Effectiveness of Repetitive Transcranial Magnetic Stimulation for Chronic Tinnitus: A Systematic Review

Zhe Peng, Xiu-Qi Chen and Shu-Sheng Gong

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What is This?
Effectiveness of Repetitive Transcranial Magnetic Stimulation for Chronic Tinnitus: A Systematic Review

Zhe Peng, MMed¹, Xiu-Qi Chen, MMed², and Shu-Sheng Gong, MD, PhD¹

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. This systematic review aimed to assess the effectiveness of repetitive transcranial magnetic stimulation (rTMS) treatment for chronic tinnitus.

Data Sources. Relevant electronic databases and a reference list of articles published up to January 2012 were searched. Randomized controlled clinical trials of all types of rTMS treatment for patients with chronic tinnitus were included.

Review Methods. A literature search was conducted with structured criteria to select studies evaluated for systematic review.

Results. Five trials (160 participants) were included in this review. Repetitive transcranial magnetic stimulation treatment showed benefits in the short term, but the long-term effects are questionable. The Tinnitus Handicap Inventory (THI) and the visual analog scale (VAS) were the major assessment methods used. After active TMS stimulation, the reduction in the THI total score and VAS was significant compared with baseline at the first time point assessed and in the short term (2 weeks and 4 weeks). The longest follow-up time was 26 weeks after treatment, and the shortest follow-up time was 2 weeks. No severe side effects were reported from the use of rTMS. Differences in age, hearing level, duration of tinnitus of the included patients, and the condition of sham treatment may influence the effect.

Conclusion. Repetitive transcranial magnetic stimulation could be a new therapeutic tool for the treatment of chronic tinnitus, and thus far we have not been able to demonstrate any substantial risk from rTMS treatment. However, the long-term effects of rTMS treatment for tinnitus are not clear and will require further study.

Keywords

tinnitus, transcranial magnetic stimulation (TMS), therapy, systematic review

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psychological state of the patient, a complete head and neck examination, and specialized testing.4,8

No single intervention has been identified that can consistently eliminate the symptoms of tinnitus. However, despite our inability to “cure” tinnitus, many medical and behavioral strategies may result in symptomatic relief. These management strategies include diet and lifestyle modification, medication and supplements, retraining and masking therapies, and repetitive transcranial magnetic stimulation.7

Transcranial magnetic stimulation (TMS) is a method of stimulating the brain through the intact scalp without causing pain at the surface.9 It is a minimally invasive method for depolarizing cortical neurons based on the principle of electromagnetic induction.10 The rhythmic application of a series of single stimuli is referred to as repetitive TMS (rTMS), a method that has been demonstrated to induce long-term potentiation (LTP) or long-term depression (LTD)–like changes of cortical excitability, which outlast the stimulation period.11 Repetitive TMS has been investigated as a therapeutic tool for depression, schizophrenia, and stroke.12 Recently, multiple studies13–16 have shown that the technique can alleviate tinnitus by modulating the excitability of neurons in the auditory cortex.

In this study, we aimed to assess whether TMS was effective in the management of tinnitus. Since the symptoms of tinnitus are subjective for a great majority of patients, we aimed to evaluate subjective improvement in the perception of these symptoms.

Methods

Study design: Criteria for considering studies for this review

Types of studies: Randomized controlled trials

Types of participants: Adults with a complaint of persistent, distressing, subjective tinnitus of any etiology. We excluded patients with pulsatile tinnitus and other somatic sounds, those with delusional auditory hallucinations, and patients who were undergoing concurrent psychotherapeutic interventions.

Types of interventions: Studies in which patients received rTMS were included. Comparisons performed included the following:

1. Repetitive TMS vs placebo
2. Repetitive TMS vs drug/other therapy

Search Methods for Identification of Studies

We conducted systematic searches for randomized controlled trials. There were no restrictions on language, publication year, or publication status. The date of the last search was January 2012. We also performed thorough examinations of international reference lists and manually searched the Index Medicus and specialty journals. Certain publication types (ie, letters to the editor, abstracts, proceedings from scientific meetings) were excluded because of a lack of data.

