Brain Stimulation: New Vistas for the Exploration and Treatment of Tinnitus

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Keywords

Cortical stimulation; Neurophysiology; Therapy; Tinnitus; Transcranial direct current stimulation; Transcranial magnetic stimulation.

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doi: 10.1111/j.1755-5949.2010.00169.x

SUMMARY

Aims: Tinnitus, the perception of sounds or noise in the absence of auditory stimuli, is a frequent and often severely disabling symptom of different disorders of the auditory system. Attempts to develop evidence-based therapies have been thwarted by a poor understanding of the underlying pathophysiology. However, recent work points toward a pivotal role of maladaptive cortical reorganization in the generation and perpetuation of tinnitus. Changes in the representation of sounds, abnormalities of oscillatory activity, and hyperactivity in higher order areas of auditory processing have been linked with the perception of tinnitus. Brain stimulation techniques have entered the field and have opened exciting new perspectives for the modulation of dysfunctional brain activity. In this review, a comprehensive overview on the use of brain-stimulation techniques in the exploration and experimental treatment of tinnitus is provided. **Discussions:** Noninvasive and invasive brain stimulation techniques, for example, transcranial magnetic stimulation (TMS), direct current stimulation (tDCS), and direct electrical cortical stimulation gave rise to a new line of investigation in tinnitus research. First, it has been shown that focal interference with presumably pathological cortical function can reduce tinnitus at least transiently. Second, the reduction of tinnitus-associated enhancement of cortical activity by neuronavigated TMS has been demonstrated to ameliorate tinnitus. Third, preliminary data suggest that repeated application of TMS or continuous cortical stimulation may lead to a longer lasting suppression of tinnitus. **Conclusions:** These proof of principle studies point toward a new option for the investigation and neurophysiology based treatment of tinnitus. Based on these findings, larger scale randomized clinical trials are needed to explore the efficacy of different brain stimulation techniques and parameters as well as the optimal target sites and treatment schedules. Particularly, a careful evaluation of clinical relevance under consideration of an adequate sham control and attention to possible unwanted side effects of these new interventions are indispensable.

Introduction

Tinnitus is the perception of elementary sound or noise in the absence of auditory stimuli. In 10–15% of the population this auditory phantom perception is persistent [1,2] with higher prevalence at older age and after hearing loss [3]. In about 1–3% of the general population tinnitus

causes severe impairment of the quality of life involving psychiatric comorbidities, such as sleep disturbance, depression, anxiety, and even suicidality [4–8].

However, specific pharmacological treatments that provide a reliable, persistent effect on tinnitus that is superior to placebo are currently not available [9]. Antidepressants, anticonvulsants, and benzodiazepines

can offer some relief but address mainly the comorbidity rather than the phantom perception proper. Hearing aids, or electronic devices, producing a white noise that covers up the annoying perception, can be of help [10]. The combination of sound therapy and counseling, based on a specific neurophysiological tinnitus model is called 'Tinnitus Retraining Therapy' (TRT). It is aimed at the habituation of reactions evoked by tinnitus and subsequent habituation of the tinnitus perception [11]. Its use in the management of chronic tinnitus has been shown to cause a significant and sustained improvement [12]. While behavioral treatments can often effectively reduce tinnitus distress [13,14], the development of therapies is constrained by the growing but still limited pathophysiological knowledge.

It has been shown that tinnitus can persist after ablation of the cochlea or the acoustic nerve [15,16] and that the attentional and emotional state of the patient is involved in tinnitus annoyance and distress [17,18]. These findings point to the pathophysiological relevance of higher order centers of the auditory system. Hence, it has now become widely accepted that maladaptive changes of central information processing triggered by central deaf-ferentation, even if audiometrically detectable hearing loss is not detectable [19] are critically involved in tinnitus perception and generation [20–22]. Reorganization of the tonotopic structure of the primary auditory cortex [23] as well as hyperexcitability most likely due to loss of surround inhibition [24] was found to be positively correlated with the subjective strength of tinnitus. Furthermore, disturbance of long-range connectivity was shown to be strongly correlated with tinnitus [25,26] pointing toward a disorder of functional integration of different brain areas. Structural alterations of the brain in correlation with tinnitus were documented. Particularly a reduced volume of the medial partition of the Heschl's gyrus [27], the right inferior colliculus and the left hippocampus [28] as well as the subcallosal region including the nucleus accumbens [29] indicate an involvement of both the sensory and the limbic system. However, the functional relevance of the various deviations from normal brain function or structure in tinnitus patients needs to be elucidated.

