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Review

Neuromodulation for the Treatment of Tinnitus

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Tinnitus is a perception of sounds in the absence of external noise. Tinnitus can affect an individual's life, prevent productive work or impair the quality of life. There are 2 types of tinnitus, objective and subjective, the latter being the most challenging of hearing disorders. Tinnitus has various forms and it can be difficult to relate a specific event with the appearance of tinnitus. Moreover, detection of tinnitus and evaluation of its severity is impossible. Therefore, treatment is usually based on the patient's own assessment. To date, various forms of treatment have been administered with minimal success. Many different treatments have been attempted and then discontinued. The treatment goal of eliminating symptoms for severe tinnitus is rarely achieved. However, some symptoms of tinnitus can often be reduced to improve the patient's quality of life allowing him or her to work despite residual effects of the disorder. In the present study we evaluated electrical stimulation, including transcranial direct current stimulation, transcranial magnetic stimulation for the treatment of tinnitus.

Key Words: Tinnitus; Electric Stimulation; Transcranial Direct Current Stimulation; Transcranial Magnetic Stimulation

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INTRODUCTION

Chronic tinnitus is a perception of sound in the absence of sound stimuli that affects approximately 10-15% of the adult population [1]. Various hypotheses have been proposed regarding the cause of tinnitus, however the exact pathophysiology remains unknown. Various treatments such as retraining, medication, sound stimulation, neuromonics or surgical treatments have been used, however, an effective treatment method has not been found. Among these, electrical stimulation is reportedly effective in many patients who do not benefit from other treatments.

Electrical stimulation for the suppression of tinnitus has been used in the past. Feldmann reported that Grapergiesser first suppressed tinnitus by transcutaneous stimulation with Volta's platinum-zinc cell [2]. Since then, numerous investigators have performed electrical stimulation using different wave forms with electrodes placed at various sites. Graham [3] used a transtympanic electrode and House [4] reported a reduction in tinnitus during electrical stimulation in patients with cochlear implants. Kitahara and Okusa [5] reported the effectiveness of suppressing tinnitus with electrical promontory stimulation. In this study, we introduce electrical stimulation of the round window and brain cortex as treatments for tinnitus.

ELECTRICAL STIMULATION OF THE ROUND WINDOW

Based on the theory of abnormal electrical activity within the auditory pathways and hyperactive hair cells or neurons [6,7], a promising therapeutic approach is a device that would restore the physiological function within the auditory system and resynchronize the peripheral and/or the central neurons of the auditory pathway. Electrical stimulation has been known for more than 200 years to induce hearing sensations [8] and Grappengiesser reported this stimulation may have an effect on tinnitus.

Research on electrical promontory stimulation (EPS) showed temporary and partial tinnitus suppression. Reportedly, approximately 82% of patients experienced immediate relief of tinnitus and 45% of those patients showed longer-term tinnitus suppression. [9]. Rubinstein et al. [10] also reported the effect of high-frequency EPS on tinnitus and suggested that the effect should be investigated with an implantable device. There are indications that cochlear implants may provide long-term tinnitus suppression in patients with severe sensorineural hearing loss and reportedly provide tinnitus relief in up to 90% of patients. Deafferentation of the auditory pathway is a main cause of tinnitus, and presumably, electrical stimulation of the auditory system via EPS or cochlear implants could reverse the effect. Single-sided deafness (SSD) with concomitant incapacitating tinnitus is a new indication for cochlear implants [11].

Portmann [7] suggested that the effectiveness of electrical stimulation may be based on electrode placement and found that electrical stimulation at the round window was better than stimulation at the promontory. Additionally, positive electrical pulses were the most effective in temporary tinnitus suppression. In the reported studies, the efficacy of EPS to suppress tinnitus was achieved using very brief stimulation in acute experimental settings. Repeatability of tinnitus suppression using EPS remains uncertain and the long-term effects of EPS on the cochlea and acoustic thresholds have not been thoroughly investigated [10].

Using cochlear implants to suppress tinnitus implies that electrical stimulation of the auditory nerve can reverse the reorganization associated with peripheral deafferentation thus reversing plastic changes which may have led to tinnitus. Additionally, increased activation of the auditory nerve may inhibit cells in the auditory nervous system and influence its effect on tinnitus.

Psychological factors may also contribute to tinnitus suppression obtained after cochlear implantation. For example, the recovery of auditory function may help assure patients and minimize tinnitus annoyance.

