CHAPTER 11

Transcranial Magnetic Stimulation for Tinnitus

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TINNITUS: INTRODUCTION

Tinnitus refers to a condition in which a patient has a hearing percept that can take the form of ringing, buzzing, roaring or hissing (among others) in the absence of an external sound (Eggermont, 2007; A. R. Moller, 2007b). Tinnitus can be classified as being either objective or subjective. In the objective form, which is rare, a real sound is generated by an internal biological source, reaching the ear through conduction in body tissues. The source can be vascular turbulence, pulsations or spasm of the muscles in the middle ear, Eustachian tube or soft palate. Unlike subjective tinnitus, an observer, using a stethoscope, can often hear objective tinnitus. Subjective tinnitus refers to a phantom auditory sensation for which no objective sound can be identified and only the person who has the tinnitus can hear it. Some patients perceive the phantom sound as

Neurofeedback and Neuromodulation Techniques and Applications
DOI: 10.1016/B978-0-12-382235-2.00011-1

coming from inside the ear, others report that the phantom sound is located inside the head, while a few perceive the phantom sound as coming from outside the head. Some patients experience bilateral tinnitus, while others hear it in just one ear. Subjective tinnitus is by far more prevalent than objective tinnitus and is the subject of this present chapter.

Subjective tinnitus is often associated with a lesion of the peripheral auditory system, such as presbyacusis, Menière's disease, noise trauma, sudden deafness or drug-related ototoxicity (Eggermont, 2007). However these pathologies are not directly causing tinnitus. Rather the neuroplastic changes that occur in the brain as reaction to sensory deafferentation represent the neural correlate of tinnitus (A. R. Moller, 2007a). Thus, the mechanisms involved in tinnitus generation share similarities with those responsible for phantom pain after limb amputation (A. R. Moller, 2007a).

With a prevalence of 10% in the adult population, tinnitus is a very common symptom (Axelsson & Ringdahl, 1989). Approximately 1 percent of the population is severely affected by tinnitus with major negative impacts on quality of life (Axelsson & Ringdahl, 1989). Severe tinnitus is frequently associated with depression, anxiety, and insomnia (Cronlein, Langguth, Geisler, & Hajak, 2007; Dobie, 2003; Langguth et al., 2007) and is very difficult to treat (Dobie, 1999). The most frequently used therapy techniques consist of auditory stimulation and cognitive behavioral treatment that improve habituation and coping strategies. However, more causally oriented treatment strategies are missing. Therefore, new treatment strategies need to be developed, which directly act on the pathophysiological mechanisms that cause the auditory phantom perception phenomenon.

Even if the pathophysiology of the different forms of tinnitus is still incompletely understood, there is growing consensus in the neuroscientific community that chronic tinnitus as an auditory phantom perception might be the correlate of maladaptive attempts of the brain at reorganization due to distorted sensory input (A. R. Moller, 2007a).

In animal models a large variety of neuroplastic changes have been demonstrated after sensory deafferentation, including an increased neuronal firing rate, increased neural synchronicity, and alterations of the tonotopic map (Eggermont, 2007). These findings are paralleled by results from functional imaging and electrophysiological studies in tinnitus patients where functional and structural alterations in the central auditory system have been observed. Both positron emission tomography (PET) (Arnold, Bartenstein, Oestreicher, Romer, & Schwaiger, 1996; Giraud et al., 1999; Lanting, de Kleine, & van Dijk, 2009; Lockwood et al.,

1999; Lockwood et al., 2000) and functional magnetic resonance imaging (fMRI) (Lanting et al., 2009; Melcher, Sigalovsky, Guinan, & Levine, 2000; Smits et al., 2007) have demonstrated changes of neuronal activity in central auditory pathways in tinnitus patients. Electroencephalography (EEG) and magnetoencephalography (MEG) data have shown a reduction of alpha power and an increase in slow waves and in gamma activity in auditory areas (Llinas, Ribary, Jeanmonod, Kronberg, & Mitra, 1999; Lorenz, Muller, Schlee, Hartmann, & Weisz, 2009; van der Loo et al., 2009; Weisz et al., 2007). The model of thalamocortical dysrhythmia, which has been elaborated by Llinas and colleagues (Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005; Llinas et al., 1999), provides an explanation for the findings in tinnitus patients. According to this model, thalamic deafferentiation from auditory input, e.g. due to hearing loss, may produce slow theta-frequency oscillations in thalamocortical ensembles due to changes in firing patterns of thalamic relay cells. As a consequence, reduced lateral inhibition at the cortical level is thought to generate high-frequency activity in the gamma band that could be the neuronal correlate of the tinnitus percept (Llinas et al., 2005, 2009). This increased synchronized firing in the gamma band together with decreased lateral inhibition after deafferentation may induce cortical reorganization via a simple Hebbian mechanisms (Eggermont & Roberts, 2004) and neural plasticity which finally results in alterations of the tonotopic map. Such a shift in the tonotopic map has been demonstrated at the tinnitus frequency by magnetic source imaging (Muhlnickel, Elbert, Taub, & Flor, 1998).

However, imaging studies in patients with impaired consciousness clearly demonstrate that activity in the auditory cortex is not sufficient for conscious auditory perception (Boly et al., 2004). Persisting connectivity with frontal and temporoparietal areas is required for conscious auditory processing. Increased activity in frontal and temporoparietal areas has been identified by functional imaging studies in tinnitus patients (Andersson et al., 2000; Giraud et al., 1999; Lockwood et al., 1998; Mirz et al., 2000; Plewnia, Reimold, Najib, Brehm et al., 2007). Based on the clinical analogies between tinnitus distress and pain distress and based on neuroimaging data it is tempting to speculate that the tinnitus distress network and the pain matrix involve similar brain structures (Moisset & Bouhassira, 2007). Unpleasantness of pain activates the anterior cingulate (Price, 2000) and orbitofrontal cortices, amygdala, hypothalamus, posterior insula, primary motor cortex, and frontal pole (Kulkarni et al., 2005). One may

further speculate that the perception of tinnitus and pain intensity could be related to auditory and somatosensory cortex activation, respectively, but that the distress associated with its perception might be related to activation of a common general non-specific "distress network". This notion is supported by a recent study which demonstrates activation of this distress network during unpleasant symptoms in a somatoform disorder, even in the absence of a real physical stimulus (Landgrebe, Barta et al., 2008). Furthermore, distress due to dyspnoea in asthma activates the same network (von Leupoldt et al., 2009).

Even though no specific studies have been performed for selectively identifying neural activation underlying tinnitus distress, PET studies comparing tinnitus patients and healthy controls have demonstrated activation of brain areas such as anterior cingulate (ACC) (Plewnia, Reimold, Najib, Reischl, Plontke, & Gerloff, 2007) or the anterior insula (Lockwood et al., 1998).

Synchronization analysis based on MEG data has shown that functional connectivity between ACC and right frontal lobe is correlated to tinnitus intrusiveness, a measure of tinnitus distress (Schlee, Weisz, Bertrand, Hartmann, & Elbert, 2008). A recent MEG study looking at phase-locked connectivity in the tinnitus network suggests that the tinnitus network changes over time (Schlee, Hartmann, Langguth, & Weisz, 2009). In patients with a tinnitus history of less than 4 years, the left temporal cortex was predominant in the gamma network whereas in patients with tinnitus duration of more than 4 years the gamma network was more widely distributed, including more frontal and parietal regions (Schlee, Hartmann et al., 2009).