We searched the following electronic databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, Issue 3); PubMed; EMBASE; Ovid; CINAHL (Cumulative Index to Nursing and Allied Health Literature); IndMed; PakMediNet; CAB Abstracts; Web of Science; CNKI (China National Knowledge Infrastructure); nRCT (Current Controlled Trials); ClinicalTrials.gov; and ICTRP (International Clinical Trials Registry Platform). The search combined terms related to transcranial magnetic stimulation (magnetic stimulation, transcranial; magnetic stimulations, transcranial; stimulation, transcranial magnetic; stimulations, transcranial magnetic; transcranial magnetic stimulations; transcranial magnetic stimulation, paired pulse; transcranial magnetic stimulation, repetitive; transcranial magnetic stimulation, single pulse) with terms related to tinnitus (tinnitus ear, buzz, ring, roar, click, pulse) and therapy (magnetic field therapy, therapies, magnetic stimulation therapy, treatment). We contacted experts in the specialty and searched the reference lists from primary and review articles.

Types of Outcome Measures

Primary Outcomes. Patients’ subjective assessment of tinnitus before, during, and after treatment:

1. Changes in overall severity of tinnitus and/or impact on quality of life. The questionnaires included the Tinnitus Handicap Inventory (THI),17 the Tinnitus Questionnaire (TQ),18 and the visual analog scale (VAS).
2. Change in loudness of tinnitus.

Secondary Outcomes

1. Adverse effects (ie, worsening of symptoms, suicidal tendencies, negative thoughts)

Data Collection and Analysis

Two review authors (ZP and X-QC) independently selected relevant articles and assessed their eligibility according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion. We checked titles and abstracts and obtained the full text for those articles identified as either relevant or possibly relevant. Only those studies that met the predetermined inclusion criteria were included, and the authors independently extracted data concerning details of patients’ characteristics, study methods, interventions, and outcomes.

Quality Assessment

Two authors (ZP and X-QC) independently assessed methodological quality using the criteria that are described in the Cochrane Handbook for Systematic Review of Interventions,
including adequate sequence generation, allocation concealment, blinding, whether incomplete outcome data were addressed, and whether the data were free of selective reporting and bias.

**Data Extraction and Management**

The authors extracted data independently onto standardized data forms. Studies that had incomplete or ambiguous reporting of data were clarified by discussion between the authors.

**Assessment of Risk of Bias in Included Studies**

The criteria for quality assessment were based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*, version 4.2.1, Section 6 (updated December 2003).

### Table 1. Inclusion and Exclusion Criteria of Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anders et al, 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Unilateral or bilateral tinnitus of at least 6 months' duration, pharmacological treatment for at least 3 months without significant clinical response, identical doses of current pharmacological treatment for at least 6 weeks, age-adjusted normal sensorineural hearing determined by audiogram within the last 6 weeks prior to study.</td>
<td>Concurrent other forms of tinnitus treatments, a history of neuropsychiatric disorder, abnormal electroencephalogram (EEG), intracranial hypertension, history of dizziness, significant head injury, stroke, aneurysm, brain malformation, neurodegenerative disorder affecting the brain, previous cranial neurosurgery, presence of acoustic neuroma, glomus tumor, brain tumor, profound hearing loss &gt;90-dB threshold at 4000 Hz or active Ménière’s disease, pacemaker and other metal implants, implanted medication pump, pregnancy, lactation, presence of other significant medical condition, concomitant psychotropist medication or medication that lowers seizure threshold or reduces cortical excitation. Excluded patients with clinically relevant concomitant axis I psychiatric disorders.</td>
</tr>
<tr>
<td>2. Khedr et al, 2008&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Chronic tinnitus (6 months to 25 years).</td>
<td>Patients taking anticonvulsant or tranquilizer medication and patients with neurological, psychiatric, or severe systemic disease or with a history of ototoxic drug intake, as well as patients with contraindication for magnetic stimulation.</td>
</tr>
<tr>
<td>3. Marcondes et al, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Uni- or bilateral tinnitus of at least 3 months’ duration, age older than 18 years and normal pure-tone audiometry (thresholds ≤25 dB hearing level in all frequencies from 250-8000 Hz).</td>
<td>Neurologic or psychiatric disorders, especially epilepsy, migraine, depression, or anxiety; the intake of antidepressant, neuroleptic, or anticonvulsant drugs; cardiac pacemaker or other implanted devices; intracranial metallic objects; pregnancy, and inability to fulfill the study requirements. Comorbid psychiatric diseases. None of the controls fulfilled the criteria of major depression or an anxiety disorder according to the fourth edition of the <em>Diagnostic and Statistical Manual of Mental Disorders</em>.</td>
</tr>
<tr>
<td>4. Plewnia et al, 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>One woman and 5 men, 49 to 68 years old, with chronic (&gt;1 year) bilateral tinnitus.</td>
<td>Patients with heart disease, history of seizures or brain lesions, metal implants, cardiac pacemaker, and current use of psychotherapeutic drugs were excluded.</td>
</tr>
<tr>
<td>5. Rossi et al, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Presence of mono- or bilateral tinnitus for more than 1 year, normal neurological examination, and normal cranial magnetic resonance.</td>
<td>History of neuropsychiatric disorders or neuroactive treatments (with the exception of antidepressant therapy previously taken for tinnitus therapy, withdrawn for at least 1 month) and presence of other significant medical illness.</td>
</tr>
</tbody>
</table>

