Repetitive transcranial magnetic stimulation effectivity in treating tinnitus: A literature review

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KEYWORDS
tinnitus, transcranial magnetic stimulation, treatment, neuromodulation

ABSTRACT

Background : The pathophysiology mechanisms of idiopathic tinnitus remain unclear. Cure for the most common causes of tinnitus remains elusive. Recent studies demonstrated focal brain activation in the auditory cortex of patients with chronic tinnitus. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive means of inducing electrical currents in the brain, and has received increasing attention in recent years for tinnitus treatment.

Methods : This study is a literature review of research article and clinical trial. Search articles from five central databases and publisher websites, Pubmed, Cochrane library, ResearchGate, SAGE journals, and Web of Science. A thorough search of the tinnitus and TMS literature was conducted, and all available relevant material was examined. The reviewed aspects of the protocols included baseline evaluation, the total number of sessions, frequency and the total number of stimuli, the location of treatment, and the outcome measures.

Result : A review of the current literature revealed significant improvements in the perceptual properties of tinnitus, including intensity, annoyance, and distress, as well as its impact on the quality of life, following treatment with rTMS. Beneficial effects of this treatment have been consistently demonstrated in several small controlled studies. However, results are characterized by high interindividual variability and only a moderate decrease of the tinnitus. The role of patient-related (for example, hearing loss, tinnitus duration, age) and stimulation-related (for example, stimulation site, stimulation protocols) factors still remains to be elucidated.

Conclusion: There is a convincing body of evidence that rTMS represents a promising tool for pathophysiological assessment and therapeutic management of tinnitus. Further development of this technique will depend on a more detailed understanding of the neurobiological effects mediating the benefit of TMS on tinnitus perception. Moreover, clinical studies with larger sample sizes and longer follow-up periods are needed.

INTRODUCTION

Tinnitus is described as auditory hallucinations received in the ear with absence of an external auditory stimulus (Lewis, et al., 2020). It can be caused by several different underlying conditions such as injury of the peripheral cochlea and the participation of the brain networks of the auditory and non-auditory systems, leading to changes in brain plasticity. However, the exact mechanism of tinnitus generation and maintenance is still remained unclear (Henton & Tzounopoulos, 2021). The prevalence of tinnitus is expected to increase due to population development and increased occupational and recreational noise exposure. It is known that around 10–15% of the United States population has reported experiencing tinnitus to varying degree (Frodl, et al., 2018). Prevalence of tinnitus in Indonesia is not known with certainty. Research was conducted at the Outpatient Unit Division of Neurotology Dr. Soetomo General Hospital shows 420 patients experiencing tinnitus. In this study, it was mentioned that tinnitus occurs most often in men in the age group of 31-40 years (Purnami & Thriesnarsandhi, 2020).

Available treatment options for tinnitus are limited. Cognitive behavioral therapy may help in reducing tinnitus related annoyance and handicap, but there is no established treatment with supporting evidence from randomized controlled studies for reducing tinnitus loudness (Langguth, 2020). Among the most recent treatment methods is the utilization of non-invasive techniques that focus on the electrical or magnetic stimulation of specific brain regions that are known to be associated with tinnitus. Though a newer therapy, many studies have examined the utilization of repetitive magnetic transcranial stimulation as a novel therapeutic tool for tinnitus (Han&Lee, 2021).

Repetitive magnetic transcranial stimulation is a non-invasive neuromodulation modality that has been utilized within the neurological and psychiatric communities for conditions such as depressive disorders, pain, aphasia, movement disorders, motor stroke, multiple sclerosis, epilepsy, disorders of consciousness, Alzheimer's disease, schizophrenia, substance abuse, and addiction (Barredo & Berlow, 2021). Considering the beneficial effects, there has been an emerging interest in utilizing rTMS for auditory disorders such as tinnitus (Horton&Ibrahim, 2021). The objective of the present study was to review recent literature about the efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of tinnitus.

METHODS

This study is a literature review of research article and clinical trial. Search articles from five central databases and publisher websites, Pubmed, Cochrane library, ResearchGate, SAGE journals, and Web of Science. A thorough search of the tinnitus and TMS literature was conducted, and all available relevant material was examined. The reviewed aspects of the protocols included baseline evaluation, the total number of sessions, frequency and the total number of stimuli, the location of treatment, and the outcome measures.