Even if the central auditory system has been the primary focus of interest of neurobiological tinnitus research, theoretical considerations, pathophysiological models of tinnitus (Jastreboff, 1990; Jastreboff, Brennan, & Sasaki, 1988; Moller, 1994, 2003) and neuroimaging data (Giraud et al., 1999; Lockwood et al., 1998, 1999; Mirz et al., 2000; Plewnia, Reimold, Najib, Brehm et al., 2007) all support critical involvement of non-auditory brain areas in the pathophysiology of chronic tinnitus.

TRANSCRANIAL MAGNETIC STIMULATION

In 1985 Barker and colleagues demonstrated that it is possible to depolarize neurons in the brain using external magnetic stimulation (Barker, Jalinous, & Freeston, 1985).

The stimulator delivers a short-lasting (100–300 μs) high current pulse in an insulated coil of wire, which is placed above the skull over the region

of particular interest. This induces a magnetic field (1.5−2 Tesla) perpendicular to the coil which penetrates the scalp and brain with little impedance. An electrical field is induced perpendicular 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 maximal current at the intersection of the two round components (Ridding & Rothwell, 1997). Due to the strong decline of the magnetic field with increasing distance from the coil, direct stimulation effects are limited to superficial cortical areas. However, stimulation effects can be propagated to functionally connected remote areas.

Whereas single magnetic pulses do not seem to have longer-lasting effects, the application of multiple pulses in rhythmic sessions, called repetitive transcranial magnetic stimulation (rTMS), can have effects that outlast the stimulation period. These effects resemble those seen in animal experiments where repeated stimulation of many pathways has been shown to produce changes in the effectiveness of synapses in the same circuits (Post & Keck, 2001). Low frequency ($\leq$1 Hz) rTMS has been repeatedly shown to result in a decrease in cortical excitability (Hallett, 2000; Hoffman & Cavus, 2002), whereas high-frequency (5−20 Hz) rTMS results in an increase in excitability (Pascual-Leone, Grafman, & Hallett, 1994). Low-frequency and high-frequency TMS of the auditory cortex have been linked to long-term potentiation and long-term depression (LTP and LTD) respectively (Wang, Wang, & Scheich, 1996), which are thought to be important in learning and memory (Wang et al., 1996).

rTMS can also be used to transiently disturb on-going neural activity in the stimulated cortical area, thus creating a transient functional lesion. Such an approach can help to identify whether a given brain area is critically involved in a specific behavioral task.

Because of these unique and powerful features, rTMS became increasingly popular in various fields, including cognitive neuroscience and clinical application (for review see Simons & Dierick, 2005; Walsh & Rushworth, 1999). However, despite its utility, the exact mechanisms of how rTMS stimulates neurons and interferes with neural functions are still incompletely understood (Ridding & Rothwell, 1997).

Rationale for the Use of Neuromodulation in Investigation, Diagnosis, and Treatment of Tinnitus

As described before, the phantom perception of sound seems to be a consequence of altered activity in the central nervous system. An increasing

number of animal and human studies have contributed to a more and more detailed identification of the neural correlate of tinnitus. In short, alterations of neural firing and oscillatory activity (Llinas et al., 1999, 2005; van der Loo et al., 2009; Weisz et al., 2007), alterations of neural synchrony (Seki & Eggermont, 2003) and changes in the tonotopic maps (Muhlnickel et al., 1998) have been observed. These changes are not restricted to one specific brain area. Rather they can be conceived as alterations of a network involving auditory and non-auditory brain areas (Schlee et al., 2008; Schlee, Hartmann et al., 2009; Schlee, Mueller, Hartmann, Keil, Lorenz, & Weisz, 2009). These changes of neural activity seem to arise from dysfunctional plastic responses to altered sensory input, which is auditory deprivation in most cases (Norena, Micheyl, Chery-Croze, & Collet, 2002; Norena & Eggermont, 2005, 2006). Frontal and parietal brain areas seem to have an important modulatory role (Lockwood et al., 1998; Schlee, Hartmann et al., 2009). However, neuroimaging studies represent only a correlative approach with its inherent limitations. Thus it remains unclear whether the observed alterations are critically involved in the pathophysiology or whether they represent epiphenomena. Interfering with neural activity in these regions with single sessions of rTMS can be used as a non-invasive test to probe their relevance for the pathophysiology of tinnitus (Plewnia, Bartels, & Gerloff, 2003). This method can potentially also be further developed as a diagnostic test to differentiate pathophysiologically distinct forms of tinnitus.

Any causally oriented therapy of tinnitus should aim at normalizing the tinnitus-related disturbed neuronal network activity. In principle there are two possibilities. The first approach consists of restoring the disturbed auditory input to the auditory cortex. This can be done indirectly by hearing aids (Moffat et al., 2009), cochlear (Brackmann, 1981; Van de Heyning et al., 2008), auditory nerve (Holm, Staal, Mooij, & Albers, 2005), and brainstem implants (Soussi & Otto, 1994) which have all been shown to improve tinnitus in selected patients. Another option is to supply the missing information directly to the auditory cortex (De Ridder & Van de Heyning, 2007) or to interfere with the distributed "tinnitus network" directly. This can be done at the auditory cortex by implanted electrodes (De Ridder, De Mulder, Menovsky, Sunaert, & Kovacs, 2007; De Ridder, De Mulder, Verstraeten et al., 2007; De Ridder et al., 2006; De Ridder et al., 2004; Friedland et al., 2007; Seidman et al., 2008), tDCS (Fregni et al., 2006; Vanneste et al., 2010) or rTMS (De Ridder et al., 2005; Khedr, Rothwell, & El-Atar, 2009; Kleinjung et al., 2005;

Londero, Langguth, De Ridder, Bonfils, & Lefaucheur, 2006) or potentially at other hubs of the distributed "tinnitus network" (Schlee, Hartmann et al., 2009; Schlee, Mueller et al., 2009), or combined (Kleinjung, Vielsmeier, Landgrebe, Hajak, & Langguth, 2008). Also neurofeedback has been proposed to normalize pathological oscillatory activity directly (EEG-based) (Dohrmann, Weisz, Schlee, Hartmann, & Elbert, 2007) or indirectly (fMRI-based) (Haller, Birbaumer, & Veit, 2010). Whereas stimulation by implanted electrodes or pharmacotherapy can be performed permanently, rTMS, tDCS or neurofeedback can only be applied for a limited amount of time. Nevertheless these methods hold therapeutic potential, since all of them can induce plastic changes which outlast the treatment period (Allen, Pasley, Duong, & Freeman, 2007; Wang et al., 1996). These long-lasting effects with limited treatment time can be either explained by learning-like effects, or by the disruption of dysfunctional networks, which then allow the re-establishment of a more physiological state.

