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Strategies for Enhancement of Transcranial Magnetic Stimulation Effects in Tinnitus Patients

Tobias Kleinjung[1] and Berthold Langguth[2]

[1] *Department of Otorhinolaryngology and Interdisciplinary Tinnitus Center and* [2] *Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany*

Abstract: Tinnitus is an auditory phantom sensation characterized by the perception of elementary sound or noise in the absence of any acoustical sound source. Tinnitus is a frequent disorder and is difficult to treat. Compelling evidence corroborates the perception of chronic tinnitus as associated with regional changes in cortical excitability. Repetitive transcranial magnetic stimulation (rTMS) over the temporal or the temporoparietal cortex has recently been introduced as a new treatment strategy for tinnitus. The technique has been applied in two different ways in tinnitus patients. Single sessions of high-frequency rTMS have been successful in transient reduction of tinnitus perception, whereas repeated sessions of low-frequency rTMS have resulted in longer-lasting tinnitus reduction, indicating therapeutic potential. However, treatment outcome so far is characterized by high interindividual variability and only moderate effect size. This study reviews different approaches for enhancement of rTMS effects in tinnitus patients. The different strategies include the combined stimulation of nonauditory and auditory brain areas, the variation of stimulation frequencies and intensities, and the comparison of different firing modes (burst vs. tonic stimulation). Furthermore, the value of optimum patient selection is discussed. Another approach consists of a combination of rTMS administration with pharmacological intervention. Repetition of rTMS treatment in treatment responders seems to be a promising approach for the prolongation of treatment effects. A pilot study suggests further that treatment effects can be enhanced by combined stimulation of auditory and nonauditory brain areas. Moreover, clinical data such as tinnitus duration and the dimension of hearing loss seem to have an important impact on treatment effects. Successful enhancement of treatment effects will depend on a more detailed understanding of the neuronal correlates of the different forms of tinnitus and the mechanisms by which rTMS exerts its effects.

Key Words: coil localization; stimulation frequency; tinnitus; transcranial magnetic stimulation

Subjective tinnitus is defined as the perception of sound in the absence of an internal or external sound source. The biological mechanisms leading to the perception of tinnitus are still not completely understood. Increasing agreement, however, posits that different forms of tinnitus may differ in their pathophysiological mechanisms. Also generally accepted is that most forms of subjective chronic tinnitus are the consequence of central nervous system reorganization processes induced by altered peripheral auditory and somatosensory input [1]. This theoretical framework is supported by electrophysiological data from animal models [2] and functional neuroimaging data in humans [3]. In detail, peripheral deafferentation may result in an imbalance between excitatory and inhibitory function, causing maladaptive plastic changes in the structural and functional organization of the auditory system at several levels (dorsal cochlear nucleus, inferior colliculus, medial geniculate body, and auditory cortex). Alterations of structure and function in the central auditory pathways in tinnitus patients are confirmed by functional magnetic

Reprint requests: Tobias Kleinjung, MD, Department of Otorhinolaryngology, University of Regensburg, Franz Josef Strauss Allee 11, 93053, Regensburg, Germany. Phone: +49 9419449505; Fax: +49 9419449512; E-mail: tobias.kleinjung@klinik.uni-regensburg.de

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resonance imaging [3–5], positron emission tomography [6–8], and structural magnetic resonance imaging [9–11]. Electroencephalography and magnetoencephalography further suggest that tinnitus is related to alterations in thalamocortical oscillations, characterized by reduced alpha activity and increased low-frequency and gamma activity [12–14]. According to Llinas's model of thalamocortical dysrhythmia, such changes may be the consequence of thalamic deafferentation [15].

However, data from patients in a persistent vegetative state suggest that hyperactivity within primary sensory areas is not sufficient for conscious perception. Rather, synchronized coactivation of frontal and parietal areas seems to be necessary for conscious auditory perception [16]. In line with these data, recent magnetoencephalography studies show that tinnitus distress is related to functional connectivity between frontal and parietal cortical areas [17]. Furthermore, the tinnitus-related network has been shown to change over time, and the auditory cortex becomes less relevant with increasing tinnitus duration [18].

BACKGROUND

The noninvasive technique of rTMS is used to apply electromagnetic fields to the brain. A wired coil is held over the region of interest in the patient's head. A strong electric current in the coil produces an electromagnetic field that induces neuronal depolarization in superficial cortical areas. Several studies demonstrated that this technique represents a capable tool in the treatment of neuropsychiatric disorders associated with focal brain hyperactivity [19]. The electrical current induced in the brain tissue can excite or inhibit neuronal activity, depending on various stimulation parameters.