**Data Synthesis**

For dichotomous data, we calculated the odds ratio and number needed to treat. For continuous data, we calculated the standardized mean difference. The main analysis was an examination of severity (subjective loudness) of tinnitus and its effect on depression and quality of life, during and after the period of treatment. We also planned to collect and analyze data on any adverse reactions due to treatment.

**Results**

**Description of Studies**

A total of 5 randomized clinical trials were included in the review (Table 1 and Figure 1). Two trials were excluded because the control designs were not randomized, and the Smith et al<sup>19</sup> study was excluded because it was a pilot study that was not randomized. The Khedr et al<sup>20</sup> study was a...
comparative study and focused on contralateral vs ipsilateral rTMS for the treatment of tinnitus without a sham group.

Trial Quality
The quality of allocation concealment was considered adequate in 2 trials and unclear in 3 trials. There were 4 trials mentioned in which blinding was used, and there was no mention in 1 trial. Incomplete outcome data were addressed in all 5 trials, and all trials were free of selective reporting and other bias (Figure 2).

Effects of Interventions
Repetitive TMS showed a benefit in the short term, but the long-term effects are questionable. The THI and the VAS were the major assessment methods (Table 2). After active TMS stimulation, reductions in the THI and VAS scores were significant compared with baseline at the first assessment time point and in the short term (2 weeks and 4 weeks) (Table 3). The longest follow-up time was 26 weeks after treatment, and the shortest follow-up time was 2 weeks (Table 4). No severe side effects were reported from the use of rTMS. The left temporoparietal cortex was used as the stimulation position in 4 studies, and the stimulation parameters were 1 Hz, 5 daily sessions for 1 or 2 weeks (Table 5). Differences in age, hearing level, duration of tinnitus of the included patients, and the condition of sham treatment may influence the effect (Tables 5 and 6).

The 5 included studies were varied in design, with significant evaluation of subjective tinnitus perception with different scores, scales, tests, and questionnaires. Therefore, meta-analysis was not performed in this study.

Discussion
Summary of the Main Results
Three included studies used the THI as the primary outcome to assess the treatment effect of tinnitus (Table 2). After active TMS stimulation, the reduction of the THI total score was significant compared with baseline at the first assessed time point. In the Anders et al study, the reduction of the total THI score only persisted to week 26 (P = .058) after TMS stimulation and to month 6 (P = 0.496) after TMS stimulation in the Marcondes et al study. The VAS score in the Rossi et al study also suggested only a transient improvement in perception of tinnitus after TMS. Therefore, the short-term effect of TMS for tinnitus is more obvious than the long-term effects, and further studies will be needed to determine the long-term effects.