Single Sessions of rTMS

Within the last years several studies with single sessions of rTMS have been performed with the goal to transiently reduce tinnitus perception (see Table 11.1). In these types of studies, results were largely based on the administration of high-frequency rTMS (10−20 Hz). In a pilot trial, stimulation of the left temporoparietal cortex with high-frequency rTMS (10 Hz) resulted in a transient reduction of tinnitus in 57% of the participants (Plewnia et al., 2003). This result has been confirmed in a large series of 114 patients with unilateral tinnitus (De Ridder et al., 2005). rTMS at frequencies between 1 and 20 Hz was applied over the auditory cortex contralateral to the site of tinnitus perception. Better tinnitus suppression was achieved with higher stimulation frequencies and shorter tinnitus duration, indicating the potential of TMS as a diagnostic tool for differentiating different forms of chronic tinnitus. Single TMS sessions have also been used as a screening method to select patients for surgical implantation of cortical electrodes (De Ridder, De Mulder, Menovsky et al., 2007; De Ridder et al., 2006; De Ridder, De Mulder, Verstraeten et al., 2007).

Two studies (Folmer, Carroll, Rahim, Shi, & Hal Martin, 2006; Fregni et al., 2006) confirmed the result of transient tinnitus reduction after high-frequency stimulation of the left temporoparietal cortex,

Table 11.1 Effects of single sessions of rTMS on tinnitus

Authors	Stimulation site	Coil positioning	Frequency	Intensity	Pulses/ session	Control condition	Results
Plewnia et al., 2003	Various scalp positions	10–20 EEG system	10 Hz	120% MT	30	Stimulation of non-auditory cortical areas	In 8 patients (58%) tinnitus suppression after left temporal/ temporoparietal stimulation
De Ridder et al., 2005	Auditory cortex contralateral to tinnitus site	Anatomical landmarks	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., 2006	Left temporoparietal areas	10–20 EEG system	10 Hz	120% MT	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 rTMS conditions
Folmer et al., 2006	Left and right temporal cortex	10-20 EEG system	10 Hz	100% MT	150	Sham coil	In 6 patients (40%) tinnitus suppression after active rTMS, in four of the patients after contralateral rTMS in two patient after ipsilateral TMS; in

							2 patients suppression after sham rTMS
Londero et al., 2006	Contralateral auditory cortex	fMRI-guided neuronavigation	1, 10 Hz	120% MT	30	Stimulation over non-auditory cortical areas	8 patients were stimulated over the auditory cortex with 1 Hz ; in 5 of them (62.5%) tinnitus suppression; no suppression after 1 Hz rTMS of non-auditory targets; no suppression after 10 Hz, in 2 patients suppression after stimulation of a control position
Plewnia et al., 2007	Area of maximum tinnitus-related PET activation (temporoparietal cortex),	Neuronavigational system, based on H_2O PET with and without lidocaine	1 Hz	120% MT	300, 900, 1800	Control position (occipital cortex)	In 6 patients (75%) tinnitus reduction after active rTMS, better suppression with more pulses
De Ridder et al., 2007	Auditory cortex contralateral to tinnitus site	Anatomical landmarks	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 to tonic

(*Continued*)

Table 11.1 (Continued)

Authors	Stimulation site	Coil positioning	Frequency	Intensity	Pulses/ session	Control condition	Results
							TMS, whereas for pure tone tinnitus no difference was found between burst and tonic
Poreisz et al., 2009	Inferior temporal cortex	10–20 EEG electrode system, T3	Continuous theta burst, intermittent theta burst, immediate theta burst	80% MT	600	No placebo condition	Significant tinnitus reduction only for continuous theta burst immediately after stimulation
Meeus et al., 2009	Auditory cortex contralateral to tinnitus site	Anatomical landmarks	1, 5, 10, 20 Hz tonic; 5, 10, 20 Hz burst	50% maximal stimulator output (independently of individual MT)	200	Coil angulation	No difference between tonic and burst rTMS in pure tone tinnitus (about 50% average suppression in unilateral and 30% in bilateral tinnitus). For bilateral narrow band tinnitus superiority of burst stimulation compared to tonic stimulation; better effects in patients with lower MT

MT = Motor threshold.

whereas one study (Londero et al., 2006) demonstrated reliable tinnitus suppression in only 1 out of 13 subjects after a single session of high frequency rTMS. Additionally, in one small study it has been shown that the participants with significant tinnitus reduction after rTMS also had good response to anodal transcranial direct current stimulation (tDCS) (Fregni et al., 2006). In order to try to improve TMS results, PET scans have been used to determine the stimulation target, based on changes of cerebral blood flow before and after lidocaine injection (Plewnia, Reimold, Najib, Brehm et al., 2007): single sessions of low frequency (1 Hz) rTMS with the coil navigated to the individually determined areas in the temporoparietal cortex resulted in tinnitus reduction in 6 out of 8 patients lasting up to 30 minutes.

Repeated Sessions of rTMS in Tinnitus

The application of low-frequency rTMS in repeated sessions was motivated by positive results of 1 Hz rTMS in the treatment of auditory hallucinations and other neuropsychiatric disorders characterized by focal hyperexcitability (Hoffman & Cavus, 2002). In the temporal cortex of rodents the induction of LTD- and LTP-like effects had been demonstrated (Wang et al., 1996) and in humans low-frequency rTMS reliably reduced cortical excitability in the motor cortex (Chen et al., 1997) and in the frontal cortex (Speer et al., 2001). Based on these data, low-frequency rTMS has been proposed for achieving longer-lasting improvement of tinnitus complaints by reducing auditory cortex hyperactivity (Eichhammer, Langguth, Marienhagen, Kleinjung, & Hajak, 2003; Langguth et al., 2003). An increasing amount of studies using this approach as a treatment for tinnitus have been published (Table 11.2). Most rTMS treatment studies applied low-frequency rTMS in long trains of 1200–2000 pulses repeatedly over 5–10 days. In all controlled studies a statistically significant improvement of tinnitus complaints has been documented. However, the quantity of improvement and also the duration of treatment effects varied across studies, probably due to differences in study design, stimulation parameters and patient populations.

Repetitive TMS has been applied over temporal or temporoparietal areas. In the first clinical study to verify whether low-frequency rTMS could induce long-lasting effects, [^{18}F]deoxyglucose (FDG) PET was performed in 14 patients and a neuronavigational system allowed the positioning of the TMS coil exactly over the site of maximum activation in

Table 11.2 Effects of repeated sessions of rTMS in tinnitus patients

Authors	Stimulation site	Coil positioning	Frequency	Intensity	Sessions	Pulses/ session	Design	Control condition	Results
Kleinjung et al., 2005	Area of maximum PET activation in the temporal cortex (12 left, 2 right)	Neuro-navigational system, based on FDG-PET	1 Hz	110% MT	5	2000	Sham-controlled, crossover	Sham coil	Significant reduction of tinnitus after active rTMS as compared to sham rTMS; lasting tinnitus reduction (6 months)
Langguth et al., 2006	Left auditory cortex,	10–20 EEG system	1 Hz	110% MT	10	2000	Open	No control condition	Significant reduction of tinnitus until end of follow-up (3 months)
Plewnia et al., 2007	Area of maximum tinnitus related PET activation (temporoparietal cortex; 3 left, 3 right)	Neuro-navigational system, based on H_2O PET with and without lidocaine	1 Hz	120% MT	10	1800	Sham-controlled, crossover	Occipital cortex	Significant reduction of tinnitus after active rTMS, as compared to the control condition; no lasting effects
Kleinjung et al., 2007	Left auditory cortex	Neuro-navigational system, based on structural MRI	1 Hz	110% MT	10	2000	Open	No control condition	Significant tinnitus reduction after rTMS, lasting up during follow-up period (3 months) responders were characterized by shorter tinnitus duration and less hearing impairment
Rossi et al., 2007	Left secondary auditory cortex	8 patients: neuronavigational system 8 patients: according to 10–20 EEG system, halfway	1 Hz	120% MT	5	1200	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

		between T3 and C3/T5							
Smith et al., 2007	Area of maximal PET activation in the temporal cortex, neuronavigational system	Neuro-navigational system, based on FDG-PET	1 Hz	110% MT	5	1800	Sham-controlled, crossover	Coil angulation	Modest response to active treatment in 3 patients (75%)
Khedr et al., 2008	Left temporoparietal cortex	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 to the control condition; tinnitus reduction lasting during follow-up period (4 months and 12 months)
Langguth et al., 2008	Left auditory cortex	Neuro-navigational system, based on structural MRI	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., 2008	Left temporoparietal cortex	??	0.5 Hz	100% MT	5	600	Open study	No control condition	No significant reduction of tinnitus
					10	2000			

