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Review:

Neuromodulation for tinnitus treatment: an overview of invasive and non-invasive techniques

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Abstract: Tinnitus is defined as a perception of sound without any external sound source. Chronic tinnitus is a frequent condition that can affect the quality of life. So far, no causal cure for tinnitus has been documented, and most pharmacologic and psychosomatic treatment modalities aim to diminish tinnitus' impact on the quality of life. Neuromodulation, a novel therapeutic modality, which aims at alternating nerve activity through a targeted delivery of a stimulus, has emerged as a potential option in tinnitus treatment. This review provides a brief overview of the current neuromodulation techniques as tinnitus treatment options. The main intention is to provide updated knowledge especially for medical professionals counselling tinnitus patients in this emerging field of medicine. Non-invasive methods such as repetitive transcranial magnetic stimulation, transcranial electrical stimulation, neurofeedback, and transcutaneous vagus nerve stimulation were included, as well as invasive methods such as implanted vagus nerve stimulation and invasive brain stimulation. Some of these neuromodulation techniques revealed promising results; nevertheless, further research is needed, especially regarding the pathophysiological principle as to how these neuromodulation techniques work and what neuronal change they induce. Various studies suggest that individually different brain states and networks are involved in the generation and perception of tinnitus. Therefore, in the future, individually tailored neuromodulation strategies could be a promising approach in tinnitus treatment for achieving a more substantial and longer lasting improvement of complaints.

Key words: Tinnitus; Neuromodulation; Invasive technique; Non-invasive technique
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1 Introduction

Tinnitus is defined as a perception of sound (usually a tone or buzzing, but also other sounds) without any external sound source. About 10% to 15% of the population of Europe and the USA are currently experiencing tinnitus, and are seeking medical evaluation and therapy (Axelsson and Ringdahl, 1989; Hoffman and Reed, 2004; de Ridder et al., 2014a). Chronic tinnitus can lead to a lower health-related quality of life (Nondahl et al., 2007; Prestes and Daniela, 2009) and depressive symptoms (Folmer et al., 1999; Dobie, 2003; Weidt et al., 2016). In about 90% of people with chronic tinnitus, some forms of hearing loss have been documented (Davis and Rafaie, 2000; Adjamian et al., 2014). The pathophysiology of tinnitus is not yet thoroughly understood. In the distant past, most forms of tinnitus were assumed to be generated in the inner ear or in the cochlear nerve. The fact that tinnitus usually persists after auditory nerve section (Jackson, 1985) implicates the essential involvement of the central nervous system in the pathophysiology of tinnitus generation and perception. Nevertheless, tinnitus is still thought to be triggered by a peripheral lesion of hair cells in the cochlea, which results in a loss of input to the central auditory

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areas. This theory is supported by different studies (van de Heyning et al., 2008; Punte et al., 2011; Ramos et al., 2012) examining cochlear implantation as an effective treatment option for single-sided deaf patients with tinnitus. Besides cochlear implants, other techniques, which aim at restoring hearing function, like conventional hearing aids, also play an important role in the therapy of tinnitus patients. In the initial theories about the involvement of the central nervous system in tinnitus generation, the reorganization of the auditory cortex was considered to be the origin of all further developments. However, various functional imaging studies and animal models have demonstrated that non-auditory areas as well as the auditory cortex are involved and play an important role in chronic tinnitus patients (Schlee et al., 2008, 2009; Vanneste et al., 2010b). The involvement of central nervous structures in the pathophysiology of tinnitus has had great implications for further therapeutic attempts to reduce tinnitus-related complaints. This development is reflected by the fact that, on the basis of meta-analytic reviews, most guidelines recommend cognitive behavioral therapy as the standard treatment for chronic disabling tinnitus.

Different underlying theories assume that a peripheral lesion of the cochlear hair cells induces a suboptimal or maladaptive plasticity of the central nervous system, inducing reorganization and hyperactivity in central auditory and non-auditory structures (Mühlnickel et al., 1998; Kaltenbach and Afman, 2000; Salvi et al., 2000; Eggermont and Roberts, 2004; Vanneste and de Ridder, 2012; Hoare et al., 2016).

One such theory focuses on the alteration in the tonotopic organization of the central auditory specificity as induced by hearing loss due to hair cell damage. Neurons with a loss of afferent sound input in the affected frequencies could still respond to input from nearby intact frequency regions. This could lead to a shift in the neuron's characteristic frequency, thus resulting in an over-representation of frequencies near the edge of the hearing loss (Eggermont and Roberts, 2004; Adjamian et al., 2014).