Repetitive TMS is a safe treatment for chronic tinnitus, and the side effects observed were mild and tolerable. Studies regarding the use of rTMS for chronic tinnitus showed that the severity of tinnitus could be reduced by rTMS. Because tinnitus is a subjective symptom, it is hard to evaluate via objective criteria, and the trials included were highly heterogeneous. The heterogeneity that we considered included inclusion and exclusion criteria (these include the duration of tinnitus, as well as the age and hearing level of the included patients), stimulation parameters, follow-up period, and assessment methods.

Duration of Tinnitus
Auditory system plasticity has been recognized as an important change resulting from tinnitus. The degree of maladaptive neuroplastic changes in auditory and non-auditory brain structures may depend on tinnitus duration. The effects of rTMS also depend on the history of synaptic activity of the stimulated brain region. Although this study included patients with chronic tinnitus, the duration...
of tinnitus was varied. Khedr et al\textsuperscript{23} showed that the response to rTMS depended on the duration of tinnitus. This is likely because the central network became less plastic if the duration of tinnitus was too long, rendering it less responsive to rTMS interference. The duration of tinnitus of the included patients ranged from 3 months to 25 years\textsuperscript{21-25} making it difficult to merge the outcomes in a simple way. A more exact inclusion criterion would be more conducive to assessing the efficacy of intervention. Also, if the most appropriate patients could be selected to receive the intervention, more patients would benefit, reducing unnecessary treatment.

### Hearing Level

Hearing loss in addition to tinnitus largely increases the related distress. It is widely assumed that deprivation of afferent input caused by hearing damage leads to a reduction of inhibition in central auditory structures, which results in hyperexcitability of circumscribed regions of the central auditory system\textsuperscript{28,29}. This may be a crucial step in the development of subjective tinnitus. For that reason, chronic hearing impairment might attenuate the effects of rTMS by continuously triggering neuroplastic changes in central auditory structures. Two studies\textsuperscript{23,25} included patients in whom hearing levels were unequal. Nineteen patients suffered mild to severe hearing loss.

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**Table 2. Assessment Methods of Included Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>THI</th>
<th>TQ</th>
<th>VAS</th>
<th>HAM-A</th>
<th>HAM-D</th>
<th>TCS</th>
<th>Self-rating of Tinnitus Annoyance</th>
<th>Residual Inhibition</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anders et al, 2010\textsuperscript{24}</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khedr et al, 2008\textsuperscript{23}</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcondes et al, 2010\textsuperscript{22}</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plewnia et al, 2007\textsuperscript{25}</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rossi et al, 2007\textsuperscript{21}</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Rating Scale; TCS, tinnitus-change score; THI, Tinnitus Handicap Inventory; TQ, Tinnitus Questionnaire; VAS, visual analog scale.

**Table 3. Results/Findings of Included Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. Participants</th>
<th>Results/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anders et al, 2010\textsuperscript{24}</td>
<td>Randomized, placebo controlled</td>
<td>52</td>
<td>1. There was a significant reduction between real and sham TMS groups in THI and TQ total score in the short term (week 2). 2. The reduction of TQ in the TMS group persisted to week 14 but only to week 2 in the sham group.</td>
</tr>
<tr>
<td>Khedr et al, 2008\textsuperscript{23}</td>
<td>Randomized, computer generated</td>
<td>66</td>
<td>1. THI scores decreased significantly in TMS groups (temporoparietal) but were unchanged in the sham group (occipital). 2. Decreased annoyance ratings were greater with rTMS (temporoparietal) than with sham (occipital) stimulation. 3. Duration of residual inhibition increased significantly more after rTMS (temporoparietal) than sham (occipital).</td>
</tr>
<tr>
<td>Marcondes et al, 2010\textsuperscript{22}</td>
<td>Randomized, double-blind controlled</td>
<td>20</td>
<td>1. There was a significant reduction in the total THI score at 1 and 6 months after rTMS. 2. There were no significant changes in the sham group at any time point.</td>
</tr>
<tr>
<td>Plewnia et al, 2007\textsuperscript{25}</td>
<td>Randomized, controlled</td>
<td>6</td>
<td>1. The TQ score was reduced after rTMS compared with baseline and sham stimulation. 2. Tinnitus distress returned to baseline in 5 patients 2 weeks after treatment. 3. All 6 patients showed a benefit from rTMS in terms of tinnitus loudness and annoyance vs sham stimulation.</td>
</tr>
<tr>
<td>Rossi et al, 2007\textsuperscript{21}</td>
<td>Randomized, crossover; double-blind, placebo controlled</td>
<td>16</td>
<td>1. The mean VAS score was significantly reduced at the end of active treatment and after 1 week of the true rTMS, whereas the difference was not significant after 2 weeks; however, the mean VAS score was not significantly changed by the sham. 2. HAM-A and HAM-D scores were not influenced by true or sham rTMS.</td>
</tr>
</tbody>
</table>