The publications selected for this review were obtained from the online database PubMed from January 2000 to November 2009. Further sources were the reference lists of the retrieved studies and our experience in this field. The literature search was performed using the key words "transcranial magnetic stimulation (TMS)," "transcranial direct current stimulation (tDCS)," and "cortical stimulation" combined with tinnitus, respectively.

A comprehensive overview concerning the use of brain-stimulation techniques in the exploration and ex-

perimental treatment of tinnitus is provided. Particularly in their application to (1) further clarify the pathophysiological underpinnings of tinnitus perception; (2) develop new therapeutic strategies based on a rational neurophysiological model of tinnitus; and (3) test the clinical relevance of possible treatments in clinical trials. Furthermore safety issues and limitations of these techniques are discussed and future perspectives are outlined.

Exploration of Central Pathophysiology

In order to explore the cortical pathophysiology of tinnitus, functional imaging studies have been extensively used. However, the chronic nature of tinnitus and the sensitivity for external noise poses a specific challenge to its accessibility for conventional brain imaging techniques. Therefore the less noisy magnetoencephalography (MEG) [23,26,30,31] and positron-emission tomography (PET) were more frequently used than functional magnetic imaging (fMRI) [32,33]. With PET, cerebral activity during tinnitus perception was compared to normal subjects [34] or in patients capable to modulate their tinnitus sensation by orofacial or eye movements [35–39]. Alternatively, the injection of Lidocaine was used to transiently reduce tinnitus and thus allow for a comparison of brain activity during present and absent, respectively, reduced tinnitus perception [39–42]. Tinnitus related increased activity was found in primary auditory cortex as well as in the temporoparietal auditory association cortex. The data on the laterality of these changes are inconsistent. Using functional MRI in patients with lateralized tinnitus [32] reduced activity in the contralateral inferior colliculus in response to auditory stimulation was shown, suggesting subcortical abnormalities in chronic tinnitus. However, it remains unknown, if these cortical activities are essential elements of the neuronal network underlying tinnitus perception or represent a mere epiphenomena of further processing. To this end, different brain stimulation protocols were used to modulate cortical information processing via short term interference with cortical function by high-frequency rTMS ("virtual lesion") and transient reduction of cortical excitability using low-frequency rTMS as well as tDCS.

Virtual Lesion

Cortical information processing in healthy as well as pathological conditions is based on the differential regional and interregional integration of complex neuronal activity. High-frequency rTMS interferes with the activity of these brain regions ('virtual lesion') [43]. This

interference with regular or disturbed function of neuronal circuitry can outlast the actual duration of the stimulus train for a few seconds. Therefore, it was hypothesized that if temporoparietal areas are critical for tinnitus perception, the transient disruption of their function should suppress tinnitus during and immediately after stimulation.

In a first study [44,45], the functional neuroanatomy of tinnitus was examined in 14 patients with chronic tinnitus applying 10 Hz rTMS for 3 s to eight cortical and four control positions imitating the loudness and somatosensory artifacts of stimulation. These “active” placebo conditions are essential, since importance of somatosensory system in tinnitus has been clearly documented [46] and stimulation of the scalp is inherent part of TMS. The change of tinnitus loudness was assessed by an analogue scale. Interference with function of left temporoparietal areas yielded distinct transient tinnitus suppression in contrast to stimulation of the control positions. These data provided first evidence for modulatory effects of rTMS on tinnitus and verified the hypothesis of a critical involvement of higher order auditory processing in tinnitus perception. These initial findings were replicated and extended by a large study of 114 patients with unilateral tinnitus demonstrating the transient tinnitus-suppressing effect of rTMS of different frequencies (90% MT, 1–20 Hz, 200 stimuli each) to an area near the auditory cortex on the contralateral side of the tinnitus in more than 50% of the patients. Most interestingly, the effectiveness of rTMS for tinnitus reduction decreased with the length of the medical history of tinnitus. Tinnitus duration correlated negatively with the stimulation frequency inducing maximal tinnitus suppression [47]. In a further study on seven patients [48], the application of 30 stimuli of 10 Hz rTMS resulted in partial suppression of tinnitus between 20 min and 4 days for 6 of 15 subjects. However in this study, sham stimulation was performed by an audio recording of actual TMS stimulus that was lacking the clear sensory features of rTMS and might thus be detected as placebo. The tinnitus suppressing effects of 10 Hz rTMS to the temporoparietal cortex were replicated in a study [49] comparing this intervention to 10 Hz rTMS applied to the mesial parietal cortex and sham rTMS (sham-coil mimicking the auditory artifact). In addition, transient modulation of cortical excitability and associated tinnitus perception was induced by anodal tDCS. tDCS involves the application of low currents to the scalp via cathodal and anodal electrodes and has been shown to affect a range of motor, somatosensory, visual, affective, and cognitive functions [50]. In this study anodal tDCS applied to the left temporoparietal area induced a transient tinnitus reduction, comparable to high-frequency rTMS. Repeated application of tDCS might therefore be an in-

