMS exhibited significant improvements in the tinnitus handicap inventory (THI) scores at 1 week (mean difference [MD]: -7.92, 95% confidence interval [CI]: -14.18, -1.66), 1 month (MD: -8.52, 95% CI: -12.49, -4.55), and 6 months (MD: -6.53, 95% CI: -11.40, -1.66) post intervention; there were significant mean changes in THI scores at 1 month (MD: -14.86, 95% CI: -21.42, -8.29) and 6 months (MD: -16.37, 95% CI: -20.64, -12.11) post intervention, and the tinnitus questionnaire (TQ) score at 1 week post intervention (MD: -8.54, 95% CI: -15.56, -1.52). Nonsignificant efficacy of rTMS was found regarding the THI score 2 weeks post intervention (MD: -1.51, 95% CI: -13.42, -10.40); the mean change in TQ scores 1 month post intervention (MD: -3.67, 95% CI: -8.56, 1.22); TQ scores 1 (MD: -8.97, 95% CI: -20.41, 2.48) and 6 months (MD: -7.02, 95% CI: -18.18, 4.13) post intervention; and adverse events (odds ratios [OR]: 1.11, 95% CI: 0.51, 2.42). Egger’s and Begg’s tests indicated no publication bias (P = 0.925).

Conclusion: This meta-analysis demonstrated that rTMS is effective for chronic tinnitus; however, its safety needs more validation. Restrained by the insufficient number of included studies and the small sample size, more large randomized double-blind multi-centre trials are needed for further verification.

Background

Tinnitus is a common auditory symptom that brings severe psychological stress to patients and is associated with co-existing symptoms, such as hearing loss, dizziness, and concentration problems. Studies have estimated that the incidence of tinnitus in adults ranges from 10% to 19%[1-3], and it is characterized by an experience of abnormal auditory perception in the head or ear in the absence of external acoustic or electrical stimulation. The 2019 European Multidisciplinary Tinnitus Guidelines defined it as chronic when patients have experienced related symptoms for more than 6 months[4]. Long-term tinnitus is not only annoying but often causes different degrees of mood disorders. Estimates have shown that in 1%-3% of these patients, their quality of life had seriously deteriorated[5]. A study examining a neurophysiological model of tinnitus revealed abnormal electrical activities of neurons in the peripheral and central auditory pathways (including the cerebral cortex), resulting in effective auditory detection and insights into the processing of sound perception in the cortex or subcortical centre in tinnitus[6].

In recent years, there has been a growing annual prevalence of tinnitus, which might be related to the lack of a cure for most patients and a lack of effective standardized treatments. Several studies have ascertained supportive evidence that rTMS is effective in the treatment of chronic tinnitus[5-8]. rTMS is a non-invasive technique that involves electromagnetic pulses passing through the skull into the brain that can reduce the excitability of relevant neurons and neurotransmitter systems in tinnitus[7].

Theoretically, hyperactive auditory neurons in the hearing centre can be adjusted through rTMS, thus reducing the occurrence of tinnitus and showing treatment efficacy. Although the clinical efficacy and safety of rTMS in chronic tinnitus have recently been reported, the results have been divergent and even contradictory. The efficacy of rTMS on chronic tinnitus was first systematically reviewed in 2011; the review included 5 randomized studies and concluded that rTMS was useful for tinnitus[8]. However, this review was limited due to the specificity of the population, a sample size (233 enrolled patients) that was quite small, and the inability to perform a quantitative analysis[8]. Several subsequent systematic reviews that evaluate rTMS have also reported similar problems[9-10]. The most recent systematic review, which incorporated 15 studies, showed that rTMS treatment had a significant effect on tinnitus. In this review, similar issues emerged as there were only a few studies included in the quantitative analysis, which was insufficient for assessment of publication bias and sensitivity analysis, so the reliability of the conclusion was uncertain[11]. Beyond the evaluation of efficacy, none of the previous systematic evaluations or meta-analysis studies have quantitatively analysed the safety of rTMS[8-11].

