



## **Controversy: Does repetitive transcranial magnetic stimulation/ transcranial direct current stimulation show efficacy in treating tinnitus patients?**

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## Background

Tinnitus affects 10% of the population, its pathophysiology remains incompletely understood, and treatment is elusive. Functional imaging has demonstrated a relationship between the intensity of tinnitus and the degree of reorganization in the auditory cortex. Experimental studies have further shown that tinnitus is associated with synchronized hyperactivity in the auditory cortex. Therefore, targeted modulation of auditory cortex has been proposed as a new therapeutic approach for chronic tinnitus.

## Methods

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are noninvasive methods that can modulate cortical activity. These techniques have been applied in different ways in patients with chronic 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.

## Results

Another approach that uses rTMS as a treatment for tinnitus is application of low-frequency rTMS in repeated sessions, to induce a lasting change of neuronal activity in the auditory cortex beyond the duration of stimulation. 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.

## Conclusions

Even in this early stage of investigation, 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.

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With a prevalence of 10% in the adult population, tinnitus is a very common symptom. Approximately 1% of the population is severely affected by tinnitus with major negative impacts on quality of life.<sup>1</sup> Severe tinnitus is frequently associated with depression, anxiety and insomnia<sup>2,3</sup> and is very difficult to treat.<sup>4</sup> The most frequently used therapies consist of auditory stimulation and cognitive behavioral treatment aiming at improving habituation and coping strategies. However, more causally oriented therapeutic strategies are lacking and need to be developed to relieve auditory perception disturbances.

## Rationale for the application of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) in tinnitus

Even if the pathophysiology of tinnitus remains incompletely understood, there is a growing consensus in the

neuroscientific community that dysfunctional neuroplastic processes in the brain are involved.<sup>5-11</sup> In particular, phenomenologic analogies with deafferentiation or phantom limb pain suggest that chronic tinnitus as an auditory phantom perception might be the correlate of maladaptive attempts of the brain at reorganization because of distorted sensory input.<sup>12</sup> Early support for this concept came from a magnetoencephalography study (MEG) showing reorganization of the auditory cortex with a shift in the tonotopic map of the auditory cortex contralaterally to the tinnitus.<sup>13</sup> Recent 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 asymmetry in the auditory cortices of tinnitus patients with higher levels of spontaneous neuronal activity on the left side, irrespective of tinnitus laterality.<sup>14-16</sup> Other imaging studies revealed additional changes in the middle temporal and temporoparietal regions as well as activation in frontal and limbic areas.<sup>17-20</sup>

Electrophysiologic studies in animal models of tinnitus have shown an increase of firing rate and neuronal synchrony in both the lemniscal and extralemniscal systems.<sup>21-23</sup>

Electroencephalography (EEG) and MEG studies in humans have demonstrated that tinnitus is associated with reduced alpha and increased gamma activity in the contralateral auditory cortex.<sup>24,25</sup> This appears to fit with earlier studies about auditory perception in which it was shown that gamma band activity in the auditory cortex correlates with the conscious perception of auditory signals.<sup>26</sup> Very recent MEG data indicate that the amount of tinnitus-related emotional distress correlates with the degree of synchronicity between temporal and frontal areas<sup>25</sup> and that the tinnitus-related cortical network changes over time with a more widespread distribution and less relevance of auditory areas in longer tinnitus duration.<sup>27</sup>

The model of thalamocortical dysrhythmia, which has been elaborated by Llinas et al,<sup>28</sup> could provide an explanation for the abovementioned findings in tinnitus patients. According to this model thalamic deafferentiation from auditory input, which is associated with hearing loss, may produce slow theta-frequency oscillations in thalamocortical ensembles caused by changes in firing pattern of thalamic relay cells. As an “edge effect,” a reduced lateral inhibition at the cortical level was thought to generate a high-frequency activity in the gamma band (30-50 Hz) that could be the neuronal correlate of the positive symptoms of tinnitus percept.<sup>25,28-30</sup> This in turn may participate to cortical reorganization via simple Hebbian mechanisms<sup>6</sup> and neural plasticity phenomena that occur after sensorial deafferentation and finally results in alterations of the tonotopic maps. However, even if this model of thalamocortical dysrhythmia can provide an explanation for some aspects of tinnitus generation, experimental data for its support are still very limited.