teresting new option for tinnitus treatment but respective clinical trials have not yet been performed.

In contrast to the very short lasting interference with ongoing neuronal processing as induced by high-frequency rTMS, low-frequency rTMS (~1 Hz) causes longer-lasting reductions (up to 30 min) of cortical excitability [51,52] and activity [53]. These changes can exert relevant behavioral effects [54,55] and provide an interesting technique for probing and possibly treating disorders associated with focal brain hyperexcitability [56].

In a proof-of-principle study [42] on nine patients, low-frequency rTMS apt to induce a lasting decrease of cortical excitability was individually navigated to cortical areas with excessive tinnitus-related activity as assessed by [^{15}O]H $_2$ O PET. Repetitive suprathreshold 1 Hz TMS was performed for 5, 15, and 30 min. A noncortical stimulation site with the same auditory and sensory characteristics served as sham control. After PET-guided low-frequency rTMS tinnitus reduction, lasted up to 30 min, was dependent on the number of stimuli, differed from sham stimulation, and was negatively correlated with the length of the medical history of tinnitus. These data demonstrated a lasting and dose-dependent attenuation of tinnitus induced by rTMS to the individual maximum of tinnitus related cortical activity. These effects were observed after stimulation of auditory association areas, indicating the crucial role of higher-order sensory processing in the pathophysiology of chronic tinnitus and pointing toward a possible therapeutic effectiveness of rTMS.

In contrast to continuous stimulation, different forms of TMS applied in repetitive high-frequency bursts have been evaluated in respect to its capacity to reduce tinnitus perception transiently. It has been reported that burst rTMS (3-stimuli 50 Hz-bursts applied at 5, 10, or 20 Hz) is more effective than tonic (continuous) stimulation [57]. In a further study the effects of a single session of different types (continuous, intermittent and intermediate) of theta burst stimulation (TBS) (i.e., 3-stimuli 50 Hz-bursts applied at 5 Hz) to the left inferior temporal cortex on tinnitus were assessed ($n = 20$). Here, no main effect of the type of stimulation was found. However separate examination of each stimulation protocol indicated that continuous TBS yielded a short-lasting tinnitus improvement as compared to baseline immediately after stimulation [58].

Cortical Excitability

TMS provides objective measures of cortical excitability in the motor cortex by measuring motor evoked potentials with electromyography (EMG).

In a first study on motor cortex excitability in tinnitus patients [59], an increased intracortical facilitation was found in patients compared with healthy subject. This finding was interpreted as a reflection of dysbalance between inhibitory and excitatory influences most likely mediated by an insufficient activation of GABA-B mediated inhibitory processes and a further indicator for interactions between the auditory and the motor system which have already been shown at the structural and functional level [20,46]. In turn, tinnitus improvement after TMS treatment was positively correlated with both intracortical inhibition and an extension of the cortical silent period, a further parameter of intracortical inhibitory mechanisms [60]. Accordingly, a shorter cortical silent period was also found in tinnitus patients, whereas in this study intracortical inhibition and facilitation did not show any differences in tinnitus patients as compared to normal control subjects [61]. These indicators of disturbed intracortical inhibition obtained from the motor cortex of tinnitus patients may either point toward an involvement of nonauditory areas in the pathophysiology of tinnitus or an individual most likely neurochemical characteristic of neuronal function, which predisposes to the development of tinnitus.

Experimental Treatment

Despite many therapeutic options that are offered and the fact that psychotherapy-based strategies effectively support habituation and adaptation, the outcome of present tinnitus treatment is insufficient and has been impeded by a substantial lack of pathophysiological knowledge. However, current neuroscience is collecting evidence for specific brain networks involved in the generation of this sometimes agonizing phantom sound. On the basis of this knowledge and the previously described finding that focal brain stimulation is effective to interfere with tinnitus perception, it has been proposed that this intervention may be suitable to induce relevant and lasting beneficial effects in patients with chronic tinnitus [44,45,62,63].