In this study, we retrieved the published literature on rTMS as a treatment for chronic tinnitus and extracted highly relevant data to meta-analyse its efficacy and safety. This study provides a reference and encourages more clinical studies for the treatment of chronic tinnitus.

Methods

Search strategies

This study was executed in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] and reported based on the guidelines developed by the Meta-Analysis of Observational Studies in Epidemiology group [13]. Because our analyses were performed based on previous studies, ethical approval and patient informed consent were not required. In the initial screening, two investigators (Z-RL and GC) independently conducted database searches in PubMed, Embase, and Cochrane Library to retrieve randomized controlled trials (RCTs) evaluating the efficacy and safety of rTMS for chronic tinnitus that were published from database inception to April 2020, without restrictions to languages or regions. Combined Medical Subject Headings (MeSH) and non-MeSH terms were searched as follows: transcranial magnetic stimulation, transcranial magnetic stimulations, magnetic stimulation AND transcranial, magnetic stimulations AND transcranial, stimulation AND transcranial magnetic, stimulations AND transcranial magnetic, transcranial magnetic stimulation AND single pulse, transcranial magnetic stimulation AND paired-pulse, transcranial magnetic stimulation AND repetitive,
tinnitus, ringing-buzzing-tinnitus, ringing buzzing tinnitus, tinnitus AND tensor palatini induced, tensor palatini induced tinnitus, tinnitus AND tensor tympani induced, tensor tympani induced tinnitus, pulsatile tinnitus, tinnitus AND pulsatile, tinnitus AND spontaneous otoacoustic emission, spontaneous otoacoustic emission tinnitus, spontaneous otoacoustic emission tinnitus, tinnitus AND clicking, clicking tinnitus, tinnitus AND Leudet, Leudet tinnitus, tinnitus AND Leudet’s, Leudet’s tinnitus, tinnitus AND Leudets, tinnitus AND noise-induced, induced tinnitus AND noise, noise-induced tinnitus, tinnitus AND objective, objective tinnitus, tinnitus AND subjective, subjective tinnitus, tinnitus of vascular origin, tinnitus of vascular origin, vascular origin tinnitus, tinnitus AND vascular origin. A third investigator not involved in the initial procedures was consulted in case of any discrepancies.

Eligibility criteria

Two independent investigators (Z-RL and GC) analysed the initially selected articles to verify their relevance to the topic of rTMS as the treatment for chronic tinnitus. Studies were included if they (i) reported the clinical efficacy and safety of rTMS in chronic tinnitus, (ii) were RCTs, and (iii) recruited participants without limitations to regions, ages, or social status. Studies were excluded if they fulfilled the following criteria: non-randomized controlled studies, duplicate trials or overlapping data, animal experiments, conference abstracts, letters, and review articles. In case of any disagreement, the results were discussed and a decision made by the senior authors.

Data extraction

Data were extracted from the eligible studies and independently categorized by two authors (Z-RL and GC) using a predefined data extraction form. All disagreements were resolved by discussion. The study design, baseline characteristics of the population (mean age, sample size, course of the disease, and country), interventions, scores for clinical efficacy, adverse events, and others were stratified into the rTMS and control groups using a standardized evidence table. All data were cross-checked to ensure accuracy. The procedures for study selection are shown in the PRISMA flow diagram.

Methodological quality assessment

The methodological quality of the included studies was evaluated by two independent reviewers (Z-RL and GC) using Cochrane Handbook Version 5.3 from six dimensions: random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data reporting; selective reporting of outcomes; and other sources of bias.

Statistical analysis

The meta-analysis and statistical analysis were performed using Cochrane Collaboration Review Manager software (RevMan version 5.3, Nordic Cochrane Center, Copenhagen, Denmark). We used the risk ratios (RRs) or odds ratios (ORs) for comparisons of dichotomous variables and the weighted mean difference (WMD) for comparisons of continuous variables. The I² statistic was performed to assess the influence of heterogeneity on the output of the meta-analysis. I² statistics of 0%, 25%, 50%, and 75% corresponded to no, low, medium, and high heterogeneity, respectively. According to the Cochrane review guidelines, a random effects model was used when I² ≥ 50% (high heterogeneity). Otherwise, a fixed effects model was used. A P-value of less than 0.05 was accepted as the threshold for statistical significance. The leave-one-out sensitivity analysis was conducted by removing one study at a time to evaluate the quality and consistency of the results. Publication bias was visually assessed by funnel plots and Egger's and Begg's linear regression tests using Stata 13.0 software.