RESULT

A review of the current literature revealed significant improvements in the perceptual properties of tinnitus, including intensity, annoyance, and distress, as well as its impact on the quality of life, following treatment with rTMS. Beneficial effects of this treatment have been consistently demonstrated in several small controlled studies. However, results are characterized by high interindividual variability and only a moderate decrease of the tinnitus. The role of patient-related (for example, hearing loss, tinnitus duration, age) and stimulation-related (for example, stimulation site, stimulation protocols) factors still remains to be elucidated.

DISCUSSION

Tinnitus

Tinnitus is defined as the ringing, hissing, clicking or roaring sound in the ears (either bilateral or unilateral) with the absence of any external auditory stimulus. Different classification systems have been developed characterizing tinnitus as pulsatile, subjective or objective, primary or secondary, and acute or chronic (Esmaili&Renton, 2018). Pulsatile tinnitus is specific to causes that are vascular in origin. Objective tinnitus is heard by the patient and the examiner whereas subjective tinnitus is only heard by the patient. Primary and secondary are on the basis of cause whereas acute and chronic indicate duration for which the patient has experienced tinnitus (Saeed and Khan, 2021).

Persons reporting tinnitus should be questioned about the nature of the sound (location, quality, and onset), the duration of tinnitus, the effect on daily life and associated symptoms such as hearing difficulties (Tunkel, et al 2014). A history of ear drainage, ear pain, or both would suggest possible infectious, inflammatory, or allergic ear disease; a history of vertigo and imbalance would suggest possible cochlear or retrocochlear disorders such as Meniere's disease, acoustic neuroma, or migraine-associated vertigo. Acute tinnitus should be distinguished from persistent tinnitus, although there is no well-accepted definition of chronicity. In clinical trials, the definition ranges from a minimum duration of 3 months to 12 months (Plein, et al 2016).

Comprehensive audiologic evaluation for the presence, type, severity, and symmetry of hearing loss should be performed in patients with tinnitus who report hearing difficulties. The results of these evaluations will determine whether additional audiometric tests (otoacoustic emissions test, high-frequency audiometry, or auditory brainstem response test) or diagnostic imaging (magnetic resonance imaging or computed tomography of the temporal bone) are indicated. Standardized questionnaires are available for use in clinical and research settings to assess the severity of tinnitus and its effect on specific domains of a person's daily life (communication, cognition, emotion, quality of life, and sleep). These instruments are useful in the initial assessment of tinnitus and in monitoring changes with treatment (Bauer, 2018).

Quality of Life Evaluation

The questionnaire for measuring tinnitus was aimed at assessing the influence of tinnitus on a patient's life (Yang & Byun, 2016). Since tinnitus is often connected with complicated psychological disorders, most questionnaires are concerned with emotions and the challenging thoughts that patients experience (Tunkel, et al., 2014)

Several validated questionnaires are used clinically to assess the nature and impact of tinnitus. The most frequently use were Tinnitus Handicap Inventory (THI), Tinnitus Questionnaire (TQ), Tinnitus Severity Scale (TSS), and Visual Analog Scale (VAS). There were other quistionnaires that has been developed for measuring quality of life for tinnitus patient such as Tinnitus Handicap Questionnaire, Subjective Tinnitus Severity Scale, Tinnitus Reaction Questionnaire, Tinnitus Severity Grading, Tinnitus Severity Index, and the Intake Interview for Tinnitus Retraining Therapy (Meikle, et al., 2007)

Treatment for Tinnitus

There is a general consensus that a multidisciplinary approach for tinnitus treatment is crucial for success. There are many different kinds of tinnitus and certain treatments are only effective for treating certain forms. A single treatment cannot be expected to treat all forms of tinnitus with success, which confounds the measure of that treatment's effectiveness. As the diagnostic methods to distinguish kinds of tinnitus are still limited, the best way to find a treatment is often to try different treatments and see which one works (Moller, 2016).

No current tinnitus cessation treatments can guarantee tinnitus eradication. Pharmacological treatments have had a long history in tinnitus treatment research however, no such drug has prevailed to show success result. Tinnitus masking or reducing treatments relatively show better efficacy. Some promising results in efficacy of neuromodulation such as transcranial magnetic stimulation (TMS), direct brain stimulation (DBS) and transcranial direct current stimulation (tDCS) treatments are met with issues regarding the absence of a standard treatment protocol nor having long-term efficacy. The shift towards understanding changes in functional connectivity and tinnitus networks has allowed treatment research to also shift towards targeting structures in the brain to reduce tinnitus perception. Although the current treatments are still being developed and refined, they still hold potential in eliminating tinnitus altogether (Saeed & Khan, 2021).

