
Transcranial Magnetic Stimulation: A New Diagnostic and Therapeutic Tool for Tinnitus Patients

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Abstract: Even if the pathophysiology of tinnitus remains incompletely understood, there is growing agreement that dysfunctional neuroplastic processes in the brain are involved. Repetitive transcranial magnetic stimulation (rTMS) is a potent tool for modifying neural activity at the stimulated area and at a distance along functional anatomical connections. Depending on stimulation parameters, cortical networks can be functionally disturbed or modulated in their activity. The technique can alleviate tinnitus by modulating the excitability of neurons in the auditory cortex. It is assumed that TMS decreases the hyperexcitability that is associated with some forms of tinnitus. A growing number of studies demonstrate reduction of tinnitus after repeated sessions of low-frequency rTMS and indicate that rTMS might represent a new promising approach for the treatment of tinnitus. Single sessions of high-frequency rTMS over the temporal cortex have been successful in reducing the intensity of tinnitus during the time of stimulation and could be predictive for treatment outcome of chronic epidural stimulation using implanted electrodes. Because most available studies have been performed with small sample sizes and show only moderate effect sizes and high interindividual variability of treatment effects, further development of the technique is needed before it can be recommended for use in clinical routine. Both patient-related (e.g., hearing loss, tinnitus duration, age) and stimulation-related (e.g., stimulation site, stimulation protocols) factors seem to influence treatment outcome; however, their exact impact still remains to be clarified.

Key Words: auditory cortex; functional imaging; neuronavigation; neuroplasticity; tinnitus; transcranial magnetic stimulation

In 1985, Barker et al. [1] showed that it was possible to depolarize neurons in the brain using external magnetic stimulation. This method, called *transcranial magnetic stimulation* (TMS), was much less painful than transcranial electrical stimulation. For TMS, a brief (100–300 μ sec), high-current pulse is produced in an insulated coil of wire that is placed above the skull over the region of particular interest. The strong current in the coil results in a magnetic field (1.5–2 Tesla) with

lines of flux passing perpendicularly to the plane of the coil. An electric field is induced perpendicularly to the magnetic field, resulting in neuronal depolarization of the underlying brain area.

Magnetic coils can have different shapes. Round coils are relatively powerful. Figure eight-shaped coils are more focal, with a maximum current at the intersection of the two round components [2]. Owing to the strong decline of the magnetic field with increasing distance from the coil, direct stimulation effects are limited to superficial cortical areas. Whereas single magnetic pulses do not seem to have longer-lasting effects, the application of multiple pulses in rhythmic sessions, called *repetitive TMS* (rTMS), can have effects that outlast the stimulation period. Depending on stimulation parameters,

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rTMS can excite or inhibit the brain. Low-frequency (≤ 1 Hz) rTMS has been repeatedly shown to result in a decrease in cortical excitability [3,4] and is considered to produce long-term synaptic depression, which diminishes the efficiency of intercellular links. High-frequency (5–20 Hz) rTMS results in an increase in excitability [5] and therefore might generate long-term potentiation-like effects [6]. Interestingly, these features of rTMS effects are similar to those of direct electrical cortical stimulation in animal studies [4,7]. In addition, for brief periods after stimulation, rTMS can block or inhibit a brain function and create a transient functional lesion in the immediate poststimulation period [8]. On the basis of these multiple effects, TMS is now widely used as a research tool to study the physiology and pathophysiology of the brain. As these effects can outlast the time of stimulation, the technique was considered to be potentially useful for the therapy of disorders with cortical dysfunction [2].