For the human motor cortex in general, high frequencies of rTMS have been shown to exceed—whereas low frequencies reduce—cortical excitability. This is analogous to direct electrical stimulation of cortical neurons and, therefore, high-frequency rTMS has been suggested to induce effects similar to long-term potentiation, whereas low-frequency rTMS causes effects similar to long-term depression [20]. Long-term depression effects are most pronounced when areas of increased excitability are stimulated. Accordingly, priming with high-frequency rTMS [21] and with transcranial direct-current stimulation [22] has been successful in enhancing effects of low-frequency rTMS over the motor cortex. On the basis of knowledge about direct electrical stimulation in animal experiments, an enhancement of rTMS effects by burst stimulation protocols has been tested. Preclinical data suggest much more pronounced effects of theta burst stimulation protocols as compared to tonic rTMS [23].

In tinnitus patients, rTMS has been used in two different ways [24]. Single sessions of rTMS over the temporal or temporoparietal cortex have been shown to result in a transient reduction of tinnitus intensity in a subgroup of patients and even in complete suppression of tinnitus in some cases [25–28]. This protocol has already successfully been used as a diagnostic method for screening patients before surgical implantation of epidural electrodes [29].

Repeated sessions of rTMS have been proposed as a therapeutic approach for the treatment of tinnitus [30–31]. First promising results in a pilot study [32] have been confirmed by an increasing number of sham controlled studies [33–36], all of which demonstrated a significant improvement of tinnitus after 5–10 sessions. However, treatment effects are characterized by only moderate effect sizes and a high interindividual variability. Also, a high variability is seen in the reported duration of treatment effects lasting from some days up to 1 year. Enhancement and stabilization of treatment results are preconditions before rTMS can be recommended as a routine tool in tinnitus therapy. Therefore, several studies that have been performed in the last years were aimed at identifying strategies for enhancing rTMS effects in tinnitus patients. A large variety of different strategies has been tested. These include variation of stimulation parameters such as site of stimulation, frequency, intensity and duration, priming protocols, burst stimulation protocols, combination of different stimulation targets, combination of rTMS with pharmacological intervention, and identification of treatment responders by clinical characteristics and by neuroimaging.

SITE OF STIMULATION

As mentioned, various functional neuroimaging techniques have been used for detecting tinnitus-related changes in brain activity. They converge in the finding of increased neuronal activity in the central auditory system, but they differ in the exact localization of these changes, which in turn results in uncertainty about the optimal target for rTMS treatment. Accordingly, the site of stimulation and the method for coil positioning differ across studies. In some studies, the coil has been placed over the temporal cortex, in others over the temporoparietal cortex; sometimes, rTMS has been applied contralateral to tinnitus perception, whereas in other studies best results were obtained after stimulation of the left hemisphere, independent of tinnitus laterality [37]. In some studies, coil placement has been performed with neuronavigational systems in combination with functional [32] or structural [38] imaging data; in other studies, the coil has been positioned on the basis of anatomical

landmarks or on the international 10–20 electroencephalograph system [39].

Even if comparison across studies is difficult owing to differences in study design, patient populations, and stimulation parameters, no hint suggests that one of the coil localization techniques is much superior to others. Furthermore, from currently available data, no definite conclusion can be drawn regarding which imaging method is best suited to define the target for TMS treatment of tinnitus. Thus, further studies are needed to directly compare various targets and various coil placement strategies. Moreover, determination of the optimal target for stimulation depends to a great extent on a detailed knowledge of the neurobiological mechanisms by which TMS exerts its effects on tinnitus.

VARIATION OF STIMULATION FREQUENCY

In most studies that investigated repeated sessions of rTMS as a therapeutic approach, the stimulation was performed at a frequency of 1 Hz. This was motivated by the finding that 1-Hz rTMS reduces neuronal excitability over the motor cortex [40] and by the successful use of low-frequency rTMS in neuropsychiatric disorders, which are associated with focal hyperexcitability [19]. One recent study with a relatively large sample size compared the effects of various stimulation frequencies [35]. Whereas sham rTMS treatment had no effect, active stimulation over the left temporoparietal cortex resulted in a reduction of tinnitus regardless of stimulation frequency (1 Hz, 10 Hz, and 25 Hz). One year after treatment, residual tinnitus relief demonstrated a trend toward a higher efficiency of 10- and 25-Hz frequencies as compared to 1 Hz, even if this difference did not reach statistical significance [41].

MAINTENANCE TREATMENT

As mentioned, the duration of rTMS effects varies across studies. In some studies, improvements after rTMS lasted 6 months [32] or even 1 year [41], whereas others reported a return to baseline levels after less than 2 weeks [33,34]. As tinnitus is a chronic condition, strategies for maintenance treatment are of utmost importance.