Another theory focuses on thalamocortical dysrhythmia (TCD) as a pathophysiologic model for tinnitus generation (Llinás et al., 1999; Vanneste and de Ridder, 2012). The neuronal plasticity due to the hearing loss affects the thalamocortical signal transmission, resulting in a TCD. Physiologically, an auditory stimulus increases the thalamocortical rhythms from alpha (8–13 Hz) to gamma (>30 Hz) waves (Joliot et al., 1994; Vanneste and de Ridder, 2012). In deafferentation, an increased spontaneous firing rate of neurons leads to a slowing down of resting state from alpha to theta (4–7 Hz) oscillations with an increase in surrounding gamma activity (de Ridder et al., 2015b). The consequence of specific thalamic nuclei hyperpolarization in TCD is a constant, coupled theta–gamma band activity (Vanneste and de Ridder, 2012). In correlation with electroencephalography (EEG) and magnetoencephalography (MEG) studies, tinnitus is associated with a persistent high-frequency gamma band activity in temporal brain areas (Llinás et al., 1999, 2005; Weisz et al., 2005, 2007; Vanneste and de Ridder, 2012). Furthermore, theta burst-firing increases the synchronization of neuronal oscillatory activity, which is thought to play a part in the changed neural activity gaining access into consciousness (de Ridder et al., 2015b; Hoare et al., 2016). Alternatively, a noise-cancelling mechanism involving different non-auditory brain areas has been proposed to diminish or prevent tinnitus perception (de Ridder et al., 2014a, 2015b).

The involvement of the non-auditory network in chronic tinnitus patients was first described by Jastreboff (1990). Since then, various functional neuroimaging studies have demonstrated altered brain structures in tinnitus patients, which led to the modelling of different networks involved in tinnitus generation (Schlee et al., 2008, 2009; Vanneste et al., 2010b). de Ridder et al. (2011a) and Langguth et al. (2013) identified several such networks that participate alongside the auditory cortex in tinnitus patients and generated a model of involved networks. These networks include a perception network (subgenual and dorsal anterior cingulate cortices, posterior cingulate cortex, precuneus, parietal cortex, and prefrontal cortex), salience network (anterior cingulate cortex, anterior insula), distress network (anterior cingulate cortex (subgenual and dorsal anterior cortical cortices), anterior insula and amygdala), and memory areas (parahippocampal area, amygdala, and hippocampus).

As previously mentioned, a different concept focuses on a dysfunctional noise-cancelling mechanism, which seems to be driven by the limbic frontostriatal network (de Ridder et al., 2014a; Leaver et al.,

2011, 2012, 2016a; Mühlau et al., 2006; Rauschecker et al., 2010, 2015; Seydell-Greenwald et al., 2012, 2014). Various imaging studies have demonstrated structural and functional changes in the ventromedial prefrontal cortex, nucleus accumbens and medial dorsal nucleus in the thalamus (Pandya et al., 1994; Tanibuchi and Goldman-Rakic, 2003; Mühlau et al., 2006; Leaver et al., 2011, 2012, 2016a, 2016b; Meyer et al., 2016). It is theorized that the limbic structures suppress auditory activity via projections from the ventromedial prefrontal cortex to the thalamic reticular nucleus (Mühlau et al., 2006; Rauschecker et al., 2010; Leaver et al., 2011, 2016a).

All the above-mentioned theories are based on functional imaging studies, which can only indicate the underling mechanism in tinnitus generation. Recently, Sedley et al. (2015) demonstrated the appropriateness of these theories through the intracranial mapping of the cortical tinnitus in a patient. Another way to gain more information about the essential contributions of specific brain areas could be to investigate the behavioral effects resulting from the transient disturbance of neural activity in these regions due to the different neuromodulation methods (Langguth et al., 2012).

These interventions can be divided into invasive (e.g. epidural/subdural or deep brain electrical stimulation) and non-invasive methods (Langguth et al., 2012). Particularly, the non-invasive methods can be furthermore divided into direct (e.g. transcranial magnetic or electrical stimulation) and indirect neurostimulation (e.g. neurofeedback, acoustic coordinated reset (CR) neuromodulation, and tailored notched music therapy). So far, none of the neuromodulation procedures have been established as a routine therapy method in tinnitus patients. This review covers most of the neuromodulation methods, but the ones induced by different ways of acoustic stimulation were excluded (e.g. cochlea implantation as an invasive neuromodulation, acoustic CR neuromodulation and tailored notched music therapy as an indirect neurostimulation).