UNDERLYING PRINCIPLE FOR THE USE OF rTMS IN TINNITUS

Tinnitus is a very frequent clinical condition, which is often associated with a lesion of the peripheral auditory system, such as presbycusis, Ménière's disease, noise trauma, sudden deafness, or drug-related ototoxicity [9,10]. However, there is increasing agreement that deafferentation-induced neuroplastic processes in the brain are also critically involved in the pathophysiology of tinnitus [11,12]. In particular, phenomenological analogies with phantom limb pain suggest that chronic tinnitus as an auditory phantom perception might be the correlate of maladaptive attempts at cortical reorganization owing to distorted sensory input from a peripheral lesion [13]. Support for this model comes from magnetoencephalography studies showing reorganization of the auditory cortex as reflected by a shift in the tonotopic map of the auditory cortex contralateral to the tinnitus [14]. Functional imaging studies demonstrated that tinnitus is associated with neuroplastic alterations in the central auditory system and associated areas. Positron emission tomography (PET) investigations showed abnormal asymmetry in the auditory cortices of tinnitus patients with higher levels of spontaneous neuronal activity on the left side, irrespective of tinnitus laterality [15–17]. Other studies revealed additional changes in the middle temporal and temporoparietal regions as well as activation in frontal and limbic areas [18–22]. Electrophysiological studies in animal models of tinnitus have shown an increase of firing rate and neuronal synchrony in both the lemniscal and extralemniscal systems [23–25]. Electroencephalography (EEG) and magnetoencephalography studies in humans have demonstrated that tinnitus is as-

sociated with reduced alpha and increased gamma activity in the contralateral auditory cortex [26,27]. As rTMS has the ability to modulate cortical activity focally, there was a rationale to assume that TMS could interfere with cortical hyperexcitability and, therefore, influence the tinnitus sensation. Moreover, repeated applications of rTMS might represent a potential treatment by producing longer-lasting modulation of cortical activity. The rationale was confirmed by promising results obtained by the use of rTMS as a therapeutic tool in various neurological and psychiatric conditions, in which increased cortical activity as underlying pathophysiology is assumed [28–32].

SAFETY ASPECTS

The notion that rTMS is safe and well tolerated by patients within a range of parameters defined according to a consensus on a safety guideline [33] is proven by an extensive body of data. Most data are available from rTMS studies in depressed subjects. After 2–4 weeks of daily prefrontal rTMS, there was no sign of structural magnetic resonance imaging changes [34], no significant changes in auditory thresholds, and no significant EEG abnormalities [35]. Adverse auditory effects, such as hearing loss or auditory hallucinations, have not been reported to date after temporal rTMS. The risk of high-intensity and high-frequency rTMS-induced epileptic seizures that had been reported in individual cases has been largely reduced since the introduction of safety guidelines [33]. Mild adverse effects, such as physical discomfort on the skull during stimulation or transient headache after stimulation, are reported by approximately 10% of stimulated patients. It is essential that contraindications, such as electronic implants (e.g., cardiac pacemakers, cochlear implants), intracranial pieces of metal, or previous epileptic seizures, be considered.

SINGLE SESSIONS OF rTMS AS A DIAGNOSTIC TOOL

Several studies with single sessions of rTMS have been performed to transiently disrupt tinnitus perception (Table 1). In this type of study, mainly trains of high-frequency rTMS (10–20 Hz) were administered. Plewnia et al. [36] applied high-frequency rTMS (10 Hz) to eight scalp positions according to the 10-20 EEG system to interrupt tinnitus by creating a “virtual lesion.” As control conditions, the researchers chose four positions with the coil tilted 90 degrees behind both ears and the coil on the insertion of both sternocleidomastoid muscles at the mastoid. When stimulation was administered to the left temporoparietal cortex—corresponding to the area of the secondary auditory cortex—a significant transient