Repetitive Transcranial Magnetic Stimulation (rTMS)

In analogy to reports on the improvement of depression [64] and auditory hallucinations [54] with rTMS comprising a treatment course of several days or weeks, a number of pivotal treatment trials have been performed in order to assess the capacity rTMS as a new therapeutic tool based on pathophysiological evidence (Table 1). In contrast to the studies described in the previous section where brain stimulation and the associated tran-

sient modulation of tinnitus were used to explore tinnitus pathophysiology, in the following studies rTMS was applied over a treatment course of one or more weeks to induce a lasting improvement of tinnitus.

In a first case series including three subjects, five daily sessions of low-frequency rTMS (1 Hz, 2000 stimuli per day, 110% of the motor threshold) were applied above the individual maximum of [^{18}F]deoxyglucose (FDG) PET activation in the auditory cortex of each patient using a TMS-navigation device. A crossover design was applied using a sham-coil to mimick the noise of rTMS. Here, a benefit of rTMS treatment was shown in two out of three patients [63]. Continuation of treatment over a 4-week period in one of the responding subjects did not yield a further enhancement of this effect [65]. Extending these studies, 1 Hz rTMS for 5 days was applied in 14 patients again navigated to the PET-maximum in the auditory cortex [66]. Active treatment resulted in a discrete but lasting reduction of tinnitus distress by 8% as quantified with the tinnitus questionnaire. No change was found after placebo treatment. In an open study involving 28 patients with chronic tinnitus and adopting the above described parameters a heterogeneous treatment response was found ranging from slightly increased tinnitus complaints in two patients to a 'remarkable reduction of tinnitus complaints' in 19 patients [67]. However, a significant improvement compared to baseline was demonstrated.

In a further pilot study on the therapeutic effects of rTMS [68], six patients with chronic tinnitus were enrolled in a sham-controlled crossover trial and treated with 2×2 weeks of suprathreshold (120%) 1 Hz rTMS (30 min) applied to the region with maximal tinnitus-related increase in regional cerebral blood flow as identified by functional imaging with [^{15}O]H $_2$ O PET and compared with the control stimulation of a noncortical site eliciting equivalent noise and sensations. Tinnitus-related distress was assessed before and after each treatment and 2 weeks after the end of the 4-week course of stimulation using the tinnitus questionnaire (TQ) [69]. Compared to sham treatment, rTMS induced greater reduction of the TQ score in five of six patients. In two patients, secondary outcome measures (analogue scores of tinnitus change, tinnitus loudness, and tinnitus annoyance) showed unequivocal improvement. However, 2 weeks after the last rTMS session, tinnitus had returned to baseline in all patients but one. Of note, the degree of response in the tinnitus questionnaire score was correlated with tinnitus-associated activation of the anterior cingulate cortex.

On the basis of this data, it has been concluded that repeated sessions of rTMS are effective in decreasing tinnitus-related distress in a subgroup of patients. However, the magnitude of reduction is only moderate;

Table 1 Clinical trials ($n > 3$) on the effects of rTMS and cortical stimulation for the reduction of tinnitus

	Design	N	Frequency/ intensity	Duration of treatment (d)	Localization	Results	Duration
Kleinjung et al. (2005)	Cross-over	14	1 Hz/110%	5	FDG-PET	8% Reduction; 12% after 6 Mo	>6 months
Rossi et al. (2007)	Cross-over	14	1 Hz/110%	5	Left temporo-parietal	35% Reduction; 8/16: 60% reduction	<2 weeks
Plewnia et al. (2007)	Cross-over	6	1 Hz/110%	10	H ₂ O-PET	20% Reduction; 2/6 subj. effectivity	<2 weeks
Smith et al. (2007)	Cross-over	4	1 Hz/110%	5	FDG-PET	Reduction in 4/4	<4 weeks
Khedr et al. (2008)	Parallel	66	1/10/25 Hz/100/100/90%	10	Left temporo-parietal	Verum: -50%; Placebo: -20%	>4 months
Marcondes et al. (2009)	Parallel	19	1 Hz/110%/1020 ppd	5	Left temporo-parietal	Verum: -35% (1 mo), -24% (6 mo); placebo: no change	>6 months
Langguth et al. (2006)	Open	28	1 Hz/110%/2000 ppd	10	Left temporal	Remarkable reduction' in 19; 'slightly increased' in 2	-
Lee et al. (2008)	Open	8	0.5 Hz/600 ppd	5	Left temporo-parietal	No significant improvement	-
Kleinjung et al. (2008)	Parallel (with vs. without prior rTMS to DLPFC)	32	1 Hz/110%/2000 ppd	10	Left temporo-parietal/left DLPFC	12% Reduction in both groups; 20% reduction after 3 Mo in the conditioned group	>3 months with DLPFC conditioning
Kleinjung et al. (2009)	Parallel (with vs. without L-DOPA)	32	1 Hz/110%/2000 ppd	10	Left temporo-parietal	10% With L-Dopa/12% without L-Dopa	>3 months without L-Dopa
Friedland et al. (2007)	Cross-over (followed by continuous stimulation)	8	Epidural stimulation	2 Weeks/continuous	fMRI/posterior superior temporal	No effect after blinded period/after 12 weeks reduction in 2, 'short periods of total suppression in 6	Delayed improvement >12 weeks
De Ridder et al. (2006)	Open	12	Epidural and intradural stimulation	Continuous	fMRI	97% Pure tone tinnitus reduction/24% white noise tinnitus reduction/no improvement in patients with bilateral tinnitus	-