Auditory cortex stimulation using rTMS or tDCS could interfere with cortical oscillations and thereby influence the tinnitus sensation. Moreover, repeated applications of rTMS or tDCS might represent a potential treatment, by producing longer-lasting modulation of cortical activity. This approach is further supported by animal studies that have shown lasting alterations of neuronal activity after rTMS of the visual<sup>31</sup> and auditory cortex.<sup>32</sup> Additional support comes from various clinical trials that used rTMS in the attempt to treat other pathologic conditions with potential cortical hyperactivity such as auditory hallucinations,<sup>33-35</sup> writer's cramp,<sup>36</sup> or obsessive-compulsive disorders.<sup>37</sup>

In tinnitus alterations of neuronal activity have also been suggested in nonauditory brain areas according to pathophysiologic models,<sup>6,38</sup> neuroimaging studies,<sup>17-20</sup> and motor cortex excitability studies using single and paired TMS pulses<sup>39,40</sup>

### Clinical effects of tDCS and rTMS in tinnitus

In recent years an increasing amount of rTMS studies on tinnitus have been published. Study designs and results are

summarized in Tables 1 and 2. Single sessions of rTMS have been performed to transiently disrupt tinnitus perception (Table 1). In these types of studies mainly trains of high-frequency rTMS (10-20 Hz) have been administered to induce an immediate, short-lasting interruption of tinnitus perception. The second approach consists of repeated sessions of rTMS on consecutive days (Table 2). These types of studies mainly use low-frequency (1 Hz) rTMS and aim at inducing a lasting modulation of tinnitus-related neural activity as a potential therapeutic application (Table 2). Other differences in study design consist in the methods for target detection, coil localization, and the control condition.

### Studies using single sessions of tDCS and rTMS

Plewnia et al<sup>41</sup> investigated 14 chronic tinnitus patients to find out whether focal stimulation of different cortical areas can transiently suppress tinnitus. High-frequency rTMS (10 Hz) was applied to 12 different positions over the scalp. A significant reduction of tinnitus was observed when stimulation was administered to the left temporoparietal cortex. This result suggests that the secondary auditory areas (Brodmann area [BA] 42 and 22) are critically involved in tinnitus perception. In a large series of 114 patients with unilateral tinnitus, de Ridder et al<sup>42</sup> investigated tinnitus suppression by different frequencies of rTMS (between 1 and 20 Hz). The coil was placed over the sylvian fissure contralateral to the site of the tinnitus. The large sample allowed the establishment of 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. Higher frequency was more effective than lower frequency for tinnitus of short duration and vice versa and tinnitus with longer duration was more difficult to suppress. Especially the latter result suggests the potential of TMS as a diagnostic tool for differentiating pathophysiologically distinct forms of chronic tinnitus. Two recent studies of Fregni et al<sup>43</sup> and Folmer et al<sup>44</sup> confirmed the findings of transient tinnitus reduction after high-frequency stimulation of the left temporoparietal cortex. Both found similar response rates of patients (42% and 40%) compared with Plewnia's (57%) and de Ridder's (53%) studies. In addition Fregni et al<sup>43</sup> found that the same patients who had significant reduction in tinnitus after rTMS also showed good response to anodal tDCS, applied over the auditory cortex. Interestingly, a single, short-session of excitability-diminishing cathodal tDCS had no effect on tinnitus reduction in this study. Two recent studies combined TMS with different functional imaging techniques: Plewnia et al<sup>20</sup> investigated tinnitus patients in whom tinnitus could be suppressed by an intravenous bolus of lidocaine. By using [<sup>15</sup>O]H<sub>2</sub>O PET before and after lidocaine injection, they identified changes in neuronal activity in the left middle and inferior temporal

(BA 37), in the right temporoparietal cortex (BA 39), and in the posterior cingulum. Then, single sessions of 5-, 15-, and 30-minute low-frequency (1 Hz) rTMS were performed in a sham-controlled design with the coil localized over the brain areas where lidocaine exerted maximal effects. Tinnitus reduction occurred in six of eight subjects and lasted up to 30 minutes. There was a high variability in the treatment results with better efficacy with the longer stimulation protocols and in patients with shorter tinnitus duration. In another recent study,<sup>45</sup> functional magnetic resonance imaging (fMRI) was used for target detection and the effects of high- and low-frequency rTMS were compared in 13 patients. Auditory stimulation with either a text or a musical theme resulted in fMRI activation of the auditory cortex contralateral to the perceived tinnitus. High-frequency rTMS trains over this area resulted only in one patient in any reliable tinnitus suppression. On the other hand, after one long-single train of low-frequency rTMS, the majority of investigated patients reported a reduction of their tinnitus. The duration of effects was highly variable, lasting up to 10 days. It is tempting to conclude from these results that a single session of low-frequency rTMS could provide tinnitus relief for 30 minutes up to several days beyond stimulation, whereas high-frequency rTMS only suppresses tinnitus during the time of stimulation.