The aim of this review is to give a short and updated overview of the different neuromodulation approaches in tinnitus research out of the plenty of new literature, especially for medical professionals counselling tinnitus patients. Due to the fact that there is no causal therapy for tinnitus, it is not unusual that often well-informed patients ask medical professionals about a specific neuromodulation therapy which they heard or read about. In the last years more and more data on neuromodulation strategies are available and new techniques were introduced into the field. This article reviews the newest literature of neuromodulation techniques in tinnitus treatment so that medical professionals can counsel their patients according to the latest information and their respective implications in the possible future treatment options of tinnitus. Furthermore, the present value of each technique in clinical routine will be discussed in the particular section.

2 Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive type of neuromodulation. Intermittent magnetic fields are produced by a coil that is in contact with the subject's scalp and that delivers electromagnetic pulses (Theodoroff and Folmer, 2013). These magnetic fields pass largely undistorted through the cranium and affect the neuronal activity of the brain beneath (Kleinjung et al., 2005). Different magnetic fields are generated according to the coil design. Figure-eight coils are often used due to their focused pattern of activation, but other coil types are also used (Soleimani et al., 2016). In repetitive TMS (rTMS), several TMS pulses are applied to the subject's head during one session. The utilized frequency of rTMS modulates the cortical activity differently. In the motor cortex, high-frequency rTMS (i.e. 5–20 Hz) transiently increases the cortical excitability, while low-frequency rTMS (i.e. 1 Hz) usually leads to a reduction of neural activity (Chen et al., 1997; Siebner et al., 2003; Zaghi et al., 2010b). This reduction has led to the proposal of low-frequency rTMS as an innovative treatment strategy for tinnitus, which is a condition associated with increased cortical activity in temporal brain areas (Hoffman and Cavus, 2002; Theodoroff and Folmer, 2013). A selection of literature (Kleinjung et al., 2005; Rossi et al., 2007; Khedr et al., 2008, 2009; Anders et al., 2010; Marcondes et al., 2010; Mennemeier et al., 2011; Chung et al., 2012; Lee et al., 2013) has shown that repeated sessions of low-frequency rTMS applied to temporal or temporoparietal cortical areas had a possible therapeutic efficacy in terms of tinnitus suppression, but

the effect at clinical level was usually partial and temporary (Lefaucheur et al., 2014). Sham stimulation failed to demonstrate any beneficial effect. Further studies have suggested that the therapeutic efficacy of rTMS could be enhanced by stimulating frontal or prefrontal cortical areas in addition to the temporoparietal cortex (Kleinjung et al., 2008; Kreuzer et al., 2011; de Ridder et al., 2013; Lehner et al., 2013a, 2013b; Langguth et al., 2014; Lefaucheur et al., 2014). Most recently, studies have combined high-frequency rTMS of the left dorsolateral prefrontal cortex with low-frequency rTMS of the right, left or both temporoparietal cortical areas and have demonstrated a larger tinnitus improvement than unilateral low-frequency rTMS of the temporoparietal cortex alone (Lehner et al., 2013a, 2013b, 2015; Lefaucheur et al., 2014). Furthermore, a new stimulation design has applied burst rTMS to the auditory cortex for tinnitus suppression (de Ridder et al., 2007a, 2007b). In contrast to tonic TMS, which mainly inhibits pure tone tinnitus, burst stimulation transiently suppressed both pure tone and narrow-band tinnitus (de Ridder et al., 2007a, 2007b).

Despite some promising results, the therapeutic effect of rTMS on chronic tinnitus is usually partial and temporary. Furthermore, the long-term effects of TMS are still not known yet. For these reasons, rTMS is not recommended as a therapeutic option in clinical routine. Nevertheless, rTMS qualifies as a diagnostic method in research investigating which brain areas are involved in tinnitus generation. On that basis, rTMS has been used for localization purposes in other neuromodulation methods targeting different brain areas for tinnitus suppression. For this purpose, mainly high-frequency rTMS was used, e.g., for determining the correct position of an implanted epidural electrode.