Neuromodulation for Tinnitus

Tinnitus is a result of neuroplastic changes in auditory and non-auditory central nervous structures that occur as a consequence of peripheral deafferentation. Neural connections between the auditory and somatosensory systems located at the dorsal cochlear nucleus also have an impact on neuronal activity in the central auditory system and can play a role in tinnitus perception as well (Shore, *et al*., 2016).

If tinnitus is resulting from functional changes of neuronal activity, then there is no reason why tinnitus cannot be efficiently treated by neuromodulation or pharmacotherapy. Brain structures gained increased focus as potential targets for treatment. The primary focus of neuromodulatory treatments was the auditory cortex. With the advancement in knowledge about involved brain networks in tinnitus, non-auditory structures such as cranial nerves were also identified as potential targets (Langguth, 2020).

These interventions can be divided into invasive (e.g. epidural/subdural or deep brain electrical stimulation) and non-invasive methods (Langguth et al., 2012). The non-invasive methods can be furthermore divided into direct (e.g. transcranial magnetic or electrical stimulation) and indirect neurostimulation (e.g. neurofeedback, acoustic coordinated reset (CR) neuromodulation, and tailored notched music therapy). So far, none of the neuromodulation procedures have been established as a routine therapy method in tinnitus patients (Peter, 2018).

rTMS

Transcranial magnetic stimulation (TMS) uses magnetic fields for non-invasive brain stimulation. A coil that is connected to a stimulation machine is positioned over the subject's scalp. A strong electrical current in the coil produces a magnetic field that passes, largely undistorted, through the cranium and induces neuronal activity in superficial cortical areas. In repetitive TMS (rTMS), a large number of TMS pulses (typically between 100 and 3,000) are applied in a rhythmic pattern during one session. The effects of stimulation depend on the complex interaction of many factors. The most important factors are the activity of the stimulated area and the utilized frequency of rTMS (Rossini, et al., 2015).

In rTMS electromagnetic field is applied closely to the scalp of patients at the location of interest with multiple pulses, ultimately modulating the excitability of the neurons within the cortex. The pulses generated by this magnetic field can be either excitatory, with a frequency greater than 5 hertz (Hz), or inhibitory, with a lower frequency, that is usually <1 Hz. The application of either frequency depends on the specific treatment goals (Figure 1) (To & Ridder, 2018).

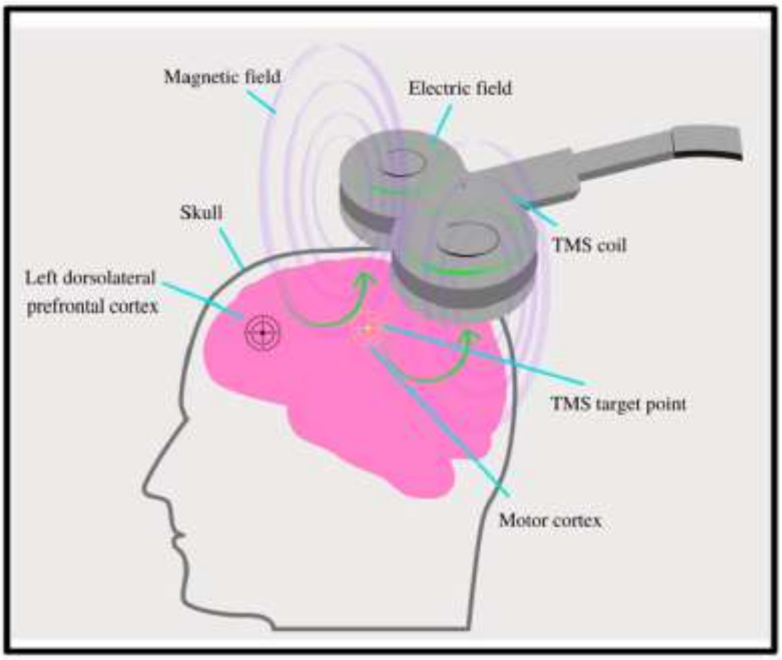

Figure 1. Components of repetitive magnetic transcranial stimulation (rTMS): rTMS is a non-invasive therapy that utilizes a wire coil connected to a magnetic stimulator.