Recently the clinical effect of single sessions of theta, alpha, and beta burst rTMS on tinnitus has been investigated.<sup>46,47</sup> Theta burst stimulation has been shown to be more powerful in activating corticospinal excitability than tonic stimulation<sup>48</sup> and bursts may activate neurons that are not activated by tonic stimulations.<sup>49</sup> The effects of both tonic and burst rTMS at frequencies of 5 Hz (theta), 10 Hz (alpha), and 20 Hz (beta) were investigated in 46 patients. The TMS results demonstrated that narrow band/white noise tinnitus was better suppressed with burst rTMS in comparison with tonic rTMS, whereas for pure tone tinnitus, no difference was found between burst and tonic stimulation. On the basis of the hypothesis that white noise/narrow band tinnitus is related to hyperactivity in the nontonotopic (extralemniscal) system, whereas pure tone tinnitus is the result of hyperactivity in the tonotopic (lemniscal) system, it was suggested that burst stimulation modulates both the extralemniscal and lemniscal system, whereas tonic stimulation only affects the lemniscal system. This further indicates that there are different forms of tinnitus, which differ in their pathophysiologic properties.

### Studies using repeated sessions of rTMS

On the basis of some encouraging results in various neuropsychiatric disorders that appeared to be associated with increased cortical activity, repeated sessions of low-frequency rTMS have been proposed to treat patients with disabling tinnitus.<sup>50,51</sup> In these studies fluorodeoxyglucose-PET (FDG-PET) was performed to identify the site of

maximum activation in the auditory cortex. The use of a neuronavigational system allowed the coil to be positioned so that the magnetic field was focused on this target. Stimulation (110% motor threshold, 2000 pulses per day) was applied to three patients in a sham-controlled cross-over design on 5 consecutive days. First, encouraging results were confirmed by a sham-controlled TMS study on 14 patients using the identical study design.<sup>11</sup> A significant decrease in the score of the tinnitus questionnaire could be observed after active treatment, whereas sham treatment had no effect. At 6 months after treatment, 57% of patients reported sustained reduction in tinnitus. However, treatment results were characterized by high-interindividual variability. This motivated a new study, which focused on possible predictors for treatment response.<sup>52</sup> The main result was a significant relationship between tinnitus duration and benefit from treatment. In accordance to other studies,<sup>42,53,54</sup> shorter tinnitus duration was related to a better treatment outcome. Normal hearing has been identified as an additional predictor for favorable treatment outcome. Interestingly, both predictive factors have been demonstrated to be positive outcome predictors in other treatments for tinnitus as well.<sup>55,56</sup>

Plewnia et al<sup>54</sup> investigated a small sample of six lidocaine responsive patients by using a sham-controlled cross-over design with 2 x 2 weeks of rTMS applied over the area of maximum lidocaine-related activity change as determined by [<sup>15</sup>O]H<sub>2</sub>O PET. This sophisticated procedure resulted in stimulation of the temporoparietal cortex (BA22, BA39). There were significant beneficial effects after active stimulation; however, 2 weeks after the last session, these effects were no longer detectable.

Further support for beneficial therapeutic effects of low-frequency rTMS comes from a recent case study.<sup>57</sup> Low-frequency rTMS (1 Hz) was applied on 5 consecutive days (1800 pulses per day) to a patient with a 30-year history of bilateral tinnitus. The coil was navigated over the area of increased cortical activation as identified by 18-FDG-PET within auditory areas. The patient reported beneficial changes in tinnitus perception persisting up to 4 weeks, and there was a statistically significant improvement in objective measures of attention and vigilance. Whereas in this case report, a PET study performed 2 days after rTMS treatment did not show any relevant changes as compared with the baseline scan, a follow-up study by the same group in four patients demonstrated a reduction of metabolic activity in the stimulated area after five sessions of low-frequency rTMS. Furthermore, in all four patients a positive effect on tinnitus and an improvement of psychomotor vigilance was observed.<sup>58</sup>

Whether neuroimaging-guided coil localization is a necessary condition for treatment success of low-frequency rTMS in tinnitus patients has been investigated in a further study.<sup>59</sup> Derived from neuroimaging data an easily applicable method of coil positioning, based on the international 10-20 EEG system has been developed to target the left

**Table 1** Effects of single sessions of rTMS on tinnitus

Authors	N	Stimulation site/coil positioning	Frequency	Intensity	Pulses	Control condition	Results
Plewnia et al <sup>41</sup>	14	Various scalp positions according to 10-20 EEG system	10 Hz	120% MT	30	Stimulation of nonauditory cortical areas	In eight patients (58%) tinnitus suppression after left temporal/temporoparietal stimulation
De Ridder et al <sup>42</sup>	114	Auditory cortex contralateral to tinnitus site	1, 5, 10, 20 Hz,	90% MT	200	Coil angulation	In 60 patients (53%) good or partial tinnitus suppression after active rTMS, in 33% suppression after sham rTMS;
Fregni et al <sup>43</sup>	7	Left temporoparietal areas, according to 10-20 EEG system, anodal and cathodal tDCS of the same area (in addition to rTMS)	10 Hz	120% MT	30	Sham coil and active stimulation of mesial parietal cortex	In three patients (42%) tinnitus suppression after left temporoparietal stimulation, no effect for both control rTMS conditions; anodal tDCS resulted in tinnitus suppression in the same three patients, cathodal tDCS had no effect
Folmer et al <sup>44</sup>	15	Left and right temporal cortex, according to 10-20 EEG system	10 Hz,	100% MT	150	Sham coil	In six patients (40%) tinnitus suppression after active rTMS, in four of the patients after contralateral rTMS in two patients after ipsilat. TMS; in two patients suppression after sham rTMS
Londero et al <sup>45</sup>	13	Auditory cortex as determined by fMRI,	1, 10 Hz	120% MT	30	Stimulation over nonauditory cortical areas	Eight patients were stimulated over the auditory cortex with 1 Hz; in five of them (62,5%) tinnitus suppression; no suppression after 1 Hz rTMS of nonauditory targets; no suppression after 10 Hz, in two patients suppression after stimulation of a control position