Tinnitus can be influenced by electrical stimulation of the inner ear when it occurs in connection with sensorineural hearing loss. Electrical promontory stimulation via a transtympanic approach or round window stimulation can provide temporary tinnitus suppression. In patients with profound hearing loss, cochlear implantation can provide more permanent tinnitus relief.

ELECTRICAL STIMULATION OF THE BRAIN CORTEX

The neurophysiological hypothesis by Jastreboff implies that the autonomic nervous and limbic systems are related in processing behavioral problems and tinnitus neuronal activities [12]. If the habituation of brain reflexes persists, then subjective tinnitus occurs, indicating that an activation of neural plasticity in auditory processing areas of the central nervous system (CNS) may cause tinnitus. Therefore, tinnitus could be treated by interfering with the abnormal activity of the CNS. Based on this hypothesis, neuromodulation has emerged as a treatment for tinnitus. In several studies, neuromodulation techniques such as neurobiofeedback, epidural electrical stimulation, transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) showed promising results [13].

1. Transcranial direct current stimulation (tDCS)

The effects of noninvasive tDCS have been studied in both healthy individuals and those with neurological disorders. Based on stimulation polarity, tDCS can either increase or decrease the excitability of the underlying cortex. Anodal stimulation increases excitability with neuronal depolarization and cathodal stimulation decreases excitability with neuronal hyperpolarization [14-16]. Synaptic activity controls the changes in intracortical inhibition or facilitation and can affect the results of tDCS [17]. Anodal tDCS of the left temporoparietal area (LTA) and dorsolateral prefrontal cortex (DLPFC) are potentially the most favorable polarity and stimulation sites for tinnitus relief [18-21]. tDCS of LTA results in more widespread diffused impact on cortical areas beyond the target region. However, tDCS of DLPFC results in a more localized impact on the target region itself [22].

Anodal tDCS of the LTA has led to transient suppression of tinnitus in 42% [23] and 35% [18] of participants. A comparatively long-lasting impact on tinnitus perception, lasting up to a few days, was observed in a recent double-blind, sham-controlled study conducted by Garin et al. [18] using tDCS for 20 minutes with 1 mA current intensity. Anodal tDCS produced more favorable effects compared with cathodal or sham tDCS. Vanneste and colleagues [19] explored whether tDCS of DLPFC would suppress tinnitus and used a slightly higher current intensity (1.5 mA) than other authors [18,23]; they reported a 29.9% positive response rate with bifrontal tDCS using an anode on the right DLPFC and cathode on the left DLPFC. However, a review of studies conducted since 1998 using tDCS in humans under various clinical conditions showed that no studies used a current intensity greater than 2 mA [24]. The use of a current higher than 2 mA would require a preparatory investigation of safety issues, which was beyond the scope of this study.