(*Continued*)

Table 11.2 (Continued)

Authors	Stimulation site	Coil positioning	Frequency	Intensity	Sessions	Pulses/ session	Design	Control condition	Results
Kleinjung et al., 2008	Left auditory cortex; left dorsolateral prefrontal cortex	Neuro-navigational system, based on structural MRI	1 Hz, 20 Hz (DLPFC) + 1 Hz	110% MT			Two active treatment conditions, parallel group design	No sham control condition	Directly after stimulation significant improvement for both stimulation conditions, at 3 month follow-up significantly better results for the combined frontal and temporal stimulation
Kleinjung et al., 2009	Left auditory cortex	Neuro-navigational system, based on structural MRI	1 Hz, 1 Hz + Levodopa	110% MT	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
Marcondes et al., 2010	Left temporoparietal cortex	10–20 EEG system	1 Hz	110% MT	5	1020	Sham controlled, parallel group design	Sham coil	Significant improvement after active rTMS but not after sham rTMS, beneficial treatment effects still detectable at 6 months follow-up
Frank et al., 2010	Left temporal	10–20 EEG system	1 Hz	110% MT	10	2000	Open	No control condition	Significant tinnitus reduction after rTMS in patients with unilateral leftsided and bilateral tinnitus, but not in rightsided tinnitus, effects lasting up during follow-up period (3 months)

MT = Motor threshold.

the auditory cortex (Kleinjung et al., 2005). After active treatment, a significant decrease in the score of the Tinnitus Questionnaire was observed, whereas sham treatment showed no effect. Treatment effects were still detectable 6 months after treatment. 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_2O PET (Plewnia, Reimold, Najib, Brehm et al., 2007). This approach also resulted in moderate, but significant effects after active stimulation. Since PET scans are not readily available, easier applicable techniques have been proposed for determining coil localization, based on the 10–20 EEG coordinate system. This approach also has resulted in a significant reduction of tinnitus severity after 10 sessions of 1 Hz rTMS (Langguth et al., 2006). Beneficial effects of low frequency rTMS have been confirmed by several further controlled studies (Marcondes et al., 2010; Rossi et al., 2007; Smith et al., 2007). One study (Rossi et al., 2007) used peripheral electrical stimulation as a control condition and thus demonstrated that the reduction of tinnitus is not mediated by somatosensory afferents, but by cortical stimulation. Subsequently a study was performed using functional imaging (FDG PET) before and after rTMS (Smith et al., 2007). They demonstrated in their small sample that a clinical reduction after rTMS was paralleled by reduced metabolic activity in the stimulated area. Changes of brain activity also were demonstrated after rTMS in another study (Marcondes et al., 2010), but these changes were not exactly in the stimulated area, rather in the left inferior temporal lobe, a sensory integration area. Interestingly, this study revealed 6 months' long-lasting effects after only five stimulation sessions, which might be due to the fact that only tinnitus patients with normal audiograms were included, as it has been demonstrated that severe hearing loss worsens rTMS results (Kleinjung et al., 2007).

While some studies demonstrated effects that outlasted the stimulation period up to 6 or 12 months (Khedr et al., 2009; Kleinjung et al., 2005; Marcondes et al., 2010), others were not able to observe prolonged effects (Plewnia, Reimold, Najib, Reischl et al., 2007; Smith et al., 2007). The total amount of rTMS sessions may be an important variable in achieving long-term effects in tinnitus patients (Langguth et al., 2003), analogous to what has been observed in other rTMS applications such as depression (Gershon, Dannon, & Grunhaus, 2003) and auditory hallucinations (Hoffman et al., 2005).

A recent case report showed that it is possible to use maintenance rTMS to manage chronic tinnitus (Mennemeier et al., 2008). In this

patient, tinnitus could be improved each time it re-occurred, by applying one to three maintenance rTMS sessions. After three maintenance rTMS sessions it finally stabilized on a low level. The positive effect of this maintenance stimulation could also be confirmed by reduced cerebral metabolism in PET imaging after treatment. The rationale for using rTMS for maintenance treatment of tinnitus relies on the fact that those patients who respond once to rTMS treatment also experience positive effects from a second series of rTMS (Langguth, Landgrebe, Hajak, & Kleinjung, 2008).

The concept of specific effects of low-frequency rTMS for reducing focal hyperexcitability has been challenged by a recent study which compared effects of 1 Hz, 10 Hz, and 25 Hz rTMS (Khedr, Rothwell, Ahmed, & El-Atar, 2008). Whereas sham rTMS treatment had no effect, active stimulation over the left temporoparietal cortex resulted in a reduction of tinnitus irrespective of the stimulation frequency. Follow-up assessment one year after treatment demonstrated a trend for higher efficiency of 10 and 25 Hz as compared to 1 Hz (Khedr et al., 2009). Experimental data from motor cortex stimulation in healthy subjects indicates that LTD-like effects induced by low-frequency rTMS can be enhanced by high-frequency priming stimulation (Iyer, Schleper, & Wassermann, 2003). However, in a clinical study high-frequency priming stimulation failed to enhance the therapeutic efficacy of low-frequency rTMS for the treatment of tinnitus (Langguth, Kleinjung et al., 2008), further indicating that the mechanisms by which rTMS affects tinnitus differ from those LTD-like effects observed after motor cortex stimulation.

Repetitive TMS can be applied in a tonic and a burst mode. The burst stimulation technique has been proposed for enhancing rTMS effects. It consists of bursts of three pulses at a frequency of 50 Hz, applied every 200 ms (5 Hz, theta burst) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Burst TMS has been shown to induce more pronounced and longer-lasting effects on human motor cortex than tonic stimulation (Huang et al., 2005). Single sessions of continuous theta burst stimulation over the temporal cortex in tinnitus patients resulted in short-lasting reduction of tinnitus loudness compared to effects achieved with single sessions of tonic stimulation and other theta burst protocols had no effect at all (Poreisz, Paulus, Moser, & Lang, 2009). In two other studies single sessions of burst stimulation were compared with tonic stimulation (De Ridder, van der Loo et al., 2007a, 2007b). Burst stimulation yielded similar efficacy as tonic stimulation in patients with pure tone tinnitus, but was

superior in patients with noise-like tinnitus. A possible explanation for this finding is that pure tone tinnitus may be related to increased neuronal activity in the classical (lemniscal) auditory pathways, which mainly fire tonically, whereas noise-like tinnitus may be the result of increased activity in the non-classical (extra-lemniscal) pathways, which is characterized by burst firing. A follow-up study of the same group replicated this result for bilateral tinnitus, but not for unilateral tinnitus (Meeus, Blaivie, Ost, De Ridder, & Van de Heyning, 2009). Furthermore, results of this study suggested that higher stimulation intensity may result in slightly better tinnitus suppression.