Plewnia et al <sup>20</sup>	8	Area of maximum tinnitus related PET activation (temporoparietal cortex), neuronavigational system	1 Hz	120% MT	300, 900, 1800	Control position (occipital cortex)	In six patients (75%) tinnitus reduction after active rTMS, better suppression with more pulses,
De Ridder et al <sup>46,47</sup>	46	Auditory cortex contralateral to tinnitus site	5, 10, 20 Hz tonic; 5, 10, 20 Hz burst	90%MT	200	Coil angulation	14 placebo-negative patients were analyzed. In those with narrow band/white noise tinnitus burst TMS was more effective in tinnitus suppression as compared with tonic TMS, whereas for pure tone tinnitus no difference was found between burst and tonic.

EEG, electroencephalogram; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; fMRI, functional magnetic resonance imaging; PET, positron emission tomography.

auditory cortex. A significant reduction of tinnitus severity after 10 sessions of 1 Hz rTMS supported the accuracy of this method of coil positioning. Interestingly, a case study that investigated systematically the optimal coil position for tinnitus reduction over the temporal region, resulted in a very similar position, however on the right side.<sup>60</sup>

A very recent study addressed the question whether the clinical effects of rTMS on tinnitus might be mediated by rhythmic stimulation of peripheral nerves, because transcutaneous electric nerve stimulation (TENS) was previously shown to improve tinnitus<sup>61</sup> or whether the effects might be secondary to potential antidepressant effects of rTMS.<sup>62</sup> In this cross-over study the control condition included the electrical stimulation of the facial nerve, whereas depression scales were administered in addition to tinnitus assessment with visual analogue scales (VAS) scores. A significant improvement of tinnitus was found in the active and not in the control condition, demonstrating that rTMS efficacy was independent from the peripheral stimulation of sensory afferents. Improvement of tinnitus was also found to be independent from mood changes.

Khedr et al<sup>63</sup> compared in a large study the effects of different frequencies of stimulation. Whereas sham rTMS treatment had no effect, active stimulation over the left temporoparietal cortex resulted in a reduction of tinnitus regardless stimulation frequency (1 Hz, 10 Hz, and 25 Hz). Tinnitus relief was still detectable 4 months after treatment. In contrast to these results, no reduction of tinnitus was observed in a recent open study that investigated the effect of 5 days of 0.5 Hz to the left temporoparietal cortex.<sup>64</sup> The negative result might be due to the rather low number of TMS stimuli (600) per session.

Because the effect of 1 Hz rTMS on motor corticospinal output (MEP amplitude) was found to be enhanced by priming stimulation with 6 Hz, Langguth et al<sup>65</sup> compared in a series of patients with tinnitus a standard protocol of 1 Hz with a priming stimulation protocol in which 1 Hz rTMS was administered after 6 Hz rTMS. Both treatment protocols resulted in a reduction in tinnitus severity, without any difference between the unconditioned and the primed conditions.<sup>66</sup> The same group also studied whether a preceding stimulation performed at high frequency over the left prefrontal cortex could modify the efficacy of a subsequent stimulation performed at low frequency over a left temporal target as usual. Short-term assessment revealed similar rTMS effects on tinnitus, whatever the application of a preceding prefrontal stimulation. Conversely, 3 months after stimulation time, clinical assessment showed a remarkable benefit in favor of the combined prefrontal and temporal rTMS treatment.<sup>67</sup>

Regarding tDCS no studies, including repeated tDCS sessions, for the treatment of tinnitus have been published so far. However, because tDCS can induce sustained changes in regional brain activity<sup>68</sup> and has also shown relatively long-term clinical benefits in major depression<sup>69</sup> or chronic pain,<sup>70</sup> it might represent another promising