Abbreviations: HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; THI, Tinnitus Handicap Inventory; TMS, transcranial magnetic stimulation; TQ, Tinnitus Questionnaire; VAS, visual analog scale.
Table 4. Assessment Time of Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anders et al, 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Khedr et al, 2008&lt;sup&gt;23&lt;/sup&gt;</td>
<td>✓ ✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Marcondes et al, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>✓ ✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Plewnia et al, 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>✓ ✓ ✓ ✓ ✓ ✓</td>
</tr>
<tr>
<td>Rossi et al, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>✓ ✓ ✓ ✓ ✓</td>
</tr>
</tbody>
</table>

Abbreviations: Pre, time before the treatment; End: time at the end of treatment; P1, 1 week after treatment . . . P24-26, 24-26 weeks after treatment.

Table 5. Characteristics of Interventions of Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Position</th>
<th>Frequency</th>
<th>Timing of Treatment</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anders et al, 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Left temporoparietal cortex</td>
<td>1 Hz</td>
<td>5 daily sessions for 2 weeks</td>
<td>Given by tilting the coil 45° away from the skull</td>
</tr>
<tr>
<td>Khedr et al, 2008&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Left temporoparietal cortex</td>
<td>1 Hz; 10 Hz; 25 Hz</td>
<td>5 daily sessions for 2 weeks</td>
<td>Given over the Oz EEG site</td>
</tr>
<tr>
<td>Marcondes et al, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Left temporoparietal cortex</td>
<td>1 Hz</td>
<td>5 daily sessions for 1 week</td>
<td>Given with a sham coil system, which mimics the sound of active stimulation, without producing a magnetic field</td>
</tr>
<tr>
<td>Plewnia et al, 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>The region with maximal tinnitus-related increase by functional imaging with [15O]H₂O</td>
<td>1 Hz</td>
<td>Crossover design; 5 daily sessions for 2 weeks (TMS), then 5 daily sessions for 2 weeks (sham)</td>
<td>The coil was placed at the lower occiput at the same distance to the ear; the control stimulation was accompanied by a similar noise</td>
</tr>
<tr>
<td>Rossi et al, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Left temporoparietal region</td>
<td>1 Hz</td>
<td>Crossover design; 5 daily sessions for 2 weeks (TMS), then 5 daily sessions for 2 weeks (sham)</td>
<td>The coil was angled backward by about 45° away from the midline</td>
</tr>
</tbody>
</table>

Abbreviations: EEG, electroencephalogram; TMS, transcranial magnetic stimulation.