The neurobiology of chronic tinnitus suggests that neuronal changes are not limited to the auditory pathways (Lockwood et al., 1998; Schlee, Hartmann et al., 2009; Schlee, Mueller et al., 2009). Recent progress in consciousness research has demonstrated that hyperactivity within primary sensory areas alone is not sufficient for conscious tinnitus perception. Rather, synchronized co-activation of frontal and parietal areas seems to be necessary (Boly et al., 2004). This suggests that tinnitus might be an emergent property of a network, rather than just an expression of hyperactivity in the auditory cortex. Therefore it may be better to modulate more than one area involved in the tinnitus network. In one pilot study 32 patients received either low-frequency temporal rTMS or a combination of high-frequency prefrontal and low-frequency temporal rTMS (Kleinjung, Eichhammer et al., 2008). Immediately after therapy there was an improvement of the Tinnitus Questionnaire score for both groups but no differences between groups. However, after 3 months a remarkable advantage for combined prefrontal and temporal rTMS treatment was noted. These data indicate that modulation of both frontal and temporal cortex activity might represent a promising enhancement strategy for improving TMS effects in tinnitus patients.

Combination of rTMS with pharmacologic intervention also has been suggested for potentiating rTMS effects, analogous to what has been described for tDCS (Nitsche et al., 2006; Terney et al., 2008). It is known from animal experiments that neuronal plasticity can be enhanced by dopaminergic receptor activation (Otani, Blond, Desce, & Crepel, 1998). However, in a clinical pilot study the administration of 100 mg Levodopa before rTMS was not successful in enhancing rTMS effects in tinnitus patients (Kleinjung et al., 2009).

There are few prognostic factors that determine the rTMS outcome for tinnitus. Several studies reported that shorter tinnitus duration was

related to better treatment outcome (De Ridder et al., 2005; Khedr et al., 2008; Kleinjung et al., 2007; Plewnia, Reimold, Najib, Brehm et al., 2007). Normal hearing was also suggested as a positive clinical predictor for good treatment response (Kleinjung et al., 2007; Marcondes et al., 2010). Interestingly, short tinnitus duration and normal hearing have been demonstrated to be positive predictors in other treatment options for tinnitus as well (De Ridder et al., 2010; M. B. Moller, Moller, Jannetta, & Jho, 1993; Ryu, Yamamoto, Sugiyama, & Nozue, 1998).

Methodological Considerations

Evaluation of treatment efficacy requires adequate methodology for control of unspecific treatment and placebo effects. The majority of controlled studies published to date have used placebo treatment in cross-over designs. Potential shortcomings of this approach include carry-over effects and missed long-term effects due to limited observation periods. Different methods have been reported to control for placebo effects. Besides the sham coil system (Kleinjung et al., 2005), which mimics the sound of the active coil without generating a magnetic field, an angulation of an active coil tilted 45° (Smith et al., 2007) or 90° (De Ridder et al., 2005; Rossi et al., 2007) to the skull surface, and stimulation of non-auditory brain areas (Plewnia, Reimold, Najib, Brehm et al., 2007) have been described. Another option is to use two coils, with the inactive coil positioned on the target and the active coil 90° perpendicular to and on top of it (Meeus, De Ridder, & Van de Heyning, 2009). This has the advantage that the sensory perception of the coil is the same (apart from the muscle contractions). Finding an optimal control condition for treatment studies is difficult due to limitations in blinding of patient and operator to different stimulus conditions, and due to the fact that TMS itself results in auditory and somatosensory stimulation in addition to its brain stimulation activity. One possible solution is a control condition that involves electrical stimulation of the facial nerve (Rossi et al., 2007). But even this method has to be considered with care as modulating the motor system can alter tinnitus perception. This has become clear with the tinnitus modulating effects of ventral intermedius nucleus stimulation performed in the setting of movement disorders (Shi, Burchiel, Anderson, & Martin, 2009).

In most studies validated tinnitus questionnaires and visual analogue scales serve as primary outcome measurements due to the lack of objective parameters. The improvement in tinnitus rating after stimulation is

associated with a reduction of metabolic activity on PET scan (Smith et al., 2007). Therefore functional imaging might evolve as an objective marker of treatment effects in the future.

Safety Aspects

An extensive body of literature demonstrates that rTMS is a safe and well tolerated technique (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), at least if stimulation is performed according to published safety guidelines (Rossi et al., 2009; Wassermann, 1998). Most data are available from rTMS studies in depressed subjects. In an analysis of 10 000 cumulative rTMS sessions performed for depression no deaths or seizures were encountered (Janicak et al., 2008). Most adverse events in this analysis were mild to moderate in intensity. Transient headaches and scalp discomfort were the most common adverse events. Auditory threshold and cognitive function did not change. There was a low discontinuation rate (4.5%) due to adverse events during acute treatment (Janicak et al., 2008). Another study demonstrated that after 2−4 weeks of daily prefrontal rTMS there was no sign of structural MRI changes (Nahas et al., 2000), no significant changes in auditory thresholds and no significant electroencephalogram abnormalities (Loo et al., 2001). It is essential that contraindications such as electronic implants (e.g. cardiac pacemakers, cochlea implants), intracranial pieces of metal or previous epileptic seizures are considered.

CONCLUSION

Available literature converges in the finding that rTMS seems to be a promising tool for investigating the pathophysiology of tinnitus. Data also indicate its diagnostic potential for differentiating pathophysiologically distinct forms of tinnitus.

An increasing number of clinical studies also suggest a therapeutic potential for rTMS. Even though there are now six placebo-controlled studies from six different centers, all demonstrating a beneficial effect of rTMS in equal percentages of responders, these results must be considered preliminary, due to small sample sizes, methodological hetereogeneity, and high inter-subject variability. The duration of treatment effects remains inconclusive. Effects outlasted the stimulation period up to 12 months in some studies whereas others could not demonstrate any after-effects. Replication in multicenter trials with a large number of patients and

long-term follow-up are needed before further conclusions can be drawn (Landgrebe, Binder et al., 2008). Further clinical research is needed to define those subgroups of patients which benefit most from rTMS. Better understanding of the pathophysiology of the different forms of tinnitus on one side and the neurobiological effects of rTMS on the other side will be critical for optimizing and individualizing treatment protocols.

REFERENCES

Allen, E. A., Pasley, B. N., Duong, T., & Freeman, R. D. (2007). Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. *Science*, *317*(5846), 1918–1921.

Andersson, G., Lyttkens, L., Hirvela, C., Furmark, T., Tillfors, M., & Fredrikson, M. (2000). Regional cerebral blood flow during tinnitus: A PET case study with lidocaine and auditory stimulation. *Acta Otolaryngology*, *120*(8), 967–972.