**Table 2** Effects of repeated sessions of rTMS in tinnitus patients

Authors	N	Stimulation site / coil positioning	Frequency	Intensity	Sessions	Pulses / session	Design	Control condition	Results
Kleinjung et al <sup>15</sup>	14	Area of maximal PET activation in the temporal cortex, neuronavigational system	1 Hz,	110% MT	5	2000	Sham-controlled, cross-over	Sham coil	Significant reduction of tinnitus after active rTMS as compared with sham rTMS; lasting tinnitus reduction (6 mo)
Langguth et al <sup>60</sup>	28	Left auditory cortex, according to 10-20 EEG system	1 Hz	110% MT	10	2000	open	No control condition	Significant reduction of tinnitus until end of follow-up (3 mo)
Plewnia et al <sup>55</sup>	6	Area of maximum tinnitus related PET activation (temporoparietal cortex), neuronavigational system	1 Hz	120% MT	10	1800	Sham-controlled, cross-over	Occipital cortex	Significant reduction of tinnitus after active rTMS, as compared with the control condition; no lasting effects
Kleinjung et al <sup>53</sup>	45	Left auditory cortex, neuronavigational system	1 Hz	110% MT	10	2000	open	No control condition	Significant tinnitus reduction after rTMS, lasting during follow-up period (3 mo) responders were characterized by shorter tinnitus duration and less hearing impairment
Rossi et al <sup>63</sup>	16	Left temporoparietal cortex, neuronavigational system / according to 10-20 EEG system	1 Hz	120% MT	5	1200	Sham-controlled, cross-over	Coil angulation + electrical stimulation of facial nerve	Significant reduction of tinnitus after active rTMS, as compared with the control condition, no lasting effects
Smith et al <sup>59</sup>	4	Area of maximal PET activation in the temporal cortex, neuronavigational system	1 Hz	110% MT	5	1800	Sham-controlled, cross-over	Coil angulation	Modest response to active treatment in three patients (75%)
Khedr et al <sup>64</sup>	56	Left temporoparietal cortex, according to 10-20 EEG system	1 Hz, 10 Hz, 25 Hz	100% MT	10	1500	Sham-controlled, parallel group design	Occipital cortex	Significant reduction of tinnitus after all three active rTMS conditions, as compared with the control condition; tinnitus reduction lasting during follow-up period (4 mo)
Langguth et al <sup>67</sup>	32	Left auditory cortex, neuronavigational system	1 Hz, 6 Hz + 1 Hz	110% MT (90% MT for 6 Hz rTMS)	10	2000	Randomization between two active treatment conditions, parallel group design	No sham control condition	Significant improvement for both stimulation conditions, no difference between conditions, no lasting effects

Lee et al <sup>65</sup>	8	Left temporoparietal cortex	0,5 HzHzH	100%MT	5	600	Open study	No control condition	No significant reduction of tinnitus
Kleinjung et al <sup>68</sup>	32	Left auditory cortex, neuronavigational system; left dorsolateral prefrontal cortex	1 Hz, 20 Hz (DLPFC) + 1 Hz	110%MT	10	2000	Two active treatment conditions, parallel group design	No sham control condition	Directly after stimulation significant improvement for both stimulation conditions, at 3-mo follow-up significantly better results for the combined frontal and temporal stimulation

PET, positron emission tomography; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; EEG, electroencephalogram; DLPFC, dorsolateral prefrontal cortex.

treatment approach for chronic tinnitus. Nonetheless, the mechanisms of action of tDCS and rTMS are likely different, the former being a purely neuromodulatory intervention whereas the latter exerting both, neurostimulatory and neuromodulatory effects.<sup>71</sup>

### Safety

Given extensive clinical experience in other indications, it can be said that rTMS in general is a safe and well-tolerated method of treatment. The risk of high-intensity and high-frequency rTMS-induced epileptic seizures, which had been reported in individual cases, has been largely reduced since the introduction of safety guidelines.<sup>72</sup> Safety studies reported no deterioration in neuropsychologic performance, no significant mean changes in auditory threshold, and no significant abnormality in EEG after 2-4 weeks of rTMS.<sup>73-75</sup> It is essential that contraindications such as electronic implants (for example, cardiac pace makers), intracranial pieces of metal or previous epileptic seizures are considered. Light local sensations of pain during stimulation or transient headache after stimulation are reported by about 10-20% of stimulated patients. With respect to temporal or temporoparietal stimulation for tinnitus, no specific side effects have been reported; however, the number of treated patients is still relatively small and most studies did not assess systematically potential subclinical side effects, for example, by audiometry or neuropsychologic tests. In case of decreased sound tolerance (hyperacusis), emitted noise during rTMS stimulation might be uncomfortable to some patients. For this reason and also to avoid potential noise trauma, ears plugs were offered to patients in most studies. Interestingly a reactivation and an increase of tinnitus has been reported as a side effect of prefrontal rTMS in patients with depression.<sup>76</sup>

The safety of tDCS has been addressed in a considerable number of studies. So far there has been no evidence of brain tissue damages induced by tDCS as currently conducted in humans, verified by EEG, contrast-enhanced MRI, and serum neurone-specific enolase levels. However, stimulation with higher currents and longer duration might induce adverse effects on the brain and therefore safety guidelines have been recently established.<sup>77</sup>