Table 6. Characteristics of Participants in Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Tinnitus Characteristic</th>
<th>Hearing Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anders et al, 2010&lt;sup&gt;24&lt;/sup&gt;</td>
<td>rTMS group: mean, 48.09 y; min, 20 y; max, 69 y</td>
<td>No description</td>
<td>All normal</td>
</tr>
<tr>
<td></td>
<td>Sham group: mean, 50.05 y; min, 27 y; max, 66 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khedr et al, 2008&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Mean, 41 ± 15 y</td>
<td>Bilateral, n = 12; left side, n = 32; right side, n = 22</td>
<td>Normal, n = 53; 40 dB, n = 5; 40-55 dB, n = 5; 70 dB, n = 5</td>
</tr>
<tr>
<td>Marcondes et al, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Older than 18 years; no details</td>
<td>No description</td>
<td>All normal</td>
</tr>
<tr>
<td>Plewnia et al, 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Range, 49 to 68 y</td>
<td>Bilateral</td>
<td>4 patients had high-frequency hearing loss; 2 patients had pancochlear hearing loss</td>
</tr>
<tr>
<td>Rossi et al, 2007&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Range, 35 to 72 y</td>
<td>Bilateral, n = 7; left side, n = 4; right side, n = 3</td>
<td>No description</td>
</tr>
</tbody>
</table>

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.
However, 2 separate studies\textsuperscript{21,22} recruited patients with normal hearing. Yet another study did not describe hearing levels.\textsuperscript{21} Marcondes et al\textsuperscript{22} showed that baseline scores of the THI were relatively low because they only included patients with a normal audiogram. This suggests that hearing loss may be a negative predictor for the effects of rTMS treatment outcome. The relationship between hearing loss and tinnitus is still unknown, but the mechanisms involved in simple tinnitus and those involved in hearing loss in addition to tinnitus may be different. As a result, we feel it will be necessary to perform a subgroup analysis to make the results more reliable.

**Age**

Neuroplastic processes play a crucial role in both the generation of tinnitus and the degree of suffering.\textsuperscript{30} Many aspects of brain structure, function, and plasticity change with age in a complex way.\textsuperscript{31} Both the generation of tinnitus and the amount of tinnitus distress are thought to depend on adaptive and compensatory brain mechanisms.\textsuperscript{32} Age strongly influences tinnitus prevalence,\textsuperscript{33} and “age of onset” has been added as an additional factor underscoring the relevance of time-related aspects in the pathophysiology of tinnitus.\textsuperscript{34} Information regarding age in 5 of the included trials is shown in Table 6. All the participants were older than 18 years, but none of the trials divided the patients by age. One study acknowledged that patients’ age played a role and that it would be appropriate to divide the sample into age clusters.\textsuperscript{24} However, it was impossible for us to divide the patients into subgroups by age because the included studies did not provide details regarding the ages of patients. In fact, 1 study determined that age did not influence tinnitus annoyance as assessed by the THI.\textsuperscript{35} Therefore, more work must be done to determine the role of age in this process.

**Stimulation Parameters**

The stimulation parameters included control conditions, frequency, intensity, and coil localization. Finding an optimal control condition for treatment studies is also difficult, owing to limitations in the ability to blind the patient and operator to different stimulus conditions and because TMS itself results in auditory and somatosensory stimulation in addition to actual brain site–specific effects.

The design of the sham group was also a source of heterogeneity. Sham was performed over the Oz electroencephalogram (EEG) site in the Khedr et al\textsuperscript{23} study and given with a sham coil system that mimics the sound of active stimulation, without producing a magnetic field, in the Marcondes et al\textsuperscript{22} study. This was carried out by tilting the coil 45° away from the skull with 1 wing touching the skull in the Anders et al\textsuperscript{24} study. Control conditions were a limitation of these studies, as the sham coil can mimic the sound of active rTMS but lacks somatosensory sensation. Controlling for somatosensory stimulation seemed to be critical since somatosensory input was able to modulate tinnitus sensation.\textsuperscript{36} Also, Anders et al\textsuperscript{24} speculated that subjects can easily distinguish the difference between real and sham stimulation. However, patients were not able to identify whether they were stimulated with active or sham rTMS. Therefore, the crossover design studies may have an advantage, as they contained a self-controlling group as a sham group, as opposed to other studies.\textsuperscript{21,25}

The amount of tinnitus suppression was correlated positively with stimulation frequency.\textsuperscript{37} Most rTMS is performed in long trains of 1200 to 2000 pulses repeatedly over 5 to 10 days.