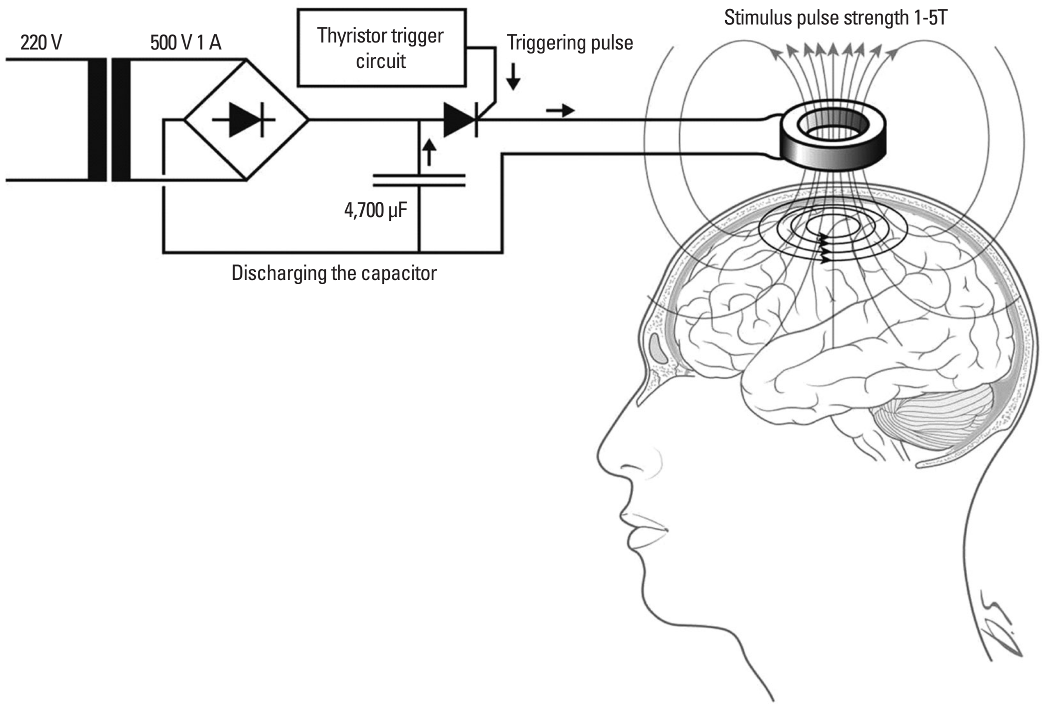

Fig. 1. Diagram of the underlying principle of transcranial magnetic stimulation (TMS). The strong current in the coil produces a magnetic field perpendicular to the plane of the coil. The magnetic field passes unimpeded through the skull and induces an oppositely directed electric current in the brain.

tDCS can potentially be applied in clinical settings for patients with tinnitus, although more research is needed in this area.

2. Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation (TMS) is a non-invasive tool that can be used to modulate neural activity. TMS delivers a high intensity and short-lasting current pulse via an insulated stimulating coil. This produces a magnetic field perpendicular to the coil which penetrates the underlying scalp and brain at a reduced intensity ultimately affecting the activity of cortical neurons in the brain region beneath the coil (Fig. 1). TMS can be administered as a single pulse or as paired pulses.

The magnetic field reaches a maximum of 1.5-2 T (same size as a MRI scanner) in approximately 100 μs and then decays back to zero [25]. The magnetic coils have different shapes. Round coils are the most powerful. Figure-eight-shaped coils or double-cone coils are more focused with a maximal current delivered at the intersection of the 2 round components which can deliver the current to the targets more precisely (Fig. 2).

Reportedly, single magnetic pulses have no long-lasting effects on the brain, however multiple pulses of rTMS tend to show prolonged effects on the brain. Cortical excitability was repeatedly decreased with low-frequency (≤1 Hz) rTMS [26], while high-frequency (5-20 Hz) rTMS resulted in increased excitability [27].

These types of stimulations are used for neurophysiological exploratory purposes. rTMS administers multiple TMS pulses to a patient's head during a single period [28]. Repetitive magnetic fields produced by rTMS can decrease neural overactivity in cortical areas and alleviate tinnitus [29]. Specifically, rTMS of the auditory cortex is effective in the treatment of tinnitus [30]. Neuroplastic changes in the brain, as a reaction to sensory deafferentation, are considered a cause of tinnitus [31]. Networks of several cortical areas may cause tinnitus, but the exact area remains unknown. Progress in functional imaging has helped explain the pathophysiology and identified brain lesions related to tinnitus [32]. Several studies have reported that positron emission tomography (PET) can be used to identify the region of unbalanced cortical activity where rTMS could be applied [33,34]; however, controversy remains regarding the usefulness of PET for rTMS targeting [35] and the function of PET and other neuroimaging modalities in determining the stimulation site is debatable. Rossi [36] reported that stimulation (5 days, 1-Hz rTMS) in the left temporoparietal area was effec-