### Methodologic considerations

#### The role of coil placement

Practically all studies thus far have targeted temporal or temporoparietal cortical areas. However, the methods for coil placement have varied across studies, ranging from highly sophisticated neuronavigation-based techniques to easy applicable methods. Most studies used neuronavigation-guided coil localization based on different functional

neuroimaging techniques to target areas of tinnitus-related changes in brain activity.<sup>15,20,45,50,54</sup> However, results from different functional imaging techniques that have been used for target detection (FDG-PET, H<sub>2</sub>O-PET with lidocaine and functional MRI) were not identical: FDG-PET studies demonstrated increased metabolic activity in the left temporal lobe in the majority of the patients, independent from the laterality of the perceived tinnitus<sup>14-16</sup>; H<sub>2</sub>O-PET with lidocaine resulted in tinnitus related activity in temporoparietal regions,<sup>20,78</sup> and fMRI has shown activation in the auditory cortex contralateral to the perceived tinnitus.<sup>45</sup> These divergent results are probably because of crucial differences between the different imaging approaches: FDG-PET relies on permanent alterations of metabolism, whereas auditory stimulation in the fMRI gives information about alterations of neuronal processing in the auditory system. The measurement of changes of cerebral blood flow with H<sub>2</sub>O-PET during lidocaine-based suppression of tinnitus allows a direct “on-off” comparison; however, activation changes reflecting tinnitus perception have to be differentiated from unspecific lidocaine effects on cerebral blood flow.<sup>78</sup> Furthermore, only a subgroup of tinnitus patients respond to lidocaine, H<sub>2</sub>O-PET is only available in few centers and the intravenous application of lidocaine needs special monitoring of cardiovascular parameters. Therefore, at the moment no definitive conclusion regarding the optimal imaging method to define the TMS target for tinnitus can be drawn from currently available data. Thus, more sophisticated imaging studies to guide the placement of the TMS coil and thus define the brain region to target seem desirable.

Also, in those studies in which coil localization was not based on individual functional imaging data the laterality of stimulation varied between stimulation on the left side in all patients and stimulation contralateral to tinnitus laterality. Some of these studies used a neuronavigation system in combination with structural imaging data, focusing on the primary auditory cortex.<sup>52,66</sup> Easier applicable techniques include coil localisation according to the 10-20 EEG coordinate system<sup>41,43,44,59,63</sup> and optimization techniques based on clinical effects.<sup>42,57,60</sup>

When comparing the different methods for target detection and coil placement, it has to be considered that placing the magnetic coil over the sylvian fissure and targeting the primary auditory cortex does not necessarily result in stimulation of the primary auditory cortex. Because the primary auditory cortex is located in mediolateral direction in the sylvian fissure, the magnetic field rather spreads in the more superficial secondary or tertiary auditory areas. This is similar to what has been described for electrical stimulation of the auditory cortex via extradural stimulation.<sup>53,79</sup> As the applied current of the electrical stimulation only penetrates millimeters deep, it cannot reach the auditory cortex directly. The tinnitus suppressing effect of this form of stimulation has been explained by activation of the functional connections that exist between the secondary

auditory cortex, which can be reached directly by the current, and primary auditory cortex.<sup>53</sup> This also might explain, that based on the available studies there is no hint that one of the coil localization techniques is much superior to others. However, no study compared directly the different coil localization strategies, and a comparison across the studies is difficult because of further differences in the study designs.

Because the optimal coil placement strategy is still a matter of debate, further studies are needed, which directly compare different coil localization strategies. Even comparison of noninvasive with invasive stimulation strategies is complex on a variety of methodologic differences, it is noteworthy that for tinnitus suppression by direct electrical stimulation of the secondary auditory cortex the localization of the implanted epidural electrodes is critical.<sup>79</sup> Therefore, better knowledge about the optimal coil placement might improve rTMS treatment outcome significantly.

### Study design and control condition

Evaluation of treatment efficacy in patients with chronic subjective tinnitus requires adequate methodology to control for unspecific treatment effects. The majority of controlled studies, published so far, have used cross-over designs with the inconvenience of limited observation periods and carry-over effects as potential confounding factors. Therefore, further studies using parallel group designs are needed.<sup>80</sup>

Different methods have been used as placebo conditions in TMS studies: Sham stimulation has been performed (1) by angulation of the active magnetic coil 45° or 90° away from the skull, (2) by using a so called “sham-coil system”, which mimics the sound of a real coil without generating any magnetic field, (3) by stimulating nonauditory brain areas, and (4) by stimulating head- or neck-muscles without reaching brain areas.