The placement of TMS coil on patient's scal leads to a transynaptic activation of pyramidal cells evoking descending volleys in the pyramidal axons projecting on spinal motoneurons, also termed the corticospinal tract. Motoneuron activation in response to corticospinal volleys induced by TMS leads to a contraction in the target muscle evoking a motor-evoked potential (MEP) on electromyography (EMG) recorded by using surface electrodes applied over the muscle belly. Its peak-to-peak amplitude is used to estimate excitability of the corticospinal tract (Figure 2) (Denton, et al., 2021).

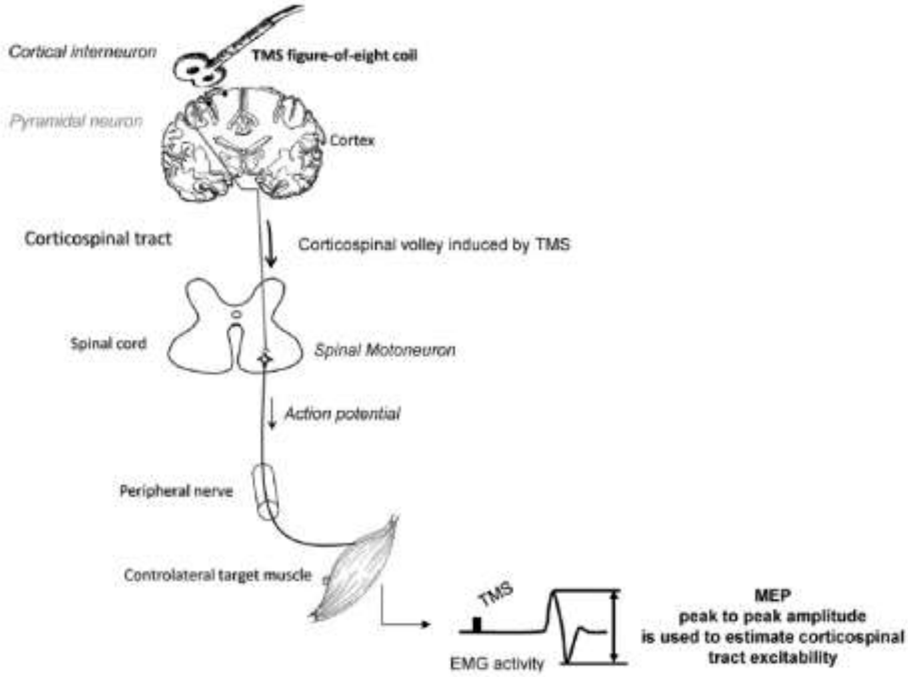

Figure 2. Transcranial magnetic stimulation (TMS) applied over the motor cortex preferentially activates interneurons oriented in a plane parallel to the brain surface

rTMS has been used in tinnitus research in two different ways. First, single sessions of rTMS have been used to investigate the possible transient suppression of tinnitus perception by the modulation of activity in cortical areas. This has been demonstrated in the temporal and frontal cortices in a subgroup of patients (Lefaucheur, et al., 2014). Second, repeated sessions of low-frequency rTMS of the temporal cortex have been proposed as an innovative treat- ment strategy for tinnitus based on the assumption that it is related to increased neuronal activity in the auditory cortex (Eichammer, et al., 2003).

Repeated sessions of low-frequency rTMS of the temporal cortex have been proposed as an innovative treatment strategy for tinnitus based on the assumption that it is related to increased neuronal activity in the auditory cortex. This approach has been investigated in a large number of studies with somewhat conflicting results (Schoisswohl, et al., 2019).

Eichammer, et al (2003) conducted a case series in three patients suffering from chronic tinnitus. Low frequency (1 Hz) rTMS on auditory cortex activity was evaluated, using a sham controlled double-blind crossover design. Repetitive transcranial magnetic stimulation was administered 5 days of treatment with 2000 stimuli perday. Tinnitus complaints were assessed at baseline, immediately after the last rTMS session, and 3 and 6 days after rTMS treatment for both stimulation conditions using Tinnitus Questionnaire. Two of three patients revealed clearly increased metabolic activity in circumscript areas of the primary auditory cortex (PAC), allowing a selective stimulation of these cortical areas with low-frequency rTMS. Considerable improvement in tinnitus was achieved in these patients (Eichammer, et al., 2003).

Plewnia et al. (2003) applied high frequency (10 Hz) targeting left temporal cortex, left temporoparietal cortex and dorsolateral prefrontal cortex with five stimulation trains at different scalp positions in 14 tinnitus patients. They found only a significant reduction in tinnitus when targeting the left temporal and left temporoparietal cortex (targeting the DLPFC did not yield in significant results) using a self-rating tinnitus reduction scale (Plewnia, et al., 2003).