Table 1. Effects of Single Sessions of rTMS in Tinnitus Patients

Authors	No. of Subjects	Stimulation Site/Coil Positioning	Frequency (Hz)	Intensity (% MT)	Pulses	Control Condition	Results
Plewnia et al. [36]	14	Various scalp positions according to 10-20 EEG system	10	120	30	Stimulation of nonauditory cortical areas	In 8 patients (58%), tinnitus suppression after left temporal/ temporoparietal stimulation
De Ridder et al. [37]	114	Auditory cortex contralateral to tinnitus site	1, 5, 10, 20	90	200	Coil angulation	In 60 patients (53%), good or partial tinnitus suppression after active rTMS; in 33%, suppression after sham rTMS
Fregni et al. [40]	7	Left temporoparietal areas, according to 10-20 EEG system	10	120	30	Sham coil and active stimulation of mesial parietal cortex	In 3 patients (42%), tinnitus suppression after left temporoparietal stimulation; no effect for both control conditions
Folmer et al. [41]	15	Left and right temporal cortex, according to 10-20 EEG system	10	100	150	Sham coil	In 6 patients (40%), tinnitus suppression after active rTMS; in 4 of the patients after contralateral rTMS; in 2 patients after ipsilateral TMS; in 2 patients, suppression after sham rTMS
Londero et al. [42]	13	Auditory cortex as determined by fMRI	1, 10	120	30	Stimulation over nonauditory cortical areas	In 5 patients (38%), tinnitus suppression after 1-Hz rTMS of the auditory cortex; no suppression after 10 Hz; in 2 patients, suppression after stimulation of a control position
Plewnia et al. [22]	8	Area of maximum tinnitus-related PET activation (temporoparietal cortex), neuronavigational system	1	120	300, 900, 1,800	Control position (occipital cortex)	In 6 patients (75%), tinnitus reduction after active rTMS; better suppression with more pulses

EEG = electroencephalography; fMRI = functional magnetic resonance imaging; MT = motor threshold; PET = positron emission tomography; rTMS = repetitive transcranial magnetic stimulation.

reduction of tinnitus was observed in 57% of the participants. This result has been confirmed in a large series of 114 patients with unilateral tinnitus. De Ridder et al. [37] studied the method of creating a virtual lesion with rTMS at frequencies between 1 and 20 Hz over the auditory cortex contralateral to the site of the tinnitus. The large sample allowed the establishment of a statistical relationship between optimum tinnitus suppression, optimum stimulation frequency, and tinnitus duration. The amount of tinnitus suppression was correlated positively with stimulation frequency and negatively with tinnitus duration, indicating the potential of TMS as a diagnostic tool for differentiating pathophysiologically distinct forms of chronic tinnitus. This approach has already been successfully used as a screening method to select patients for surgical implantation of cortical electrodes [38,39]. Patients responding to this type of rTMS with a short-lasting suppression of tinnitus perception were considered as good surgical candidates for permanent electrical stimulation of the auditory cortex.

Two recent studies by Fregni et al. [40] and Folmer et al. [41] confirmed the findings of transient tinnitus reduction after high-frequency stimulation of the left temporoparietal cortex, whereas Londero et al. [42] demonstrated reliable tinnitus suppression in only 1 of 13 subjects after a single session of high-frequency rTMS. In the latter study, functional magnetic resonance imaging with an acoustic paradigm was used for target detection within the auditory cortex. Plewnia et al. [22] chose another sophisticated method for the detection of tinnitus-related changes in the brain. Only patients in whom tinnitus could be suppressed by an intravenous lidocaine bolus were included. Changes of neuronal activity before and after lidocaine injection were observed in the left middle and inferior temporal cortex, in the right temporoparietal cortex, and in the posterior cingulum by [¹⁵O]H₂O PET. Single sessions of low-frequency (1 Hz) rTMS with the coil navigated to these activated areas resulted in tinnitus reduction lasting up to 30 minutes in six of eight patients.

REPEATED SESSIONS OF rTMS AS A THERAPEUTIC TOOL

In recent years, an increasing number of studies on rTMS for the treatment of tinnitus have been published (Table 2). Most rTMS treatment studies applied low-frequency rTMS in long trains of 1,200–2,000 pulses repeatedly over 5–10 days. Even if the quantity of improvement varied across studies, a stable statistically significant improvement of tinnitus complaints could be observed. Differences in study design, stimulation parameters, and patient population render a further comparison of results difficult.