Both animal models and functional imaging data in tinnitus patients suggest that tinnitus is associated with increased neuronal activity, increased synchronicity, and functional reorganization in the auditory cortex.\textsuperscript{38,39} As a result, different functional neuroimaging techniques are used to detect tinnitus-related changes in the brain. These converge in the finding of increased neuronal activity in the central auditory system but differ in the exact localization of these changes, which in turn results in uncertainty regarding the optimal target for rTMS treatment. Currently available studies do not demonstrate clear evidence for the superiority of neuro-navigational coil positioning.\textsuperscript{50}

Further development of rTMS as a treatment for tinnitus will depend on a more detailed understanding of both the neuronal correlates of the different forms of tinnitus and of the neurobiological effects mediating the benefit of TMS on tinnitus perception.

**Follow-up Period**

The follow-up periods were different in the included studies. There was not enough evidence from the available literature to determine whether the follow-up period was suitable to assess the treatment effect of rTMS for tinnitus. Through the included studies, we concluded that pretreatment and end-of-treatment time points were necessary but that the follow-up period must be determined through further study.

**Assessment Methods**

Tinnitus is a purely subjective phenomenon that is difficult to measure. An expert consensus for treatment outcome measurements in tinnitus patients has been published only recently.\textsuperscript{41}

However, the intensity of tinnitus, as well as the amount of distress, annoyance, and impact on daily living, is important to determine. The methods for assessing tinnitus in the included studies mainly included the THI, VAS, tinnitus-change score (TCS), and self-rating of tinnitus annoyance and residual inhibition. The THI was used in 3 studies.\textsuperscript{22-24} The THI score included total score and several domains (physical, emotional, and catastrophic). The VAS was used in the Rossi et al\textsuperscript{21} study, and TCS was used in the Plewnia et al\textsuperscript{25} study. Because of the subjective nature of tinnitus, standards are required to evaluate the effects of rTMS.

The evidence to support (or refute) the use of rTMS in the management of tinnitus was not definite. We encountered difficulties in extracting the benefit from rTMS therapy from scales with different standards. Some studies used dichotomous data to express outcome, such as the Khedr et al\textsuperscript{23} study. We contacted the author for raw data, but no further information was available at the time of manuscript.
preparation. We found a study protocol describing the design of a placebo-controlled, randomized study of the use of rTMS for chronic tinnitus by Landgrebe et al., published in 2008. The duration of this study is estimated to be about 3 years, and it will provide more information regarding the efficacy of rTMS in the treatment of chronic tinnitus in the near future.

Except for subjective assessment, an increasing amount of data from pilot studies indicates considerable potential for a variety of electrophysiological and neuroimaging methods to assess alterations in brain structure and function in patients with tinnitus. A study by Smith et al demonstrated for the first time that an improvement in tinnitus rating after stimulation was reflected by a reduction of activity in the positron emission tomography (PET) scan after rTMS when compared with pretreatment values. Therefore, functional imaging might represent an important objective marker of treatment effects in the future.

Conclusion

Repetitive TMS provides a new therapeutic tool for chronic tinnitus. Even though the quantity of improvement varied across studies, a stable, statistically significant improvement in tinnitus complaints could be observed. Differences in study design, stimulation parameters, and patient population render a further comparison of results difficult, and the long-term outcome of positive effects will require further study.

Moreover, the most effective stimulation parameters, particularly the optimal brain area and hemisphere, as well as the most favorable treatment schedules, are unknown. This has given rise to several attempts to optimize treatment strategies.

Future studies should be based on a consensus as to the most appropriate outcome measures of tinnitus. There is currently not enough evidence to determine a correlation between the duration of tinnitus and the effects of rTMS, and more work must be done to clarify this in the near future, if optimization of treatment strategies is to be achieved.

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Author Contributions

Zhe Peng, writing the article, searching, selection of studies, data extraction, drafting and co-drafting of the protocol/review, assistance with statistics, data analysis and data presentation; Xiu-Qi Chen, selection of studies, data extraction, assistance with statistics, data analysis; Shu-Sheng Gong, lead author, selection of studies, assistance with statistics.

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