Results

Study selection process

During our database search, 897 studies were initially retrieved, and 524 were selected after eliminating duplicates. Then, 477 studies without high relevance to our topic were discarded after reading titles and abstracts, and 47 studies were further evaluated by reading the full manuscripts. As a result, 18 full-text articles were abandoned for the following reasons: 4 described topics irrelevant to the efficacy and safety of rTMS on chronic tinnitus; 1 was a viewpoint; 2 were protocol designs; 8 were non-randomized controlled studies; and 3 did not provide free online full-text materials. Ultimately, 29 RCTs with 1,228 patients were included in this systematic review and meta-analysis. The flow chart depicting the study selection process is shown in Figure 1.

Study characteristics and methodological quality

The 29 eligible studies were randomized controlled studies published from 2004 to 2017. Six were conducted in the USA, 4 in Germany, 3 in China (including 1 in Taiwan), Turkey, and South Korea, 2 in the Czech Republic, and 1 in Italy, Egypt, Brazil, Australia, Netherlands, Finland, the UK, and Belgium. These clinical trials exhibited sample sizes that varied between 8 and 146 participants, a mean duration of tinnitus between 6 and 420 months, and a mean treatment course between 5 and 20 days. Of the 29 studies included (34 comparisons), 27 studies (32 comparisons) assessed the auditory cortex, 1 examined the motor cortex, and 1 did not target a specific cerebral area. Among the 32 comparisons in the 27 studies focusing on the auditory cortex, 19 comparison analyses showed the superiority of rTMS over sham-rTMS. Additionally, the 1 study focusing on the motor cortex confirmed the advantage of rTMS compared to sham-rTMS. In terms of the number of rTMS sessions, 11 studies (15 comparisons) reported a treatment time of 10 days, 12 (12 comparisons) of 5 days, 4 (4 comparisons) of 20 days, 1 (1 comparison) of 4 days, and 1 (2 comparisons) did not provide the stimulation duration. Regarding insights into different courses of rTMS treatment, 9 comparison analyses about a 5-day treatment showed that rTMS had better efficacy than sham-rTMS; however, the advantage of rTMS was nonsignificant after 20 days of treatment in all studies. Of the 29 studies (34 comparisons) included, 20 (23 comparisons) explored the left auditory cortex in patients with unilateral or bilateral tinnitus. In all eligible studies, 2 included only patients with bilateral tinnitus, 3 did not describe the tinnitus-affected side, and the remaining 24 included patients with either unilateral or bilateral tinnitus. Fifteen studies (18 comparisons) reported hearing loss in some or all of the
Evaluation of publication bias

Sensitivity analyses were performed for the selected studies to identify outliers that affected the overall results. There was a nonsignificant difference in the stability of the results (Fig. 8), which validated the rationality and reliability of our meta-analysis.

Evaluation of publication bias
Visual inspection of funnel plots was adopted in this evaluation (Fig. 9). Egger's and Begg's analyses showed no publication bias in our meta-analysis ($P = 0.925$).