Arnold, W., Bartenstein, P., Oestreicher, E., Romer, W., & Schwaiger, M. (1996). Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: A PET study with [18F]deoxyglucose. *ORL: Journal of Otorhinolaryngology and Related Specialties*, *58*(4), 195–199.

Axelsson, A., & Ringdahl, A. (1989). Tinnitus – a study of its prevalence and characteristics. *British Journal of Audiology*, *23*(1), 53–62.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet*, *1*(8437), 1106–1107.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., et al. (2004). Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. *Archives of Neurology*, *61*(2), 233–238.

Brackmann, D. E. (1981). Reduction of tinnitus in cochlear-implant patients. *Journal of Laryngology and Otology*, *4*(Suppl), 163–165.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, *48*(5), 1398–1403.

Cronlein, T., Langguth, B., Geisler, P., & Hajak, G. (2007). Tinnitus and insomnia. *Progress in Brain Research*, *166*, 227–233.

De Ridder, D., De Mulder, G., Menovsky, T., Sunaert, S., & Kovacs, S. (2007). Electrical stimulation of auditory and somatosensory cortices for treatment of tinnitus and pain. *Progress in Brain Research*, *166*, 377–388.

De Ridder, D., De Mulder, G., Verstraeten, E., Seidman, M., Elisevich, K., Sunaert, S., et al. (2007). Auditory cortex stimulation for tinnitus. *Acta Neurochirurgica*, *Suppl 97* (Pt 2), 451–462.

De Ridder, D., De Mulder, G., Verstraeten, E., Van der Kelen, K., Sunaert, S., Smits, M., et al. (2006). Primary and secondary auditory cortex stimulation for intractable tinnitus. *ORL: Journal of Otorhinolaryngology and Related Specialties*, *68*(1), 48–54, discussion 54-45

De Ridder, D., De Mulder, G., Walsh, V., Muggleton, N., Sunaert, S., & Moller, A. (2004). Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus. Case report. *Journal of Neurosurgery*, *100*(3), 560–564.

De Ridder, D., & Van de Heyning, P. (2007). The Darwinian plasticity hypothesis for tinnitus and pain. *Progress in Brain Research*, *166*, 55–60.

De Ridder, D., van der Loo, E., Van der Kelen, K., Menovsky, T., van de Heyning, P., & Moller, A. (2007a). Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? *International Journal of Medical Science*, *4*(5), 242–246.

De Ridder, D., van der Loo, E., Van der Kelen, K., Menovsky, T., van de Heyning, P., & Moller, A. (2007b). Theta, alpha and beta burst transcranial magnetic stimulation: Brain modulation in tinnitus. *International Journal of Medical Science*, *4*(5), 237–241.

De Ridder, D., Vanneste, S., Adriaenssens, I., Lee, A. P., Plazier, M., Menovsky, T., et al. (2010). Microvascular decompression for tinnitus: Significant improvement for tinnitus intensity without improvement for distress. A 4-year limit. *Neurosurgery*, *66*(4), 656–660.

De Ridder, D., Verstraeten, E., Van der Kelen, K., De Mulder, G., Sunaert, S., Verlooy, J., et al. (2005). Transcranial magnetic stimulation for tinnitus: Influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. *Otology and Neurotology*, *26*(4), 616–619.

Dobie, R. A. (1999). A review of randomized clinical trials in tinnitus. *Laryngoscope*, *109*(8), 1202–1211.

Dobie, R. A. (2003). Depression and tinnitus. *Otolaryngology Clinics of North America*, *36*(2), 383–388.

Dohrmann, K., Weisz, N., Schlee, W., Hartmann, T., & Elbert, T. (2007). Neurofeedback for treating tinnitus. *Progress in Brain Research*, *166*, 473–485.

Eggermont, J. J. (2007). Pathophysiology of tinnitus. *Progress in Brain Research*, *166*, 19–35.

Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neuroscience*, *27*(11), 676–682.

Eichhammer, P., Langguth, B., Marienhagen, J., Kleinjung, T., & Hajak, G. (2003). Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: A short case series. *Biological Psychiatry*, *54*(8), 862–865.

Folmer, R. L., Carroll, J. R., Rahim, A., Shi, Y., & Hal Martin, W. (2006). Effects of repetitive transcranial magnetic stimulation (rTMS) on chronic tinnitus. *Acta Otolaryngology*, *556*(Suppl), 96–101.

Fregni, F., Marcondes, R., Boggio, P. S., Marcolin, M. A., Rigonatti, S. P., Sanchez, T. G., et al. (2006). Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. *European Journal of Neurology*, *13*(9), 996–1001.

Friedland, D. R., Gaggl, W., Runge-Samuelson, C., Ulmer, J. L., & Kopell, B. H. (2007). Feasibility of auditory cortical stimulation for the treatment of tinnitus. *Otology and Neurotology*, *28*(8), 1005–1012.

Gershon, A. A., Dannon, P. N., & Grunhaus, L. (2003). Transcranial magnetic stimulation in the treatment of depression. *American Journal of Psychiatry*, *160*(5), 835–845.

Giraud, A. L., Chery-Croze, S., Fischer, G., Fischer, C., Vighetto, A., Gregoire, M. C., et al. (1999). A selective imaging of tinnitus. *Neuroreport*, *10*(1), 1–5.

Haller, S., Birbaumer, N., & Veit, R. (2010). Real-time fMRI feedback training may improve chronic tinnitus. *European Radiology*, *20*(3), 696–703.

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, *406*(6792), 147–150.

Hoffman, R. E., & Cavus, I. (2002). Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. *American Journal of Psychiatry*, *159*(7), 1093–1102.

Hoffman, R. E., Gueorguieva, R., Hawkins, K. A., Varanko, M., Boutros, N. N., Wu, Y. T., et al. (2005). Temporoparietal transcranial magnetic stimulation for auditory hallucinations: Safety, efficacy and moderators in a fifty patient sample. *Biological Psychiatry*, *58* (2), 97–104.

Holm, A. F., Staal, M. J., Mooij, J. J., & Albers, F. W. (2005). Neurostimulation as a new treatment for severe tinnitus: A pilot study. *Otology and Neurotology, 26*(3), 425–428; discussion 428.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201–206.

Iyer, M. B., Schleper, N., & Wassermann, E. M. (2003). Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *Journal of Neuroscience, 23*(34), 10867–10872.

Janicak, P. G., O'Reardon, J. P., Sampson, S. M., Husain, M. M., Lisanby, S. H., Rado, J. T., et al. (2008). Transcranial magnetic stimulation in the treatment of major depressive disorder: A comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *Journal of Clinical Psychiatry, 69*(2), 222–232.

Jastreboff, P. J. (1990). Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neuroscience Research, 8*(4), 221–254.

Jastreboff, P. J., Brennan, J. F., & Sasaki, C. T. (1988). An animal model for tinnitus. *Laryngoscope, 98*(3), 280–286.

Khedr, E. M., Rothwell, J. C., Ahmed, M. A., & El-Atar, A. (2008). Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: Comparison of different stimulus frequencies. *Journal of Neurology, Neurosurgery and Psychiatry, 79*(2), 212–215.

Khedr, E. M., Rothwell, J. C., & El-Atar, A. (2009). One-year follow up of patients with chronic tinnitus treated with left temporoparietal rTMS. *European Journal of Neurology, 16*(3), 404–408.