interindividual responsiveness varies and the attenuation seems to wear off within 2 weeks after the last stimulation session.

Similar results were found by a randomized, placebo controlled crossover trial of 1 Hz rTMS (120% of motor threshold; 1200 stimuli per day for 5 days) of the left temporoparietal region in 16 patients with chronic tinnitus [70]. For this study, a particular placebo stimulation was designed to more closely replicate the somatic sensation of rTMS. Eight of the patients responded to the treatment, two patients dropped out for transient worsening of tinnitus. On the group level rTMS induced a significant transient improvement of tinnitus as compared to

baseline (35%) and to sham stimulation. However, this effect declined within 2 weeks.

Transient effects of low-frequency rTMS were also described in a further controlled cross-over study on four patients with chronic bilateral tinnitus [71]. The participants received five consecutive days of low-frequency rTMS (1 Hz, 110%, 1800 stimuli) or sham treatment (stimulation coil tilted by 45°) before crossing over. The stimulation was guided to the hemisphere and area in or around the primary auditory, showing the highest PET activity. Tinnitus assessment was performed at baseline, after each treatment, and 4 weeks later. Here, all patients responded to rTMS, but not to sham treatment. This

improvement declined in all patients by 4 weeks after active treatment. Notably, all patients showed a reduced asymmetry of activation in the temporal lobes immediately after active rTMS.

In a small ($n = 8$) open trial [72] no tinnitus reducing effects of very-low frequency stimulation on 5 consecutive days (0.5 Hz, 100%, 600 stimuli) were found. However, the unusual low frequency of stimulation and the small sample size impede the interpretation of these findings.

In the largest controlled trial yet [73], daily rTMS of different frequencies (1 Hz, 10 Hz, 25 Hz) and sham stimulation (occipital, 1 Hz), was applied over the left temporoparietal cortex for 2 weeks in 66 patients with chronic tinnitus. Here, significant better tinnitus relief was found after rTMS (50%) than after control stimulation to the occipital cortex (20%). As already indicated in prior studies [42,47,74], this effect of rTMS was negatively correlated with the duration of tinnitus. A reassessment after one year revealed a persistence of this effect [75]. Remarkably, there was no difference in the effectivity of different stimulation frequencies challenging the notion of selective modulation of focal tinnitus-associated hyperactivity by frequency specific effects of rTMS.

In a recent placebo controlled parallel study including 19 patients with normal or near-normal hearing [76] clear short- (35% improvement after 1 month) and long-term effects (24% improvement after 6 months) of five sessions of 1 Hz rTMS to the left temporoparietal cortex have been reported. In contrast sham stimulation with a placebo-coil system had no effect. A distinctive feature of this study was the recruitment of patients with normal audiogram and relatively low tinnitus distress. This underlines the suggestion that hearing loss may be a negative predictor for the effects of rTMS treatment outcome [74] since it might act as an ongoing trigger for the generation of tinnitus. The comparison of single photon emission tomography (SPECT) scans before and 2 weeks after rTMS indicated a reduction of neuronal activity in both the left and the right temporal lobe.