Coil angulation has the inconvenience that a weak magnetic field effect on the brain cannot be entirely excluded.<sup>81</sup> On the other side, this technique has the advantage to produce skull sensations and thus a somatosensory stimulation, which is similar to the active rTMS condition. In contrast, the use of a sham coil does not elicit a skull sensation. This fact might be important because stimulation of peripheral nerve structures was discussed to contribute to tinnitus improvement.<sup>61,82</sup> Furthermore, in terms of blinding conditions, it is easier for patients to guess whether they receive active or sham TMS application. Stimulation of nonauditory brain areas as control condition is problematic because tinnitus-related changes in brain activity are not restricted to the auditory cortex<sup>17-20,27</sup> and therefore this technique cannot be considered as an inactive condition. Stimulation to nonbrain areas (for example, the insertion of the sternocleidomastoideus muscle) as proposed by Plewnia et al<sup>20,41,54</sup> has the advantage to control for peripheral stimulation effects. This approach has been further

developed by Rossi et al<sup>62</sup> who presented a control condition, which includes electrical stimulation of the facial nerve.

All methods have in common the limitation that the medical staff who apply stimulation are not blinded. In addition, the blinding of the patient is at best limited, particularly in cross-over designs, in which the patient can directly compare the different stimulation conditions. Recent advances in sham stimulation systems<sup>83-86</sup> might provide better control conditions, with respect to both, patient and operator blinding.

Another important issue in this context is the fact that TMS itself is a method of multimodal sensory stimulation. In addition to the actual brain site specific effects that it can induce, stimulation from TMS further gives rise to (among others), auditory sensations, somatosensory and tactile stimulation, potential startle effects, and even visual percepts in the form of phosphenes. All of these effects are dependent largely on the site and intensity of the stimulation being delivered. Completely eliminating the multimodal nature of stimulation associated with TMS is not possible. In the context of tinnitus, in addition to the specific stimulation effect on the brain, a variety of less specific effects such as startle effect, auditory or somatosensory sensations, or a combination of them could contribute to modify the perception of tinnitus. Thus, the multisensory nature of TMS needs to be considered and controlled for. Therefore, strategies need to be developed to control for these potential confounds to minimize the risk of misinterpretation of findings and drawing erroneous conclusions.

## Patient assessment and outcome measurement

Validated tinnitus questionnaires and VAS scales serve as primary outcome measurement in the majority of studies.<sup>87</sup> By quantifying the tinnitus severity, these methods determine whether rTMS-induced changes reach statistical significance, but it is not clear which amount of change is of clinical relevance. The additional use of a clinical global impression scale (CGI) may represent a first step in this direction.<sup>54</sup>

The development of objective markers for the assessment of treatment outcome is highly desirable. Because the tinnitus severity, disability, or annoyance does not correlate with tinnitus loudness or other psychoacoustic measurements,<sup>88</sup> these methods are only of limited use. Future progress in neuroimaging techniques might provide objective, comparable, and reproducible methods for monitoring therapeutic effects in tinnitus treatment studies.<sup>58</sup>

## Synopsis

There is increasing evidence from a growing amount of studies that show that modulation of cortical activity by rTMS results in alteration of tinnitus sensation. Even if all studies are characterized by high interindividual variability

of rTMS effects, the rate of responders converges across studies around 50%. Further comparison of study results is limited by multiple distinctions in study design, stimulation parameters, and patient populations.

## rTMS for tinnitus subtyping

High-frequency rTMS provides short-lasting reduction of tinnitus sensation as a robust result across studies in about 50% of investigated tinnitus sufferers. However, it has also been stated that available data do not allow final conclusions about the degree to which unspecific factors such as auditory masking, somatosensory sensations, or startle contribute to the short-lasting tinnitus suppression of single sessions of rTMS. Nevertheless, the finding that tinnitus suppression by rTMS depends on tinnitus characteristics, such as frequency width or duration, suggests the potential of rTMS as a tool for differentiating pathophysiologically distinct types of tinnitus. Moreover, this method has already been introduced as a diagnostic instrument: de Ridder et al<sup>42,53,79,89</sup> performed short trains of high-frequency rTMS as a screening method to select patients for surgical implantation of cortical electrodes. Patients responding twice in a placebo-controlled way on two separate times to this type of rTMS with a short-lasting suppression of tinnitus perception were considered as good surgical candidates for a permanent electrical stimulation of the auditory cortex. Even if these findings open up an interesting perspective, further research is needed before further conclusions about the diagnostic value of this method can be drawn.

## rTMS for the treatment of tinnitus

Most rTMS treatment studies applied low-frequency rTMS in long trains of 1200-2000 pulses repeatedly over 5-10 days. Beneficial clinical effects were observed in about 50% of treated subjects (Table 2). Only one very recent study with a relatively low number of stimuli (600 per day) was negative.<sup>64</sup> This finding might support the notion that attenuation of tinnitus is dose dependent.<sup>20</sup> Another recent study investigated the effect of repeated sessions of high-frequency rTMS. Even if results of this study are promising, replication by further studies is needed, before further conclusions about the therapeutic potential of high-frequency rTMS can be drawn.