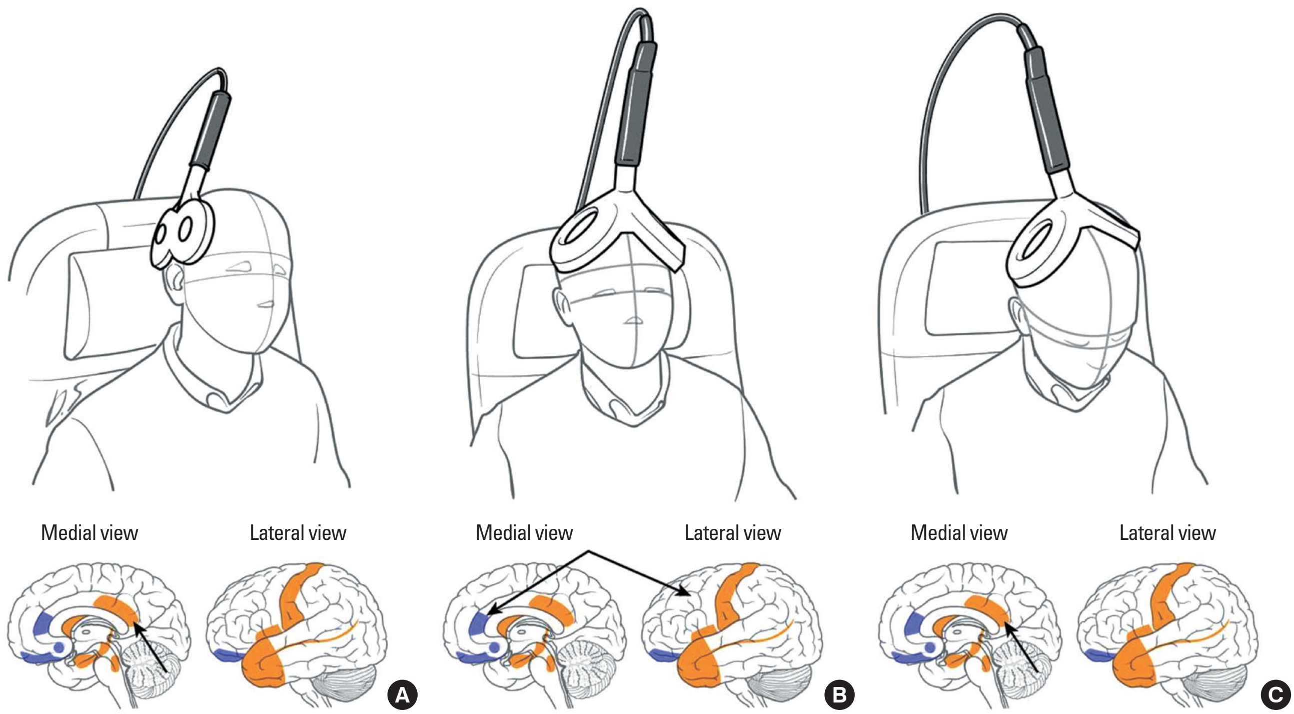

Fig. 2. (A) Stimulation of the auditory cortex. Figure-eight-shaped coils or double-cone coils are more focused with a maximal current delivered at the intersection of the 2 round components. (B, C) Double-cone-shaped coils can deliver the current to deeper targets of the brain such as anterior cingulate gyrus (B) or posterior cingulate gyrus.

tive and not related to tinnitus laterality. Moreover, only a few studies showed that stimulation of the left temporoparietal cortex produced better results than stimulation of the right cortex [36,37].

Since rTMS showed positive outcomes in treatment for tinnitus, many groups have reported their own treatment protocols and results. Specifically, Eichhammer [30] reported significant improvement in 3 patients treated with brain stimulation. Subsequently, many other studies have reported the effectiveness of rTMS stimulation in the temporoparietal region [37-39] ranging from 8-50%. Kim et al. safely applied rTMS to the temporoparietal cortex daily for 5 days with long-term benefits [40].

rTMS is widely used to treat various psychological diseases. Specifically, stimulation of the prefrontal area with rTMS was proven effective in patients with depression [41]. rTMS of the auditory cortex showed positive effects in the treatment of chronic tinnitus [30]. However, stimulation-related issues, including intensity, duration or predictors of response, are uncertain. Recently, rTMS of multiple brain cortices including the auditory cortex was performed to treat tinnitus [42]. Kleinjung reported that combined rTMS of the temporal and frontal brain cortices was more effective than rTMS of the temporal area alone [43]. Park et al. reported that combined rTMS of the auditory and prefrontal cortices was more beneficial than rTMS of the auditory cortex alone to treat tinnitus in patients with depression [44]. However, low-frequency left temporal rTMS combined with low-frequency right DLPFC rTMS did not show increased benefit [45].

Previous studies reported adverse effects including sensorineural hearing loss after temporal rTMS or epileptic seizures after high-frequency and high-intensity rTMS [46]. However, to date, the results reported showed rTMS is a well-tolerated and safe technique [47].

CONCLUSION

Electrical stimulation is an effective treatment for chronic tinnitus, but this conclusion is based on a small number of studies and should be interpreted carefully. Studies with a larger number of participants and longer follow-up period are necessary to prove the short- and long-term therapeutic effects of electrical stimulation. In addition, protocols for stable treatments should be designed.

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