3 Transcranial electrical stimulation

3.1 Transcranial direct current stimulation

In transcranial direct current stimulation (tDCS), another non-invasive method of brain stimulation, a relatively weak, constant current (between 0.5 and 2 mA) is applied via scalp electrodes and passes through the cerebral cortex (Vanneste et al., 2011a; Vanneste and de Ridder, 2012). Two saline-soaked surface sponges act as surface electrodes, one serving as the anode and the other as the cathode. Anodal tDCS induces a depolarization of neurons leading to an excitatory effect on the underlying cerebral cortex while, under the cathode, a hyperpolarization causes an inhibitory effect. Depending on the polarity of the stimulation, tDCS can increase or decrease cortical excitability in the brain regions to which it is applied (Miranda et al., 2006).

The application of tDCS led to a temporary reduction in tinnitus loudness or distress ranging from seconds to hours, depending on the location of cortical stimulation (Song et al., 2012; Shekhawat et al., 2016). Anodal tDCS over the left temporoparietal area with the cathode over the contralateral frontal scalp resulted in a transient suppression of tinnitus in up to 40% of participants (Fregni et al., 2006; Garin et al., 2011; Shekhawat et al., 2013). Furthermore, bifrontal tDCS placement of the electrodes on the dorsolateral prefrontal cortex (with either the anodal electrode on the right and the cathodal electrode on the left side, or the opposite orientation), temporarily suppressed tinnitus perception and tinnitus distress in up to 43% of participants (Vanneste et al., 2010a, 2011b, 2013a; Vanneste and de Ridder, 2011; de Ridder and Vanneste, 2012; Faber et al., 2012; Frank et al., 2012). Lastly, bilateral tDCS over the auditory cortex has been shown to suppress tinnitus loudness (Joos et al., 2014).

Due to the broad region of brain stimulation in tDCS between and underneath the electrodes, the interpretation of anatomically involved brain areas is difficult. One potential improvement to this problem is the use of high-definition tDCS (HD-tDCS) (Shekhawat et al., 2016). For controlled targeting of the stimulation, the conventional large sponge electrodes are replaced with smaller gel electrodes in HD-tDCS. In the setting of a 4×1 HD-tDCS, four electrodes are placed in a ring around a polarity determining the center electrode (Datta et al., 2009; Edwards et al., 2013). This arrangement of tDCS enables a controlled targeting of the stimulation underneath the electrodes (Shekhawat et al., 2016). Shekhawat et al. (2016) demonstrated that 77.8% of the participants responded to HD-tDCS and referred to suppression of tinnitus loudness and annoyance with equal results. This was with a stimulation location of the left temporoparietal area and right dorsolateral prefrontal cortex. In

conclusion, HD-tDCS provides an opportunity to stimulate multiple target sites simultaneously and could therefore be a promising non-invasive neuromodulation method in tinnitus treatment (Shekhawat et al., 2016), but further research is required.

3.2 Transcranial alternating current stimulation

Another technique of non-invasive transcranial electrical stimulation is based on the application of alternating currents through an electrode, and is known as transcranial alternating current stimulation (tACS). The frequency of applied alternating currents allows for the manipulation of intrinsic cortical oscillations and it is therefore possible that tACS can interact with rhythmic neuronal activity (Zaghi et al., 2010a). It follows that tACS should be able to modulate functions that are closely related to brain oscillations at specific frequencies, such as the decreased alpha and the increased gamma activity in the auditory cortex of tinnitus patients (Lorenz et al., 2009; de Ridder et al., 2011b; Vanneste et al., 2013b). The application of tACS intensifies the individual alpha frequency of the stimulated area (Zaehle et al., 2010a) and this is how tACS is presumed to modulate the tinnitus percept (Vanneste et al., 2013b).

Despite the plausibility of this theoretical model, no effect on the tinnitus percept has been obtained by alpha modulated tACS over the auditory and dorsolateral prefrontal cortex (Zaehle et al., 2010b; Zaghi et al., 2010a; Vanneste and de Ridder, 2013). Although the study of alpha-modulated tACS is at an early stage, further investigation does not seem merited (Claes et al., 2014; Hoare et al., 2016).