Successful maintenance therapy for tinnitus with rTMS has been described in a case report [42]. In this patient, who had responded to rTMS treatment (1 Hz, right temporal cortex) rTMS was started again as soon as his tinnitus loudness increased over a score of 25 on a visual analog rating (VAR 0–100). Daily treatment sessions were repeated until the score reached lower than 25. In this patient, tinnitus could be reduced to a VAR of 6 or lower each time it recurred by administration of one to three maintenance sessions of rTMS. Tinnitus loudness was reported to be below a VAR of 25 and unobtrusive in daily life when last assessed 4 months after the third and final round of maintenance treatment [42]. In a group of 12 patients who improved after one series of rTMS, a second rTMS treatment series resulted in significant improvement, suggesting that the findings reported in the study of Mennemeier et al. [42] might generalize to groups of tinnitus patients who responded once on rTMS [43].

HIGH-FREQUENCY PRIMING STIMULATION

Experimental data from motor cortex stimulation in healthy subjects indicate that the depressant effect of low-frequency rTMS can be enhanced by high-frequency priming stimulation [21]. A clinical study has investigated whether high-frequency priming improves the therapeutic efficacy of low-frequency rTMS for the treatment of tinnitus [44]. Thirty-two patients with chronic tinnitus were randomly assigned to receive either a standard protocol of low-frequency rTMS over the left auditory cortex (110% motor threshold; 1 Hz; 2,000 stimuli a day) or a stimulation protocol in which priming stimulation with 6 Hz (90% motor threshold; 960 stimuli) preceded low-frequency rTMS (110% motor threshold; 1 Hz; 1,040 stimuli a day). The treatment outcome was assessed with a standardized tinnitus questionnaire. Both stimulation protocols resulted in significant clinical improvement after 10 days of stimulation as compared to baseline, but no difference was evident between the two protocols, suggesting that higher-frequency priming does not exert an enhancing effect on low-frequency rTMS in the treatment of tinnitus.

BURST STIMULATION

Applying rTMS in bursts has been proposed for enhancing rTMS effects. Specifically, bursts of three pulses at a frequency of 50 Hz, applied every 200 msec (5 Hz, theta burst), have been shown to induce more pronounced and longer-lasting effects on human motor cortex than tonic stimulation [23]. Single sessions of these theta burst stimulation protocols over the temporal cortex in tinnitus patients resulted in only short-lasting reduction of tinnitus loudness, comparable to effects achieved with single sessions of tonic stimulation [45]. However, what has to be mentioned is that in this study, rTMS has been applied over the inferior temporal cortex, which could be the reason for the relatively small effects.

In two other studies, single sessions of burst stimulation with burst frequencies of 5, 10, and 20 Hz (theta,

alpha, and beta, respectively) were compared with tonic stimulation at the same frequencies [46,47]. Burst stimulation had effects similar to those from tonic stimulation in patients with pure-tone tinnitus but was superior in patients with noise-like tinnitus. A possible explanation for this finding may be that pure-tone tinnitus may be due to increased neuronal activity in the classic (lemniscal) auditory pathways, which mainly fire tonically, whereas noise-like tinnitus may be the result of increased activity in the nonclassic (extralemniscal) pathways, which is characterized by burst firing. A follow-up study of the same group was able to replicate this result for bilateral tinnitus but not for unilateral tinnitus [48]. Furthermore, this study suggests that higher stimulation intensity may result in slightly better tinnitus suppression.

A study that investigated the effect of repeated sessions of theta burst rTMS is under way [49]. Case reports suggest that repeated sessions of burst rTMS are well tolerated, but whether they are more beneficial than repeated tonic rTMS is unclear [50,51].

COMBINATION OF DIFFERENT STIMULATION TARGETS

New insight into the neurobiology of chronic tinnitus suggests that neuronal changes are not limited to the auditory pathways. Recent progress in neuroscientific research demonstrated that hyperactivity within primary sensory areas alone is not sufficient for conscious tinnitus perception. Rather, synchronized coactivation of frontal and parietal areas seems to be necessary [16] and, with increasing tinnitus duration, activity in the auditory cortex may become less relevant [18]. Tinnitus distress in turn may be related to coactivation of emotion-processing networks in the frontal cortex or the limbic system [52]. Besides changes in the amygdala [53], the hippocampus [10,54] and the ventral striatum [9], recent data also indicate the involvement of the anterior cingulate [33], wherein integration of cognitive and emotional processing occurs.