Summing up, the effects of rTMS as a tool for the amelioration of tinnitus are well documented. However, the magnitude of tinnitus improvement seems to be very variable with a significant number of nonresponders and the long-term outcome of positive effects is questionable. Moreover, the most effective stimulation parameters, particularly the optimal brain area and hemisphere as well as the most favorable treatment schedules are unknown. This gave rise to several attempts for an optimization of treatment strategies:

Based on the notion that attentional and emotional processes are critical involved in tinnitus perception

[8,18] and rTMS to the dorsolateral prefrontal cortex (DLPFC) has been shown to be effective in the treatment of depression [64], the combination of low-frequency (1 Hz, 1000 stimuli, 110%) left temporal and high-frequency (20 Hz, 1000 stimuli, 110%) left prefrontal rTMS was applied in 16 patients and compared to 1 Hz stimulation (2000 stimuli, 110%) of the left temporal cortex alone in another 16 subjects [77]. Immediately after 2 weeks stimulation (10 sessions) both groups showed a significant tinnitus reduction (10% combined rTMS, 12% temporal rTMS). Remarkably, tinnitus assessment after 3 months revealed an advantage for the combined treatment with a tinnitus decrease of 17% as compared to 11% after monofocal treatment.

The use of the dopamine precursor levodopa (L-Dopa), a substance enhancing neuroplastic effects induced by training [78] and brain stimulation techniques [79], did not improve the effects of 1 Hz stimulation (10 sessions of 2000 stimuli per day, 110%) to the left temporal cortex in 16 subjects as compared to 16 matched control subjects treated in previous trials with the same stimulation parameters but without L-Dopa [80].

The effect of priming low-frequency rTMS (110% motor threshold, 1 Hz, 1040 stimuli per day) to the temporoparietal cortex with 6 Hz (90% motor threshold, 960 stimuli) in order to enhance the effect of stimulation was assessed in a controlled study with two groups of 16 patients [81]. A significant tinnitus reduction was found after 2 weeks of stimulation but without difference between the primed and nonprimed (standard) stimulation (−10% after standard, −13% after primed stimulation).

Recently, transcranial magnetic TBS given in three cycles of 1-week treatment, has been shown to induce lasting improvement in a case of incapacitating tinnitus accompanied by severe depression [82]. However, the efficacy and safety of this stimulation paradigm is currently under investigation [83].

Electrical Cortical Stimulation

The observation that the interference with cortical activity involved in the generation of the tinnitus percept by rTMS can transiently reduce this sensation has prompted studies using direct electrical stimulation of the cortex to prolong and amplify this effect (Table 1). Here, electrodes were surgically implanted over the cortical areas found to be critical for tinnitus perception. The electrode lead was tunneled subcutaneously through the ipsilateral neck to the subclavicular region for placement of the neurostimulator.

In the first study on one subject, De Ridder et al. [62] used the virtual lesion paradigm to identify an area where complete suppression of tinnitus perception could be

induced by high-frequency rTMS. The following implantation of an epidural electrode led to a complete and lasting tinnitus suppression. In a following uncontrolled case series comprising 12 patients, tinnitus as measured by an analogue scale decreased from 9.5 preoperatively to 1.5 postoperatively in patients with selective pure tone tinnitus ($n = 2$), from 8.8 to 6.8 in patients with selective white noise tinnitus ($n = 5$), and from 9 to 5.6 in patients with combined pure tone and white noise tinnitus ($n = 3$) [84]. Intradural stimulation to the primary auditory cortex in addition to extradural stimulation to the secondary auditory cortex was reported to have no effect in two of the four patients. These patients had not achieved improvement with an extradural electrode alone. In two other patients who had shown unstable tinnitus improvement with extradural electrodes, the intradural positioning of the stimulation electrodes resulted in a stabilized suppression of their tinnitus.

In a prospective, controlled, single-blinded study of epidural continuous electrical stimulation to treat tinnitus on eight patients no effects of stimulation during the 2×2 weeks crossover blinded treatment was observed. However, with continuous stimulation, two patients experienced persistent reduction of pure-tone tinnitus, and six patients reported short periods of total tinnitus suppression. Most remarkably, tinnitus reduction evolved with a delay after the completion of the 4-week crossover period [85].

The treatment of two patients by targeting the tonal locations of the primary auditory cortex corresponding to the patient's tinnitus with continuous electrical stimulation led to a sustained reduction to near elimination of bilateral tinnitus in one and unsustained reduction in the other patient [86].