3.3 Transcranial random noise stimulation

A further method of non-invasive transcranial electrical stimulation that has been tested to a greater extent is transcranial random noise stimulation (tRNS). In tRNS, the generated current consists of random oscillations in a normal distribution for amplitude with a frequency spectrum between 0.1 and 640 Hz, which appears similar to “white noise” in structure (Paulus, 2011; Vanneste et al., 2013b; To et al., 2017). Potentially, the application of tRNS might disrupt tinnitus related synchrony in the auditory cortex and could thus induce an improvement of the tinnitus percept (van Doren et al., 2014). Vanneste et al. (2013b) demonstrated a larger transient suppressive effect on tinnitus loudness and tinnitus-related distress with tRNS as compared to tDCS and tACS when applying the electrodes over the auditory cortex bilaterally. In another study (Joos et al., 2015), multiple sessions of tRNS showed an increased effect on tinnitus loudness but no further effect on tinnitus distress. Furthermore, a multisite transcranial electrical stimulation protocol with bilateral auditory cortex tRNS after bifrontal tDCS showed more pronounced suppressive effects on tinnitus loudness and distress than the bifrontal tDCS protocol alone (To et al., 2017).

The whole-frequency spectrum of tRNS is often subdivided into a low- (0.1–100 Hz) and a high-frequency (100–640 Hz) tRNS, which can result in diverse effects (Terney et al., 2008; Fertonani et al., 2011; Saiote et al., 2013; Joos et al., 2015). Regarding the frequency spectrum, Joos et al. (2015) demonstrated that both low- and high-frequency tRNS reduced tinnitus loudness while only low-frequency tRNS had an effect on tinnitus-related distress. Whole-frequency tRNS applied bilaterally over the temporoparietal cortex had no significant effects on tinnitus loudness or tinnitus-related distress.

Generally, tRNS could be a potential treatment option for tinnitus, but further studies are needed to evaluate the therapeutic effect of tRNS in a clinical routine.

4 Neurofeedback

Neurofeedback is based on the principal of operant conditioning, and is another example of a non-invasive neuromodulation technique. In it, relevant aspects of brain signals acquired through EEG or other functional imaging techniques are extracted and processed into visual or acoustic signals, which are then fed back to the participant in real time. The participant has to fulfill a task using the visual or acoustic feedback signals, and gets rewarded for desired changes or punished for undesired changes in brain activity. This kind of operant conditioning of EEG rhythms has already yielded successful results in attention-deficit hyperactive disorder and epilepsy (Lubar and Bahler, 1976; Lubar and Shouse, 1976; Lansbergen et al., 2011). As tinnitus patients also demonstrate abnormal spontaneous brain activity with

higher theta (4–7 Hz), gamma (>30 Hz), beta (14–30 Hz), and lower alpha (8–13 Hz) band activity, neurofeedback has been studied as a treatment option (Gosepath et al., 2001; Schenk et al., 2005; Dohrmann et al., 2007a, 2007b; Crocetti et al., 2011; Hartmann et al., 2014). Both a single change of an increase of alpha frequency, and a combined change with an increase of alpha and a decrease of beta or delta frequency in the region of the auditory cortex correlated with reduced tinnitus distress scores (Gosepath et al., 2001; Schenk et al., 2005; Dohrmann et al., 2007a, 2007b; Crocetti et al., 2011; Hartmann et al., 2014). However, besides some methodological shortcomings, difficulties in defining outcome measurements and small group sizes with lacking control condition, the non-invasive technique of neurofeedback seems to have some future potential in the treatment of tinnitus. To date, no source localization algorithms of the EEG recordings (e.g. low-resolution electric tomography analysis (LORETA)) have been used to optimize the spatial resolution in the neurofeedback setting. Neurofeedback training protocols, which specifically focus on different brain areas of tinnitus networks by using an EEG source localization algorithm, could be investigated as an even more specific non-invasive treatment modality for tinnitus in the future.