Repetitive TMS of the left dorsolateral prefrontal cortex (DLPFC) has been demonstrated to modulate the activity of the anterior cingulate cortex [55]. A further motivation for modulating frontal cortex activity comes from electrophysiological studies suggesting that tinnitus might occur as the result of dysfunctional top-down inhibitory mechanisms originating in the prefrontal lobe [56]. These data prompted the hypothesis that high-frequency rTMS of the left DLPFC might enhance treatment effects of low-frequency temporal rTMS in tinnitus patients. In one pilot study, 32 patients received either low-frequency temporal rTMS or a combination of high-frequency prefrontal and low-frequency temporal rTMS [57]. One protocol consisted of 2,000 stimuli at a frequency of 1 Hz and an intensity of 110% motor threshold over the left auditory cortex. In the second treatment protocol (combined protocol), high-frequency stimulation (1,000 stimuli, 20 Hz, 110% motor threshold) applied to the left DLPFC preceded each session of low-frequency stimulation (1,000 Stimuli, 1 Hz, 110% motor threshold) to the left temporal cortex. Directly after therapy, an improvement was seen in the tinnitus questionnaire score for both groups, but no differences were noted between groups. Evaluation after 3 months revealed a remarkable advantage for combined prefrontal and temporal rTMS treatment. These data further support the involvement of prefrontal cortex activity in the pathophysiology of tinnitus and indicate that modulation of both frontal and temporal cortex activity might represent a promising enhancement strategy for improving TMS effects in tinnitus patients.

PHARMACOLOGICAL ENHANCEMENT

Another possible approach for potentiating rTMS effects may be the use of pharmacological interventions. Animal experiments have revealed that neuronal plasticity can be enhanced by dopaminergic receptor activation [58]. Very recently, neuroplastic changes in human motor cortex, induced by transcranial magnetic and electrical stimulation, were demonstrated to be enhanced by dopaminergic drugs. A single oral dose of the dopamine agonist Pergolide enhances the suppressing effect of 1 Hz rTMS on motor cortex excitability [59], and the duration of aftereffects of transcranial direct stimulation and paired associative stimulation is prolonged by the factor of 20 after administration of 100 mg levodopa [60].

One pilot study investigated whether administration of the dopamine precursor levodopa before each session of low-frequency rTMS enhances TMS efficacy in tinnitus treatment [61]: Sixteen patients with chronic tinnitus received 100 mg levodopa before each session of low-frequency rTMS. Results were compared with a matched control group of 16 patients who received the same treatment but without levodopa. Both stimulation protocols resulted in a significant reduction of tinnitus scores after 10 days of stimulation; however, no significant difference occurred between the two groups. One reason for the failure of levodopa to enhance rTMS effects in tinnitus treatment might be that the temporal cortex reacts differently from the motor cortex to levodopa administration. Levodopa mainly acts on nigrostriatal dopaminergic projections, resulting in a relatively specific influence on the motor system. This may be the reason that results obtained from motor cortex stimulation cannot be easily transferred to stimulation of the temporal cortex.

Further research should focus on other pharmacological agents that influence neuroplasticity.

IDENTIFICATION OF TREATMENT RESPONDERS

Some evidence from several studies suggests that patient-related data may have an important impact on the therapeutic outcome of rTMS in tinnitus patients. Several studies reported that shorter tinnitus duration was related to better treatment outcome [26,33,35,38,62]. This observation might be explained by the hypothesis that increasing chronification facilitates the involvement of nonauditory structures, which might extend the neurobiological basis of tinnitus and subsequently lower the response rate of a treatment intervention that solely targets the auditory cortex [18]. Normal hearing was also identified as a positive clinical predictor for good treatment response [38]. Indirect support for this finding comes from a very recent study [36] that demonstrated relatively pronounced improvement of tinnitus scores in a sample of normal-hearing subjects with tinnitus. Interestingly, short tinnitus duration and normal hearing have been demonstrated to be positive predictors for other treatment options for tinnitus as well [63,64].

In addition to clinical data, certain brain activation patterns that have been identified are associated with good treatment outcome. Imaging data suggest that increased activity in the anterior cingulate cortex [33] and reduced activity in the directly stimulated auditory cortex [65] are associated with good TMS outcome.

CONCLUSION

Even though accumulating evidence suggests that rTMS can interfere with neuronal mechanisms involved in the pathophysiology of tinnitus, the exact mechanisms of action of the different applications are not clear. The current knowledge about rTMS effects in the treatment of tinnitus is based mainly on analogies with direct electrical stimulation in animals or on knowledge about rTMS effects on motor cortex excitability. However, whereas studies in healthy controls have shown that effects of low-frequency rTMS over the motor cortex can be enhanced by dopaminergic drugs or by priming stimulation, these techniques seem not to increase TMS effects over the temporal cortex in tinnitus patients. Thus, rTMS may not exert its clinical effects in tinnitus via long-term depression–like mechanisms. An alternative explanation could be that rTMS disrupts the malfunctioning network involved in tinnitus generation and thereby facilitates the intrinsic ability of the brain to restore normal function. In light of recent studies demonstrating that tinnitus is a network property [18], this could explain why the combined stimulation of frontal and temporal cortical areas seems to be more efficient than temporal stimulation alone [57].

The development of further enhancement strategies will depend heavily on a deeper understanding of the mechanisms by which rTMS exerts its clinical effects in treating tinnitus.

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