These reports on tinnitus modulating effects of continuous electrical cortical stimulation point toward interesting new options for the perpetuation and amplification of noninvasive brain stimulation techniques. However, available data is very sparse and predominantly uncontrolled, reports on long term effects are missing and the clinical adequacy of this approach has to be discussed particularly for ethical reasons. Clear criteria for the inclusion of patients particularly in respect to treatment resistance are mandatory. However, further controlled trials are needed to allow an estimation of safety and efficacy of this new approach for the treatment of debilitating tinnitus refractory to conventional treatments.

Safety

On the basis of an extensive body of evidence, the noninvasive brain stimulation techniques TMS and tDCS can

be considered as safe and well tolerated when applied within the present safety guidelines [87–89]. The most relevant side effects are discomfort on the scalp during and headache after rTMS. After tDCS headache, nausea and insomnia were reported rarely in addition to a most common mild tingling sensation during tDCS.

Specific rTMS safety studies did not find long-term deterioration in neuropsychologic performance [90–92]. Although a few cases of accidental rTMS induced seizures have been reported, when given within recommended guidelines, the risk of inducing a seizure with rTMS in subjects without epilepsy is very small [93]. Since rTMS induces a clicking sound (~ 70 – 90 dB), the use of earplugs is recommended. However, no significant change in the auditory threshold after rTMS treatment has been observed in several studies [94,95].

Cortical stimulation is associated with the risks of neurosurgery like bleeding and infection and can also induce epileptic seizures. In a single case study, an increase of tinnitus after cortical stimulation [96] has been described.

However, when brain stimulation techniques are used to treat tinnitus, a strict monitoring of auditory function and speech comprehension has to be performed since stimulation is predominantly guided to areas involved in auditory and language processing and may thus interfere also with the proper function of these areas. Furthermore, the modulation of brain activity via stimulation techniques may also, at least in some cases [42,70,97], be associated with an increase of the tinnitus sensation most likely due to individual response characteristics [98] and the general fluctuating nature of tinnitus. In these cases, a stop of the treatment course is strongly recommended to prevent a persistent worsening of tinnitus due to maladaptive plastic processes.

Limitations

Previous therapeutic efforts against tinnitus were impeded by a significant lack of pathophysiological knowledge. Nevertheless, in recent years, neuroscientific research on tinnitus has expanded significantly.

Mechanisms of action

In the treatment of tinnitus, a virtue of brain stimulation techniques is their derivation from comprehensible pathophysiological models that can be tested in controlled trials. Nevertheless, the exact mechanisms of action remain unclear. One hypothesis proposes that low-frequency rTMS exerts an attenuation of tinnitus-related focal disinhibition of cortical activity. In order to verify

and optimize this approach, functional imaging was used for an individualized navigation to these cortical 'hot spots'. However, it has not been shown, that these elaborated strategies yield better effects. Moreover, a study using low- and high-frequency rTMS [73] indicates that the stimulation frequency may not be as critical as suggested by the basic model of frequency dependent activity modulation. Comparable findings were reported with anodal tDCS, that although it is known to increase cortical activity in analogy to high-frequency rTMS transiently suppressed tinnitus [49]. These unexpected response patterns might be linked to the recently shown relevance of baseline activity for the effects of rTMS referred to as homeostatic plasticity [99]. Nevertheless, other mechanisms of action are conceivable: for example, the modulation of pathological network activity [25], transsynaptic propagation of the stimuli with an effect on neurotransmission and activity in deeper brain structures [100] and the interaction with cortico-thalamic rhythms [101]. Therefore, new stimulation paradigms like theta-burst-stimulation [58, 82, 83] may be of special importance. However, it is obvious that the vast number of possible stimulation parameters complicates a systematic search for the optimal strategy.

Placebo Condition

In clinical studies, the effect of an intervention has to be documented by double-blind protocols keeping the patient and the therapist blind to treatment conditions. In the case of rTMS, the person operating the stimulator is aware of the stimulation condition. The ratings are mostly done by self-rating scales. In any case, an adequate placebo condition is indispensable and should mimic the auditory and somatosensory artifact. Most of the commonly used 'placebo coils' do not meet these requirements since they do not induce the distinctive somatosensory perception. In treatment trials on rTMS in depression, the majority of studies the coil was angled by 45° to 90° from the scalp. If the coil is tilted by 90° the somatosensory artifact is much weaker, or if the coil is tilted by 45° this may actually act as a weak active condition [102]. In respect to optimal blinding, stimulation of a cortical area, not related with tinnitus, for example, the occipital cortex [73], or a noncortical area, for example, the lower occiput behind the mastoid [68] appear to be most suitable. Alternatively, more sophisticated placebo coils could warrant an adequate sham condition [103]. However, the validity of several rTMS studies in tinnitus is limited due to lack of an adequate placebo control and as such reported results should be treated with caution.