5 Vagus nerve stimulation (VNS)

5.1 General concept of VNS

Discrimination training as a form of auditory stimulation has been postulated to reverse the pathological neuroplastic changes in the auditory system associated with hearing loss and subsequent tinnitus (Hoare et al., 2014, 2016). However, the clinical benefit of this concept of auditory stimulation has been limited and the demonstrated improvements transitory (Hoare et al., 2010, 2016). As previously mentioned, not only the central auditory structures are involved in the suboptimal or maladaptive neuroplasticity in tinnitus generation and perception; non-auditory brain areas also participate in the plastic changes. Another important part in the modulation of cortical plasticity is played by the cholinergic and noradrenergic forebrain system. Animal studies have illustrated a pronounced and long-lasting change in cortical reorganization as induced by electrical stimulation of the cholinergic nucleus basalis (Kilgard and Merzenich, 1998a). This finding led to the idea of pairing auditory stimulation with electrical stimulation of the nucleus basalis as a possible tinnitus treatment (Kilgard and Merzenich, 1998b). However, an invasive procedure has to be performed to stimulate the nucleus basalis and therefore this kind of stimulation is not practicable in an extensive application for tinnitus treatment (Hoare et al., 2016). Engineer et al. (2013) demonstrated a similar stimulation of the nucleus basalis by using a much less invasive electrical VNS in noise-exposed rats with hearing loss and behavioral evidence of tinnitus. The pairing of VNS with auditory stimulation—consisting of acoustic tones at frequencies outside the tinnitus range—reversed the abnormal neural activity and behavioral correlates of tinnitus in noise-exposed rats (Engineer et al., 2013). Neither VNS nor acoustic stimulation alone showed a similar effect (Engineer et al., 2013). It has been postulated that while acoustic tones stimulate the auditory cortex as a target for the neuroplastic change, the VNS promotes the desired cortical reorganization by inducing neuroplastic activity (Engineer et al., 2013).

5.2 Implanted VNS

Based on the above-mentioned concept of VNS, several studies have been conducted in the last few years to explore the safety and efficacy of this procedure in humans (de Ridder et al., 2014b, 2015a).

As the implantation of a stimulation electrode on the vagal nerve is an invasive procedure, there are several operative risks as well as adverse effects due to VNS. These include general anaesthesiological risks, possible infection of the surgical site by the device, hoarseness due to vocal cord hypomobility, and temporary increases of tinnitus (Hoare et al., 2016).

In a pilot study, ten participants with chronic moderate to catastrophic tinnitus severity received an implantation of the vagal nerve stimulator (de Ridder et al., 2014b). The acoustic stimulation with tones, excluding the tinnitus-matched frequency, was paired with VNS (de Ridder et al., 2014b). A clinically meaningful improvement of the tinnitus as well as physiological effects measured by EEG was reported by four of ten participants (de Ridder et al., 2014b). Furthermore, it was demonstrated that five of the participants with no improvement were taking different

medications including muscarinic antagonists, norepinephrine agonists, and γ-amino butyric acid agonists. These medications could probably interfere with acetylcholine and norepinephrine release induced by VNS.

The company MicroTransponder Inc. has recently presented its results of a double blind, randomized, multicenter study with 30 patients titled "Paired VNS™ treatment uses Vagus Nerve Stimulation (VNS) paired with tones" on their website (http://www.microtransponder.com/en-gb/tinnitus/physicians/clinical-experiences, data not yet published). The overall clinical responder rate measured with a minimum change of 20% in tinnitus handicap inventory (THI) scores (Newman et al., 1996) was 56% in the paired VNS™-treated patient group. Only mild adverse events were reported. Some degree of vocal cord paralysis was described in two patients with ongoing clinical improvement of the hoarseness or voice weakness. The promising results of paired VNS with acoustic could lead to a treatment option for tinnitus patients. However, at the moment the paired VNS™ as a tinnitus treatment is not yet US Food and Drug Administration (FDA)-approved.

5.3 Transcutaneous VNS

Transcutaneous stimulation of the vagus nerve (tVNS) via a nerval branch innervating the skin in the external auditory canal, as a non-invasive approach, has been investigated in parallel (Kreuzer et al., 2012, 2014; Lehtimäki et al., 2013). A pilot study from Kreuzer et al. (2014) demonstrated the feasibility and safety of tVNS in patients without a history of cardiac disease. However, there was no clinically relevant improvement of tinnitus complaints. Lehtimäki et al. (2013) demonstrated acute neuromodulative effects of tVNS paired with tinnitus frequency-filtered music on the evoked auditory cortical responses. Furthermore, some patients showed a significant clinical decrease in tinnitus handicap. Hyvärinen et al. (2015) showed compatible neuronal changes on MEG and that the tVNS-induced change was correlated with THI scores. At present, there is one ongoing randomized, single-blind, controlled clinical study of tVNS for tinnitus (Li et al., 2015). The results of this study are expected to be very informative and could lead to further clinical investigation about tVNS as a therapeutic option for tinnitus.