**Discussion**

In this study, we reported the results of a systematic review and meta-analysis of 29 selected RCTs showing that rTMS can effectively ameliorate chronic tinnitus. To ensure reliable conclusions, we retrieved, reviewed, and summarized previously published studies on rTMS for the treatment of chronic tinnitus, which had high quality and showed good compliance in patients, to answer various clinical questions about the efficacy and safety of this treatment. Overall, our results suggested that rTMS is effective for the treatment of chronic tinnitus. Subgroup analyses showed that rTMS started to exert its efficacy at 1 week and continued to be effective 6 months after treatment. In addition, rTMS is a safe option, as serious adverse events were evenly distributed between participants randomly assigned to the rTMS and sham rTMS groups. Of all included studies, 93.10% stimulated the auditory cortex as a predominant stimulation site, wherein 77.78% stimulated the left auditory cortex, regardless of which ear was affected. There is strong evidence that the left primary auditory cortex is a potential target for the 1-Hz rTMS treatment of tinnitus in pilot studies. This explains why most studies have chosen the left auditory cortex as a stimulus target, although a few studies did stimulate the contralateral side for unilateral chronic tinnitus. More than half of the studies reported hearing loss in some or all of the included patients, but there was no further analysis of whether hearing loss was related to tinnitus. The duration of rTMS treatment varied among studies, and the 5- (41.38%) and 10-day (37.93%) periods were the more common options. The 1-Hz stimulation was most frequently used (93.10%).

There is a high level of heterogeneity in tinnitus in the population. Although many clinical studies involving various treatments for tinnitus have been conducted, there is a lack of widespread agreement on its efficacy in reducing tinnitus loudness and the impacts of tinnitus, which might be attributed to the low level of evidence that cannot be used to verify the effects. This poses a huge challenge to ear, nose, and throat (ENT) doctors. Landgrebe et al. found that daily low-frequency rTMS exhibited a cumulative effect on chronic tinnitus that not only caused synaptic inhibition and changes in synaptic plasticity in the auditory cortex but also improved haemodynamics in the auditory cortex. Our findings regarding the efficacy of rTMS in chronic tinnitus are consistent with previous systematic evaluations and meta-analyses. Moreover, our meta-analysis showed a nonsignificant difference in safety between rTMS and sham-rTMS.

Compared with previous meta-analyses associated with rTMS and tinnitus, our study has the following advantages. First, we performed a series of assessments for the included studies to ensure the high reliability of our conclusions, including publication of the protocol, detailed and predefined sensitivity, comprehensive assessments for risks of systematic and random errors, and assessments for the quality of evidence. Second, most of the studies were single- or double-blind studies with a relatively high level of evidence, which increased the reliability of the results. Third, the rationality and reliability of our meta-analysis have been prudently and significantly improved in that the overall comprehensive estimation has been performed based on a large sample size. Additionally, sufficient sensitivity analyses and the assessment of publication bias were carried out to ensure the stability of this meta-analysis. Fourth, we conducted a quantitative analysis of the safety of rTMS for the treatment of chronic tinnitus.

In addition, some limitations of our study must be acknowledged. First, despite the inclusion of recent large randomized trials, the limited number of enrolled subjects in our meta-analysis limits more accurate analyses, and some results were nonsignificant, which might be attributed to the nature of the population receiving rTMS. Second, this study only analysed English-language references, which leads to lost data from those in other languages. Third, although Egger's and Begg's analyses showed no publication bias in our meta-analysis, because of the limited number of studies included in this analysis, the possibility of false negatives cannot be excluded.

**Conclusion**

In summary, our systematic review and meta-analysis confirms the efficacy of rTMS and shows satisfactory safety in patients with chronic tinnitus. However, its safety needs to be verified in large-sample studies. Restrained by the insufficient number of eligible studies and the nature of the target population, more proposals to encourage large-sample, multi-centre, randomized double-blind trials are needed for further verification.

**Abbreviations**

rTMS = repeated transcranial magnetic stimulation, CI = confidence interval, THI = tinnitus handicap inventory, TQ = tinnitus questionnaire, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, MeSH = Medical Subject Headings, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex, VAS = visual analogue scale.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**
All data generated or analysed during this study are included in this published article and the original studies/publications.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

ZRL conceived the study idea. ZRL, GC and LFH retrieved and screened the literature. LFH and TZ conducted data extraction and evaluation of methodological quality. ZRL and GC performed statistical analyses and interpretation of corresponding results. ZRL drafted the initial manuscript. HYJ modified the initial manuscript. HYJ and HDY had primary responsibility for the final content. All authors made critical comments for the initial manuscript. All authors read and approved the final manuscript.