Table 2. Effects of Repeated Sessions of rTMS in Tinnitus Patients

Authors	No. of Subjects	Stimulation Site/Coil Positioning	Frequency (Hz)	Intensity (% MT)	Sessions	Pulses per Session	Design	Control Condition	Results
Kleinjung et al. [16]	14	Area of maximum PET activation in the temporal cortex, neuronavigational system	1	110	5	2,000	Sham-controlled, crossover	Sham coil	Significant reduction of tinnitus after active rTMS as compared to sham rTMS; lasting tinnitus reduction (6 months), 8 responders for active TMS
Langguth et al. [45]	28	Left auditory cortex, according to 10-20 EEG system	1	110	10	2,000	Open	No control condition	Significant reduction of tinnitus until end of follow-up (3 months)
Plevnia et al. [44]	6	Area of maximum tinnitus-related PET activation (temporoparietal cortex), neuronavigational system	1	120	10	1,800	Sham-controlled, crossover	Occipital cortex	Significant reduction of tinnitus after active rTMS, as compared to the control condition; no lasting effects, 5 transient responders
Kleinjung et al. [52]	45	Left auditory cortex, neuronavigational system	1	110	10	2,000	Open	No control condition	Significant tinnitus reduction after active rTMS; improvement lasting until end of follow-up in some subjects; responders were characterized by shorter tinnitus duration and less hearing impairment (18 responders)
Rossi et al. [51]	16	Left temporoparietal cortex, neuronavigational system, according to 10-20 EEG system	1	120	5	1,200	Sham-controlled, crossover	Coil angulation + electrical stimulation of facial nerve	Significant reduction of tinnitus after active rTMS, as compared to the control condition; no lasting effects
Smith et al. [50]	4	Area of maximal PET activation in the temporal cortex, neuronavigational system	1	110	5	1,800	Sham-controlled, crossover	Coil angulation	Modest response to active treatment in 3 patients (75%); all subjects had reduced cortical activity in post-rTMS PET
Khedr et al. [53]	56	Left temporoparietal cortex, according to 10-20 EEG system	1, 10, 25	100	10	—	Sham-controlled, parallel group design	Oz EEG site	Significant reduction of tinnitus after all three active rTMS conditions as compared to the control condition; tinnitus reduction lasting during follow-up period (4 months)
Langguth et al. [47]	32	Left auditory cortex, neuronavigational system	1, 6 + 1	110 (90 for 6 Hz rTMS)	10	2,000	Randomization between two active treatment conditions parallel group design	No control condition	Significant improvement for both stimulation conditions, no difference between conditions, no lasting effects
Kleinjung et al. [46]	32	Left auditory cortex, left dorsolateral prefrontal cortex	1, 1 + 20	110	10	2,000	Parallel group design	No control condition	Significant improvement for both stimulation conditions directly after therapy; after 3 months, remarkable benefit for combined protocol

EEG = electroencephalography; MT = motor threshold; PET = positron emission tomography; rTMS = repetitive transcranial magnetic stimulation.

Nearly all studies addressed temporal or temporoparietal cortical areas. In a first study by Kleijnung et al. [16], [^{18}F]deoxyglucose PET was performed in 14 patients, and a neuronavigational system allowed the magnetic field of the TMS coil to be focused on the site of maximum activation in the auditory cortex. After active treatment, a significant decrease in the tinnitus score [43] could be observed, whereas sham treatment showed no effect. At 6 months after treatment, 57% of patients reported a remarkable, sustained reduction in tinnitus.

Another study investigated the effects of 2 weeks of rTMS applied over the area of maximum lidocaine-related activity change as determined by [^{15}O]H $_2\text{O}$ PET [44]. They reported moderate—but significant—effects after active stimulation with high interindividual variability. Attenuation effects disappeared 2 weeks after the last session. An easier applicable technique is the coil localization according to the 10-20 EEG coordinate system, which was described by Langguth et al. [45]. The clinical validation of this coil-positioning method resulted in a significant reduction of tinnitus severity after 10 sessions of 1-Hz rTMS. As there is no study so far comparing different coil-positioning strategies with treatment outcome, the optimum coil localization is still a matter of debate.

New insights into neurobiology of chronic tinnitus suggested that functional abnormalities are not limited to temporal and temporoparietal cortical areas but can occur in brain areas used for attentional and emotional processing, such as the dorsolateral prefrontal cortex. A recently published study demonstrated a more pronounced long-term effect of a combined treatment protocol of rTMS applied to the temporal and dorsolateral prefrontal cortex as compared to an exclusive stimulation of the temporal cortex [46]. Another combined treatment protocol consisting of a 6-Hz priming stimulation prior to 1-Hz rTMS of the temporal cortex resulted also in a reduction in tinnitus severity. However, this effect was not superior to 1-Hz standard rTMS alone [47].