Whereas some studies demonstrated effects that outlast the stimulation period by 3, 4, or 6 months, others were not able to observe lasting effects. The number of daily sessions may be an important issue to achieve sustained results in tinnitus patients,<sup>51</sup> as already seen in other TMS applications, such as depression<sup>90</sup> and auditory hallucinations.<sup>34,91</sup> Even if the observation of outlasting clinical effects is supported by recent findings of structural changes in the temporal cortex after one week of low frequency rTMS,<sup>92</sup> available clinical data are not sufficient to estimate the endurance of treatment effects.

The high variability of treatment results, which is encountered in all studies, supports the notion of neurobiologically distinct subtypes of tinnitus. This, in turn, implies that no single approach will be successful in every patient. In this context standardized assessment of patient characteristics for the identification of treatment predictors is of utmost importance.<sup>87</sup> Several rTMS studies indicate that treatment response depends on tinnitus duration with better outcome for shorter duration.<sup>42,52,54,63</sup> Hearing impairment has been identified as a negative predictor in one study.<sup>52</sup> Deprivation from auditory input is assumed to induce disinhibition in the central auditory system, which in turn is believed to be critically involved in the pathophysiology of tinnitus.<sup>87</sup> In this context, a high degree of hearing impairment might attenuate rTMS effects by perpetually triggering neuroplastic changes in central auditory structures.<sup>93</sup> More research is needed for identifying further clinical and neurobiologic predictors for treatment outcome. This might even result in more individualized treatment protocols.

### Neurobiologic mechanisms of rTMS

Even if there is accumulating evidence that rTMS interferes with neuronal mechanisms involved in the pathophysiology of some forms of tinnitus, the exact mechanisms of action of the different applications are not clear. Because both animal data<sup>32,94-95</sup> and longitudinal imaging or electrophysiologic data before and after temporal rTMS in control and tinnitus subjects are still very limited,<sup>51,57,58,92,96,97</sup> assumptions about the underlying neurobiologic effects remain speculative because they are mainly based on analogies with direct electrical stimulation in animals or on knowledge about rTMS effects on motor cortex excitability. Based on these data,<sup>98</sup> it has been assumed that low-frequency rTMS exerts its effects by inducing long-term depression-like effects.<sup>96,97</sup> However, whereas long-term depression-like effects should be more pronounced when areas of increased excitability are stimulated,<sup>98,99</sup> in tinnitus patients enhanced activity of the stimulated area seems not to increase TMS effects.<sup>16,20,66</sup> 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. This hypothesis is supported by the recent study of Khedr et al,<sup>63</sup> which indicates that rTMS effects in tinnitus treatment do not critically depend on stimulation frequency. Also, it is not clear whether TMS exerts its effects primarily in the directly stimulated area or whether the clinical effects are mediated by changes in more remote areas. Available electrophysiologic and imaging data suggest that TMS over the temporal cortex might modulate thalamocortical processing.<sup>92,96,97</sup> Another open question is how much the multimodal nature of TMS effects contributes to the observed clinical effects. Especially the combination of peripheral and central auditory stimulation might be of relevance.

### tDCS and tinnitus

Experience with tDCS in tinnitus is limited to one single study with a small sample size.<sup>43</sup> However, based on these pilot data and the knowledge about its mechanisms, tDCS might represent another promising new approach for the treatment of tinnitus.<sup>100</sup> Potential targets of interest include the temporal and temporoparietal cortex, but also prefrontal areas.<sup>69,71</sup> tDCS has some advantages as this technique does not induce noise nor muscle contractions (as rTMS does), therefore not adding potential confounders to the outcome. Also, it is a device that can be used as a portable device, therefore offering a potential noninvasive solution for long-term use. Finally, it offers a reliable sham condition for double-blind clinical trials as shown by a previous study.<sup>101</sup>

### Conclusions

Despite being encouraging, results from available rTMS treatment studies have to be considered as preliminary because of the small sample sizes, the methodologic heterogeneity and the high variability of results. Replication of data in multicenter trials with a large number of patients and long-term follow-up is needed<sup>80</sup> before further conclusions can be drawn. Furthermore it is far from being clear which stimulation parameters are the optimum ones. Using rTMS in combination with electrophysiologic and neuroimaging methods might allow light to be shed on the neurobiologic mechanisms, which account for the clinical effects. This knowledge, in turn, can contribute to optimizing stimulation parameters such as frequency, intensity, and coil localization. Furthermore delineation of neurobiologically distinct subgroups by imaging methods seems promising to increasing treatment efficacy by developing more individualized treatment protocols. In summarizing, available data indicate a promising potential of rTMS for therapeutic management of tinnitus. However, further clinical and neurobiologic research is needed before rTMS can be considered as a treatment option for routine use.

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