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Author details

1 Department of Otolaryngology, The First Affiliated Hospital of Jinan University, Guangzhou, China. 2 Department of Otolaryngology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China. 3 Hearing and Speech Department, Xinhua College of Sun Yat-sen University, Guangzhou, China. *Corresponding author: Haidi Yang, Department of Otolaryngology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University and Hearing and Speech Department, Xinhua College of Sun Yat-sen University, 107 West Yan Jiang Road, Guangzhou 510120, China (E-mail: yanghd@mail.sysu.edu.cn); Haiying Jia, Department of Otolaryngology, The First Affiliated Hospital of Jinan University, 601 Huangpu Avenue, Guangzhou 510632, China (E-mail: jiahaiying79@126.com).

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### Tables

**Table 1.** Characteristics of the included studies
| Included trials | Country | Interventions | Study design | Gender (male/female) | Age (years) | Duration of tinnitus (month) | Stimulation site |
|-----------------|---------|---------------|--------------|----------------------|-------------|-----------------------------|-----------------|
| Landgrebe M 2015[15] | Germany | 1-Hz rTMS (2000 stimuli, 110% motor threshold) | Sham-controlled, randomized multi-centre trial | 54/17 51/24 | 6.2±5.3 8.1±8.4 | Left temporal cortex |
| Formanek M 2018[15] | Czech Republic | 1-Hz rTMS (1000 stimuli, 110% motor threshold, the DLPFC on the left side and primary AC on both sides); 25-Hz rTMS (300 stimuli, 80% motor threshold, DLPFC) | Randomized double-blind controlled trial | 13/7 10/2 | 53.4±61.89 76.8±76.85 | DLPFC on the left side and primary AC on both sides |
| Chung HK 2012[16] | China | 5-Hz rTMS (900 stimuli, 80% motor threshold) | Parallel randomized control study | 11/1 11/1 | 53.8±18.4 51.90±15.5 | Left temporoparietal region |
| Yilmaz 2014[17] | Turkey | 1-Hz rTMS (1800 stimuli, motor threshold: unclear) | Randomized controlled trial | 27/33 27/33 | 49.8±8.03 (36-66) 49.9±8.03 (36-66) >6 >6 | Unclear |
| Rossi S 2009[18] | Italy | 1-Hz rTMS (1200 stimuli, 120% motor threshold) | Randomized, double-blind, crossover, placebo-controlled trial | 7/1 4/2 | 52.63 (35-72) 52.33 (37-62) | Left temporoparietal region |
| langguth B 2014[19] | Germany | 1-Hz rTMS (2000 stimuli, 110% motor threshold) | Randomized, double-blind, parallel-group, controlled clinical trial | 35/13 31/14 | 49.8±11.5 50.3±12.9 68.0±9.70 74.4±74.2 | PET-based neuronavigation |
| langguth B 2014[19] | Germany | 1-Hz rTMS (2000 stimuli, 110% motor threshold) | Randomized, double-blind, parallel-group, controlled clinical trial | 32/16 31/14 | 50.4±12.5 50.3±12.9 78.3±64.9 78.3±64.9 | Left AC |
| Biliçi S 2015[20] | Turkey | 1-Hz rTMS (900 stimuli, 110% motor threshold) | Randomized, double-blind, placebo-controlled study | 33/42 33/42 | 40±13.2 (20-62) 40±13.2 (20-62) >12 >12 | Left temporoparietal region |
| Biliçi S 2015[20] | Turkey | 10-Hz rTMS (600 stimuli, 110% motor threshold) | Randomized, double-blind, placebo-controlled study | 33/42 33/42 | 40±13.2 (20-62) 40±13.2 (20-62) >12 >12 | Left temporoparietal region |