Soleimani et al (2016) performed a meta-analysis on trials that examined the efficacy of rTMS on tinnitus, included 20 randomized control trial with total 1014 subjects. The treatment outcomes were evaluated by the tinnitus questionnaire (TQ) and the tinnitus inventory handicap (THI). They found 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 (Soleimani, et al., 2016).

Landgrebe et al (2017) conducted a multicenter randomized, sham controlled study to investigate the efficacy of rTMS. During the baseline visit (taking place 11 to 9 days before first treatment) a broad spectrum of psychometric as well as tinnitus specific scales (including the Tinnitus Questionnaire and the THI) were applied. In the week before first treatment, tinnitus severity was again measured with the TQ and the THI in order to obtain a stable average baseline measure of tinnitus severity. Patients received two times 5 sessions (one session daily in two weeks) of 1-Hz-rTMS (2000 stimuli per session) applied to the left primary auditory cortex. The main result of the study is that real 1-Hz-rTMS applied to the left temporal cortex did not provide any therapeutic benefit as compared to sham treatment in patients with chronic tinnitus. There was no relevant or significant difference between the real and sham-treated group in any of the outcome parameters, neither at the end of treatment, nor during the follow-up period. These findings are in contrast to results from studies with smaller sample sizes and put the efficacy of this rTMS protocol for treatment of chronic tinnitus into question (Landgrebe, et al., 2017).

Liang, et al (2020) Twenty-nine randomized studies involving 1228 chronic tinnitus patients. 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 27 studies (32 comparisons) assessed the auditory cortex, 1 examined the motor cortex, and 1 did not target a specific cerebral area. In terms of the number of rTMS sessions, 11 studies reported a treatment time of 10 days, 12 studies reported of 5 days, 4 studies reported of 20 days, 1 studies reported of 4 days, and 1study did not provide the stimulation duration. Most studies showed signifficant difference on THI Scores 1 month and six month post treatment. There was also a statistically significant difference in TQ scores 1 week post intervention between the rTMS and sham-rTMS groups. This studies confirms the efficacy of rTMS and shows satisfactory safety in patients with chronic tinnitus (Liang, et al., 2020).

A meta-analysis conducted by Yin, et al (2021) analyzes 12 studies with 717 participants. It showed active rTMS was superior to sham rTMS in terms of the short-term and long-term effects (6 months) on the tinnitus handicap inventory scores, but an immediate effect was not significant. They found that the use of active rTMS on patients with tinnitus showed a meaningful short-term effect on the THI score and it had a positive effect on the THI assessment at 1 and 6 months. These findings suggest that rTMS had a possible long-term effect up to 6 months. There was no significant immediate effect on the tinnitus questionnaire (TQ) and Beck depression inventory (BDI) scores (Yin, et al., 2021).

Schoisswohl et al (2023) investigate the treatment effect of 1 Hz rTMS using two different current flows, anterior-posterior to posterior-anterior (AP-PA) or posterior-anterior to anterior-posterior (PA-AP) flow. Nine tinnitus patients were treated in two different groups each comprised of 10 treatment sessions (2 x 5 work days, at the same time) using 3000 biphasic pulses of 1 Hz rTMS applied over the left temporo-parietal cortex using. Before and after rTMS treatment patients were requested to fill out the German versions of the Tinnitus Functional Index, the Tinnitus Handicap Inventory, the Major Depression Inventory as well as Numeric Rating Scales. The most obvious finding to emerge is that a magnetic stimulation with an induced current in PA-AP direction provoked superior alleviation of tinnitus-related symptoms in all outcome assessments especially for tinnitus unpleasantness, loudness, and distress (TFI) (Schoisswohl, et al., 2023).

CONCLUSION

rTMS is a non-invasive method of modulating brain activity with the ability to impact both neural connections between regions of the brain and the gene expression of particular neurons. It can be applied in different regions of the superficial cerebral cortex, interacting with the dysfunctional neuronal activity that is the the neural correlate of disabling tinnitus. A review of the recent literature revealed significant improvements in the perceptual properties of tinnitus, including intensity, annoyance, and distress, as well as its impact on the quality of life, following treatment with rTMS. Though it remains unclear which specific testing parameters, and in what combination, would result in the greatest improvement in tinnitus perception and reaction, the studies examined in this review suggest that rTMS may be an effective treatment modality for tinnitus. Further evaluation could help define a standardized clinical protocol and establish a path to the clinical application of rTMS in the treatment of tinnitus.

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