Duration of Effects and Maintenance

The data available provides divergent evidence on the stability of the tinnitus suppressing effects of rTMS. A decline of the effect within 2 or 4 weeks after the end of treatment was reported [68,70,71] as well as persistence of improvement over 6 [66,76] or 12 months [75]. In this respect, patient characteristics such as hearing impairment may act as a continuing trigger for tinnitus and hence impede a stabilization of the rTMS effect. However, successful maintenance treatment with rTMS in chronic tinnitus by repeated rTMS treatment was shown in a single case study following a beneficial effect of initial 1 Hz rTMS stimulation of the right superior temporal gyrus [104]. Long-term data on the effects of electrical cortex-stimulation is not yet available, but instability of the effects seems also to be a problematic factor [85,86].

Assessment and Clinical Relevance of Treatment Outcome

Treatment outcome for chronic tinnitus is predominantly based on self-assessment questionnaires and not psychoacoustic measures since suppression of loudness does not sufficiently explain therapeutic efficacy on personally experienced handicap and disability [105,106]. The perceived severity tinnitus and its impact on patients' lives are the clinically relevant factors that are measured by TQs developed, for instance, by Hallam [107] and Goebel and Hiller [69,108]. However, reported clinical effects of rTMS on these measures are still weak, even for open studies and raise the question of clinical significance of the improvement. For example, in our clinical pilot-study [68] temporoparietal rTMS shows a significant advantage of 20% over sham stimulation on the TQ immediately after the end of treatment. Four of six subjects did not appraise the tinnitus as changed. In the initial study of Kleijnung et al. [66], a change of 8% compared to baseline after 2 weeks of treatment was significantly higher than the improvement after sham stimulation. With an improvement of less than 25% and a small proportion of subjects reporting individual perception of an effect, these examples pinpoint the question of clinical significance. Therefore, issues of effectiveness and clinical suitability have to be addressed in more detail before these methods will be moved from the laboratory into clinical practice.

Conclusions and Perspectives

Brain stimulation techniques have added considerable new options for the physiological exploration of tinnitus. First treatment trials have provided promising evidence

for a clinical use of rTMS and possibly cortical electrical stimulation in tinnitus treatment. Nevertheless, we are still in an early stage of the development of brain stimulation methods and their particular use for the treatment of tinnitus. The available studies show:

(1) Short-term interference with cortical neuronal activity of temporoparietal areas involved in the perception and procession of auditory information disrupts tinnitus perception [45,47,49]. (2) The reduction of focal hyperactivity by rTMS leads to a transient suppression of tinnitus in a dose dependent manner [42,58]. (3) Repeated applications of several rTMS paradigms can reduce tinnitus loudness and distress [63,66,68,70,73]. (4) The use of electrical cortex stimulation may provide an additional option for a specific group of very severely affected and impaired patients [85,109]. However, the response rate varies, the effect is predominantly moderate and the evidence for the stability of the effect is inconsistent.

On the basis of this evidence, several future steps have to be made in order to improve the neurophysiological knowledge on tinnitus, mechanisms of action and clinical use of brain stimulation techniques:

(1) The knowledge on cortical signatures and oscillatory correlates of tinnitus has to be improved to allow for an evidence based selection and systematic evaluation of stimulation targets, parameters (intensity, frequency patterns, amount of stimuli) and paradigms (stimulation techniques, frequency, and number of stimulation sessions). (2) Evidence has to be collected for predictors of response in order to establish criteria for appropriate patient selection. (3) Larger-scale studies are warranted to test the effect size, clinical relevance, and practicability of brain stimulation techniques to treat tinnitus. At present, two study designs using low-frequency [110] and TBS [83] have recently been published. (iv) Integration of brain stimulation as an additional element of multimodal tinnitus treatment and possibly enhance its effectivity the combination with pharmaco- and behavioral therapy should be further assessed.

At the present stage of development, brain stimulation techniques should be applied primarily within scientific settings that warrant ethical standards, appropriate patient information and scientific processing, and publication of the data collected. However, new evidence from ongoing and future trials will most likely stimulate further work in this highly promising area and provide new vistas for the treatment tinnitus.

Acknowledgments

This work was funded by the German Research Council (DFG; 253 PL1-1).

Conflicts of Interest

None.

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