Kleinjung, T., Eichhammer, P., Landgrebe, M., Sand, P., Hajak, G., Steffens, T., et al. (2008). Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: A pilot study. *Otolaryngology, Head and Neck Surgery, 138*(4), 497–501.

Kleinjung, T., Eichhammer, P., Langguth, B., Jacob, P., Marienhagen, J., Hajak, G., et al. (2005). Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. *Otolaryngology, Head and Neck Surgery, 132*(4), 566–569.

Kleinjung, T., Steffens, T., Landgrebe, M., Vielsmeier, V., Frank, E., Hajak, G., et al. (2009). Levodopa does not enhance the effect of low-frequency repetitive transcranial magnetic stimulation in tinnitus treatment. *Otolaryngology Head and Neck Surgery, 140* (1), 92–95.

Kleinjung, T., Steffens, T., Sand, P., Murthum, T., Hajak, G., Strutz, J., et al. (2007). Which tinnitus patients benefit from transcranial magnetic stimulation? *Otolaryngology, Head and Neck Surgery, 137*(4), 589–595.

Kleinjung, T., Vielsmeier, V., Landgrebe, M., Hajak, G., & Langguth, B. (2008). Transcranial magnetic stimulation: A new diagnostic and therapeutic tool for tinnitus patients. *International Tinnitus Journal, 14*(2), 112–118.

Kulkarni, B., Bentley, D. E., Elliott, R., Youell, P., Watson, A., Derbyshire, S. W., et al. (2005). Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *European Journal of Neuroscience, 21*(11), 3133–3142.

Landgrebe, M., Barta, W., Rosengarth, K., Frick, U., Hauser, S., Langguth, B., et al. (2008). Neuronal correlates of symptom formation in functional somatic syndromes: A fMRI study. *Neuroimage, 41*(4), 1336–1344.

Landgrebe, M., Binder, H., Koller, M., Eberl, Y., Kleinjung, T., Eichhammer, P., et al. (2008). Design of a placebo-controlled, randomized study of the efficacy of repetitive transcranial magnetic stimulation for the treatment of chronic tinntius. *BMC Psychiatry, 8*, 23.

Langguth, B., Eichhammer, P., Wiegand, R., Marienhegen, J., Maenner, P., Jacob, P., et al. (2003). Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. *Neuroreport*, *14*(7), 977–980.

Langguth, B., Kleinjung, T., Fischer, B., Hajak, G., Eichhammer, P., & Sand, P. G. (2007). Tinnitus severity, depression, and the big five personality traits. *Progress in Brain Research*, *166*, 221–225.

Langguth, B., Kleinjung, T., Frank, E., Landgrebe, M., Sand, P., Dvorakova, J., et al. (2008). High-frequency priming stimulation does not enhance the effect of low-frequency rTMS in the treatment of tinnitus. *Experimental Brain Research*, *184*(4), 587–591.

Langguth, B., Landgrebe, M., Hajak, G., & Kleinjung, T. (2008). Re: Maintenance repetitive transcranial magnetic stimulation can inhibit the return of tinnitus. *Laryngoscope*, *118*(12), 2264; author reply 2264-2265.

Langguth, B., Zowe, M., Landgrebe, M., Sand, P., Kleinjung, T., Binder, H., et al. (2006). Transcranial magnetic stimulation for the treatment of tinnitus: A new coil positioning method and first results. *Brain Topography*, *18*(4), 241–247.

Lanting, C. P., de Kleine, E., & van Dijk, P. (2009). Neural activity underlying tinnitus generation: Results from PET and fMRI. *Hearing Research*, *255*(1-2), 1–13.

Llinas, R., Urbano, F. J., Leznik, E., Ramirez, R. R., & van Marle, H. J. (2005). Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. *Trends in Neuroscience*, *28*(6), 325–333.

Llinas, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences of the U S A*, *96*(26), 15 222–15 227.

Lockwood, A. H., Salvi, R. J., Burkard, R. F., Galantowicz, P. J., Coad, M. L., & Wack, D. S. (1999). Neuroanatomy of tinnitus. *Scandinavian Audiology*, *51*(Suppl), 47–52.

Lockwood, A. H., Salvi, R. J., Coad, M. L., Towsley, M. L., Wack, D. S., & Murphy, B. W. (1998). The functional neuroanatomy of tinnitus: Evidence for limbic system links and neural plasticity. *Neurology*, *50*(1), 114–120.

Londero, A., Langguth, B., De Ridder, D., Bonfils, P., & Lefaucheur, J. P. (2006). Repetitive transcranial magnetic stimulation (rTMS): A new therapeutic approach in subjective tinnitus? *Neurophysiology Clinics*, *36*(3), 145–155.

Loo, C., Sachdev, P., Elsayed, H., McDarmont, B., Mitchell, P., Wilkinson, M., et al. (2001). Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biological Psychiatry*, *49*(7), 615–623.

Lorenz, I., Muller, N., Schlee, W., Hartmann, T., & Weisz, N. (2009). Loss of alpha power is related to increased gamma synchronization-A marker of reduced inhibition in tinnitus? *Neuroscience Letters*, *453*(3), 225–228.

Marcondes, R. A., Sanchez, T. G., Kii, M. A., Ono, C. R., Buchpiguel, C. A., Langguth, B., et al. (2010). Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: A double-blind controlled, clinical and neuroimaging outcome study. *European Journal of Neurology*, *17*(1), 38–44.

Meeus, O., Blaivie, C., Ost, J., De Ridder, D., & Van de Heyning, P. (2009). Influence of tonic and burst transcranial magnetic stimulation characteristics on acute inhibition of subjective tinnitus. *Otology and Neurotology*, *30*(6), 697–703.

Meeus, O. M., De Ridder, D., & Van de Heyning, P. H. (2009). Transcranial magnetic stimulation (TMS) in tinnitus patients. *B-ENT*, *5*(2), 89–100.

Melcher, J. R., Sigalovsky, I. S., Guinan, J. J., Jr., & Levine, R. A. (2000). Lateralized tinnitus studied with functional magnetic resonance imaging: Abnormal inferior colliculus activation. *Journal of Neurophysiology*, *83*(2), 1058–1072.

Mennemeier, M., Chelette, K. C., Myhill, J., Taylor-Cooke, P., Bartel, T., Triggs, W., et al. (2008). Maintenance repetitive transcranial magnetic stimulation can inhibit the return of tinnitus. *Laryngoscope*, *118*(7), 1228–1232.

Mirz, F., Gjedde, A., Ishizu, K., & Pedersen, C. B. (2000). Cortical networks subserving the perception of tinnitus – a PET study. *Acta Otolaryngology*, *543*(Suppl), 241–243.

Moffat, G., Adjout, K., Gallego, S., Thai-Van, H., Collet, L., & Norena, A. J. (2009). Effects of hearing aid fitting on the perceptual characteristics of tinnitus. *Hearing Research*, *254*(1-2), 82–91.

Moisset, X., & Bouhassira, D. (2007). Brain imaging of neuropathic pain. *Neuroimage*, *37*(Suppl 1), S80–88.

Moller, A. (1994). Tinnitus. In R. Jackler, & D. Brackmann (Eds.), *Neurotology* (pp. 153–166). St Louis, MO: Mosby.

Moller, A. R. (2003). Pathophysiology of tinnitus. *Otolaryngology Clinics of North America*, *36*(2), 249–266, v-vi

Moller, A. R. (2007a). The role of neural plasticity in tinnitus. *Progress in Brain Research*, *166*, 37–45.