Because tinnitus is a subjective phantom perception of sound, it represents a condition that is susceptible for placebo effects. Evaluation of treatment efficacy requires adequate methodology for control of nonspecific treatment effects. Most controlled studies published thus far have used placebo treatment in crossover designs. Therefore, carryover effects and missed effects owing to limited observation periods cannot be entirely excluded. Further attention should be directed to studies using clear parallel group designs [48]. Studies with control groups have reported different procedures of sham stimulation. Besides the sham coil system [16,49], which mimics the sound of the active coil without producing a magnetic field, an angulation of an active coil tilted 45 degrees [50] or 90 degrees [51] to the skull surface or stimula-

tion of nonauditory brain areas [22,44] has been described. Finding an optimal control condition for treatment studies is also difficult, owing to limitations in blinding of patient and operator to different stimulus conditions and owing to the fact that TMS itself results in auditory and somatosensory stimulation in addition to the actual brain site-specific effect.

Though some studies demonstrated effects that outlasted the stimulation period by 3, 4, or 6 months [16, 52,53], others were not able to observe longer-lasting effects [44,50]. The number of daily sessions may be an important issue to achieve sustained results in tinnitus patients [54], as already seen in other TMS applications, such as depression [55] and auditory hallucinations [56].

In most studies, validated tinnitus questionnaires and visual analog scales serve as primary outcome measurement, owing to the lack of objective parameters. A 2007 study by Smith et al. [50] demonstrated for the first time that an improvement in tinnitus rating after stimulation was reflected by a reduction of activity in the PET scan after rTMS therapy as compared to pretreatment values. Therefore, functional imaging might represent an important objective marker of treatment effects in the future.

Just recently, a case report showed that using maintenance rTMS to manage chronic tinnitus is feasible [57]. In a patient in that study, tinnitus could be reduced each time it recurred using one to three maintenance sessions, and finally it remained stable on a low level after the third stimulation series. The positive effect of this maintenance stimulation could also be confirmed by reduced cerebral metabolism in PET imaging after treatment. The approach—to use rTMS for maintenance treatment of tinnitus—is further supported by the clinical observation that those patients who respond once to rTMS treatment also experience positive effects from a second series of rTMS [58].

The high variability of treatment results, which is encountered in all studies, confirms the concept of the biological heterogeneity of tinnitus. In this context, the identification of treatment predictors is of utmost interest. Several rTMS studies indicate that treatment response depends on tinnitus duration, with better outcome for shorter duration [37,44,52,53]. On the basis of findings, it is tempting to conclude that the degree of maladaptive neuroplastic changes in auditory and nonauditory brain structures may depend on tinnitus duration. Hearing impairment has been identified as a negative prognostic factor in one study [52]. Deprivation from auditory input is assumed to result in deafferentation-induced neuroplastic changes in the central auditory system that might represent the crucial step in the development of subjective tinnitus. For that reason, chronic hearing impairment might attenuate rTMS effects by continuously triggering neuroplastic changes in central auditory structures.

CONCLUSION

In summary, the results from an increasing number of studies using rTMS show that treatment of tinnitus with this method is promising. Beneficial clinical effects were observed in some 50% of treated subjects. Only one very recently published study demonstrated a negative result. This might be owing to the relatively low number of daily stimuli (600 per day) used in this investigation [59]. However, all results have to be considered as preliminary, owing to the small sample sizes, the methodological heterogeneity, and the high variability of results. Replication of data must be performed in multicenter trials with a large number of patients and long-term follow-up before further conclusions can be drawn [48]. Further research is needed for a clear definition of subgroups of patients who benefit most from rTMS. In this context, short trains of high-frequency rTMS seem to have a promising potential to select patients for surgical implantation of cortical electrodes. Still far from being obvious is determining which stimulation parameters, such as frequency, intensity, and coil localization, account for optimum treatment outcome. The monitoring of rTMS effects with electrophysiological and neuroimaging methods might contribute to a better understanding of neurobiological mechanisms that underlie the clinical effects. This knowledge should result in more individualized treatment protocols in the future.

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