| Khedr EM 2009[21] | Egypt | 1-Hz rTMS (1500 stimuli, 100% motor threshold) | Randomized controlled trial | Unclear Unclear Unclear Unclear | Left temporoparietal region |
| Khedr EM 2009[21] | Egypt | 10-Hz rTMS (1500 stimuli, 100% motor threshold) | Randomized controlled trial | Unclear Unclear Unclear Unclear | Left temporoparietal region |
| Khedr EM 2009[21] | Egypt | 25-Hz rTMS (1500 stimuli, 100% motor threshold) | Randomized controlled trial | Unclear Unclear Unclear Unclear | Left temporoparietal region |
| Marcondes RA 2010[22] | Brazil | 1-Hz rTMS (1020 stimuli, 110% motor threshold) | Randomized, double-blind, parallel design, study | >18 >18 | Left temporoparietal region |
| Folmer RL 2015[23] | The USA | 1-Hz rTMS (2000 stimuli, 110% or lower motor threshold) | Randomized, participant and clinician or observer-blinded | 25/7 26/6 | 58.3±9.5 62.8±8.3 >12 >12 | Left or right AC |
| Authors | Country | Region | Stimulation Details | sham Details | Trial Type | Sample Size | Motor Threshold | Outcome | Comments |
|---------|---------|--------|---------------------|-------------|------------|-------------|----------------|--------|----------|
| Li LPH 2019(34) | Taiwan, China | 1-Hz rTMS (1800 stimuli, 110% or lower motor threshold) | sham rTMS | Randomized controlled trial | 7/5 | 7/5 | Median 42 (22-59) | 57±10.1 | 54±7.5 | Left primary AC |
| Noh TS 2019(35) | South Korea | 1-Hz rTMS (2000 pulses over the AC and 1000 pulses over the DLPFC, 110% or lower motor threshold) | sham rTMS | Double-blind, randomized controlled trial | 14/3 | 7/6 | Median 42 (22-59) | 51.9±12.4 | 55.8±6.9 | Left primary AC and left DLPFC |
| Anders M 2019(36) | Czech Republic | 1-Hz rTMS (1500 stimuli, 110% or lower motor threshold) | sham rTMS | Randomized, placebo controlled trial | 12/10 | 17/3 | Median 42 (22-59) | 50±12 | 50±12 | Left primary AC |
| Hoekstra CEL 2019(37) | The Netherlands | 1-Hz rTMS (2000 stimuli, 110% motor threshold) | sham rTMS | Randomized, double-blind placebo-controlled clinical trial | 26/0 | 15/9 | Median 42 (22-59) | 54±4±14.2 | 54.2±14.2 | Unclear | Unclear | Left temporal cortex |
| Sahlinen H 2019(38) | Finland | 1-Hz rTMS (4000 stimuli, 110% motor threshold) | sham rTMS | Randomized, placebo controlled trial | 13/6 | 14/6 | Median 42 (22-59) | 48.9±13.1 | 51.5±10.7 | >6 | >6 | Left superior temporal gyrus |
| Wang H 2019(39) | China | 1-Hz rTMS (1000 stimuli, 110% motor threshold) | sham rTMS | Randomized controlled trial | 6/8 | 3/7 | Median 42 (22-59) | 62.1±9.81 | 56.4±11.8 | 6-72 | 6-72 | Left temporoparietal region |
| Cacace AT 2019(40) | USA | 1-Hz rTMS (1200 stimuli, 110% motor threshold) | sham rTMS | Randomized single-blinded sham-controlled crossover study trial | 30/0 | 30/0 | Median 42 (22-59) | 54.2±14.2 | 54.2±14.2 | Unclear | Unclear | Left temporal cortex |
| Piccirillo JF 2013(41) | USA | 1-Hz rTMS (1650 stimuli, 110% motor threshold) | sham rTMS | Crossover, double-blind, randomized controlled trial | 9/5 | 9/5 | Median 42 (22-59) | 56±4.9 | 50.9±7.1 | >6 | >6 | Left temporoparietal area |
| James G 2013(42) | USA | 1-Hz or 10-Hz rTMS (1800 stimuli, 110% motor threshold) | sham rTMS | Double-blind, randomized controlled clinical trial with participant crossover | 9/3 | 9/3 | Median 42 (22-59) | 49.2±15.3 | 49.2±15.3 | >6 | >6 | Posterior superior temporal gyrus |