Moller, A. R. (2007b). Tinnitus: Presence and future. *Progress in Brain Research*, *166*, 3–16.

Moller, M. B., Moller, A. R., Jannetta, P. J., & Jho, H. D. (1993). Vascular decompression surgery for severe tinnitus: Selection criteria and results. *Laryngoscope*, *103*(4 Pt 1), 421–427.

Muhlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences of the U S A*, *95*(17), 10 340–10 343.

Nahas, Z., DeBrux, C., Chandler, V., Lorberbaum, J. P., Speer, A. M., Molloy, M. A., et al. (2000). Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *Journal of ECT*, *16*(4), 380–390.

Nitsche, M. A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., et al. (2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *European Journal of Neuroscience*, *23*(6), 1651–1657.

Norena, A. J., & Eggermont, J. J. (2005). Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *Journal of Neuroscience*, *25*(3), 699–705.

Norena, A. J., & Eggermont, J. J. (2006). Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. *Neuroreport*, *17*(6), 559–563.

Norena, A., Micheyl, C., Chery-Croze, S., & Collet, L. (2002). Psychoacoustic characterization of the tinnitus spectrum: Implications for the underlying mechanisms of tinnitus. *Audiology and Neurootology*, 7(6), 358–369.

Otani, S., Blond, O., Desce, J. M., & Crepel, F. (1998). Dopamine facilitates long-term depression of glutamatergic transmission in rat prefrontal cortex. *Neuroscience*, *85*(3), 669–676.

Pascual-Leone, A., Grafman, J., & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science*, *263*(5151), 1287–1289.

Plewnia, C., Bartels, M., & Gerloff, C. (2003). Transient suppression of tinnitus by transcranial magnetic stimulation. *Annals of Neurology*, *53*(2), 263–266.

Plewnia, C., Reimold, M., Najib, A., Brehm, B., Reischl, G., Plontke, S. K., et al. (2007). Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. *Human Brain Mapping*, *28*(3), 238–246.

Plewnia, C., Reimold, M., Najib, A., Reischl, G., Plontke, S. K., & Gerloff, C. (2007). Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: A randomised, controlled pilot study. *Journal of Neurology, Neurosurgery and Psychiatry*, *78*(2), 152–156.

Poreisz, C., Paulus, W., Moser, T., & Lang, N. (2009). Does a single session of theta-burst transcranial magnetic stimulation of inferior temporal cortex affect tinnitus perception? *BMC Neuroscience*, *10*, 54.

Post, A., & Keck, M. E. (2001). Transcranial magnetic stimulation as a therapeutic tool in psychiatry: What do we know about the neurobiological mechanisms? *Journal of Psychiatric Research*, *35*(4), 193–215.

Price, D. D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science*, *288*(5472), 1769–1772.

Ridding, M. C., & Rothwell, J. C. (1997). Stimulus/response curves as a method of measuring motor cortical excitability in man. *Electroencephalography Clinics of Neurophysiology*, *105*(5), 340–344.

Rossi, S., De Capua, A., Ulivelli, M., Bartalini, S., Falzarano, V., Filippone, G., et al. (2007). Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: A randomised, crossover, double blind, placebo controlled study. *Journal of Neurology, Neurosurgery and Psychiatry*, *78*(8), 857–863.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039.

Ryu, H., Yamamoto, S., Sugiyama, K., & Nozue, M. (1998). Neurovascular compression syndrome of the eighth cranial nerve. What are the most reliable diagnostic signs? *Acta Neurochirurgica (Wien)*, *140*(12), 1279–1286.

Schlee, W., Hartmann, T., Langguth, B., & Weisz, N. (2009). Abnormal resting-state cortical coupling in chronic tinnitus. *BMC Neuroscience*, *10*, 11.

Schlee, W., Mueller, N., Hartmann, T., Keil, J., Lorenz, I., & Weisz, N. (2009). Mapping cortical hubs in tinnitus. *BMC Biology*, *7*, 80.

Schlee, W., Weisz, N., Bertrand, O., Hartmann, T., & Elbert, T. (2008). Using auditory steady state responses to outline the functional connectivity in the tinnitus brain. *PLoS ONE*, *3*(11), e3720.

Seidman, M. D., Ridder, D. D., Elisevich, K., Bowyer, S. M., Darrat, I., Dria, J., et al. (2008). Direct electrical stimulation of Heschl's gyrus for tinnitus treatment. *Laryngoscope*, *118*(3), 491–500.

Seki, S., & Eggermont, J. J. (2003). Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. *Hearing Research*, *180*(1-2), 28–38.

Shi, Y., Burchiel, K. J., Anderson, V. C., & Martin, W. H. (2009). Deep brain stimulation effects in patients with tinnitus. *Otolaryngology Head and Neck Surgery*, *141*(2), 285–287.

Simons, W., & Dierick, M. (2005). Transcranial magnetic stimulation as a therapeutic tool in psychiatry. *World Journal of Biology and Psychiatry*, *6*(1), 6–25.

Smith, J. A., Mennemeier, M., Bartel, T., Chelette, K. C., Kimbrell, T., Triggs, W., et al. (2007). Repetitive transcranial magnetic stimulation for tinnitus: A pilot study. *Laryngoscope*, *117*(3), 529–534.

Smits, M., Kovacs, S., de Ridder, D., Peeters, R. R., van Hecke, P., & Sunaert, S. (2007). Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. *Neuroradiology*, *49*(8), 669–679.

Soussi, T., & Otto, S. R. (1994). Effects of electrical brainstem stimulation on tinnitus. *Acta Oto-Laryngologica*, *114*(2), 135–140.

Speer, A. M., Repella, J. D., Figueras, S., Demian, N. K., Kimbrell, T. A., Wasserman, E. M., et al. (2001). Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. *J ECT*, *17*(4), 259–263.

Terney, D., Bergmann, I., Poreisz, C., Chaieb, L., Boros, K., Nitsche, M. A., et al. (2008). Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans. *Journal of Pain Symptom Management*, *36*(1), 79–91.

Van de Heyning, P., Vermeire, K., Diebl, M., Nopp, P., Anderson, I., & De Ridder, D. (2008). Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Annals of Otology, Rhinology and Laryngology*, *117*(9), 645–652.

van der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., et al. (2009). Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *PLoS ONE*, *4*(10), e7396: 7391-7395.

Vanneste, S., Plazier, M., Ost, J., van der Loo, E., Van de Heyning, P., & De Ridder, D. (2010). Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: A preliminary clinical study. *Experimental Brain Research*, *204*(2), 283–287.

von Leupoldt, A., Sommer, T., Kegat, S., Baumann, H. J., Klose, H., Dahme, B., et al. (2009). Dyspnea and pain share emotion-related brain network. *Neuroimage*, *48*(1), 200–206.

Walsh, V., & Rushworth, M. (1999). A primer of magnetic stimulation as a tool for neuropsychology. *Neuropsychologia*, *37*(2), 125–135.

Wang, H., Wang, X., & Scheich, H. (1996). LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. *Neuroreport*, *7*(2), 521–525.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. *Electroencephalography and Clinical Neurophysiology*, *108*(1), 1–16.

Weisz, N., Muller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *Journal of Neuroscience*, *27*(6), 1479–1484.