| Kyong JS 2019(30) | South Korea | 1-Hz rTMS (stimuli: unclear, motor threshold: unclear) | sham rTMS | Randomized controlled trial | 4/4 | 6/2 | Median 50 | 56±4.9 | 50.9±7.1 | >6 | >6 | Auditory temporal cortex |
| Kyong JS 2019(31) | South Korea | 1-Hz rTMS (stimuli: unclear, motor threshold: unclear) | sham rTMS | Randomized controlled trial | 6/2 | 6/2 | Median 50 | 50.9±7.1 | 50.9±7.1 | >6 | >6 | Auditory temporal and the frontal regions |
| Roland LT 2016(43) | USA | 1-Hz rTMS (stimuli: unclear, motor threshold: unclear) | sham rTMS | Randomized, double-blind, sham-controlled clinical trial | 11/5 | 10/4 | Median: 50 | 29-58 | >12 | >12 | Left primary AC |
| Barwood CHS 2013(44) | Australia | 1-Hz rTMS (2000 stimuli, 110% motor threshold) | sham rTMS | Single-blind, randomized controlled trial | 2/2 | 2/2 | Median: 50 | 29-58 | >12 | >12 | Temporal-parietal region of the scalp, overlying the AC |
| Godhebere J 2013(45) | UK | 5-Hz rTMS (1200 stimuli, 80% motor threshold) | sham rTMS | Two-arm, single-blind, randomized controlled trial | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Temporal-parietal region of the scalp, overlying the AC |
| Menneemeyer M 2011(46) | USA | 1-Hz rTMS (1800 stimuli, 110% motor threshold) | sham rTMS | Randomized, sham-controlled trial | 28-75 | 28-75 | Mean: 48 | Mean: 48 | Mean: 48 | The motor cortex |
| Lee HY 2013(47) | South Korea | 1-Hz rTMS (1200 stimuli, 100% motor threshold) | sham rTMS | Randomized controlled trial | 8/7 | 8/7 | Mean: 16.2 | Mean: 16.2 | Mean: 16.2 | Left AC |
| Lorenz I 2013(48) | Germany | 1-Hz rTMS (1000 stimuli, 110% motor threshold) | sham rTMS | Randomized, single-blind, sham-controlled trial | 7/3 | 7/3 | Mean: 26.1 | Mean: 26.1 | Mean: 26.1 | Left AC |
| Vanneste S 2012(49) | Belgium | 1-Hz or 10-Hz rTMS (900 stimuli, 110% or lower motor threshold) | sham rTMS | Randomized controlled trial | Unclear | Unclear | Median: 50 | 50.0±11.77 | 50.0±11.77 | >12 | >12 | Left ventrolateral prefrontal cortex |
| Outcomes                                     | Included studies (n) | Enrolled patients (T/C, n) | Heterogeneity | MD (95% CI)       | P    |
|----------------------------------------------|----------------------|---------------------------|---------------|------------------|------|
| TQ score 1 week post intervention           | 2                    | 38/34                     | P=0.55, I²=0% | -8.54 (-15.56, -1.52) | 0.02 |
| TQ score 1 month post intervention          | 2                    | 38/34                     | P=0.15, I²=53% | -8.97 (-20.41, 2.48)  | 0.12 |
| TQ score 6 months post intervention         | 2                    | 97/99                     | P=0.03, I²=79% | -7.02 (-18.18, 4.13)  | 0.22 |
| Mean change in TQ scores 1 week post intervention | 3                | 108/100                   | P=0.04, I²=69% | -3.67 (-8.56, 1.22)   | 0.14 |
| VAS score 1 month post intervention         | 2                    | 56/54                     | P=0.07, I²=69% | -0.64 (-1.77, 0.48)   | 0.26 |
| Tinnitus loudness 1 month post intervention | 2                    | 42/40                     | P=0.71, I²=0%  | -1.13 (-7.13, 4.87)   | 0.71 |

TQ=tinnitus questionnaire, VAS=visual analogue scale, CI=confidence interval.