6 Invasive brain stimulation

Based on the theory of neuronal plasticity and reorganization of the central nervous system in tinnitus generation, invasive brain stimulation focuses on altering the neuronal tinnitus network through the electrical stimulation of cortical (epidural or subdural) or deep brain areas using implanted electrodes.

6.1 Epidural and subdural cortical stimulation

de Ridder et al. (2004) published the first case report of tinnitus suppression by using invasive electrical stimulation of the primary auditory cortex in a single tinnitus patient. The patient suffered from severe left-sided tinnitus subsequent to a sensorineural deafness after acoustic neuroma surgery on the left side. After the tinnitus responded positively to TMS applied to the right auditory cortex, an extradural electrode was implanted for electrical stimulation. Initially, the electrical stimulation caused the patient's tinnitus to disappear completely. However, three weeks postoperatively, the high-pitched tinnitus returned. This was possibly due to cortical plasticity in response to the constant stimulation.

In a following case series from the same group (de Ridder et al., 2006), 12 participants with moderate-to-severe tinnitus received an implantation of two-pole electrodes, one electrode positioned intradural on the primary, and the other extradural on the secondary auditory cortex. The electrodes were then connected to an internal impulse generator which was first placed externally for one week and then implanted subcutaneously over the abdomen after beneficial effects of stimulation were noted. Overall, only two patients failed to report any improvement in their tinnitus complaints. Especially those participants with unilateral or pure tone tinnitus had better tinnitus suppression than those with bilateral or white noise tinnitus. Nevertheless, the tinnitus reappeared in all patients after a certain time of stimulation.

Based on the model of TCD with hyperactivity in the vicinity of deafferented auditory cortex, Seidman et al. (2008) attempted to stimulate these neighboring regions of the reorganized auditory cortex. After a tonotopic mapping of the areas with increased activity in Heschl's gyrus, electrode arrays were placed on these targeted sites in two participants. One participant with bilateral, high-pitched tinnitus experienced

a sustained reduction of tinnitus, whereas the other participant with unilateral, high-pitched, narrow band tinnitus did not show a decrease in tinnitus.

In another case report (de Ridder and Vanneste, 2014), the auditory cortex stimulation induced by implanted electrodes was combined with subcutaneous C2 electrical stimulation. It was hypothesized that these two neuronal pathways interact at the level of the cochlear nuclei. The participant reported a diminished noise-like tinnitus and an absent pure tone tinnitus for a period of at least five years.

The anterior cingulate cortex, a proposed responsible brain area in the tinnitus distress network, has been investigated as another location for cortical stimulation (de Ridder et al., 2016). In two participants, electrodes were implanted bilaterally over the dorsal anterior cingulate cortex. One participant responded to this kind of stimulation with a dramatic reduction of tinnitus loudness and distress, with a sustained effect for more than two years after implantation. In contrast, the other participant did not report any improvement of the tinnitus although various stimulation parameters were evaluated. It was demonstrated that the participant experiencing an improvement in tinnitus had an increased functional connectivity from the dorsal anterior cingulate cortex to a tinnitus network consisting of the parahippocampal area, subgenual anterior cingulate cortex and insula, whereas the nonresponder had decreased functional connectivity between these areas (de Ridder et al., 2016).

This example supports the assumption that there are different existing types of tinnitus according to the involved brain areas and their functional connectivity. The analysis of functional connectivity may determine at what localization a cortical implant could lead to an improvement of tinnitus. However, research about cortical stimulation in tinnitus patients is still at an early stage and further investigation is needed. Nevertheless, as an invasive neurosurgical procedure with various risks attached, cortical stimulation as a potential therapeutic option will presumably always be limited to a very select group of tinnitus patients.

6.2 Deep brain stimulation

Deep brain stimulation (DBS) of specific brain regions has become an effective treatment option in patients with therapy-resistant neurological disorders such as tremor (Koller et al., 1999; Rehncrona et al., 2003), dystonia (Vidailhet et al., 2009), Parkinson's disease (Krack et al., 2003; Bittar et al., 2005a), and chronic pain (Marchand et al., 2003; Bittar et al., 2005b; Owen et al., 2006). Thus far, an electrode for DBS has not been implanted solely for the purpose of tinnitus treatment. However, in patients with comorbid tinnitus who received DBS to alleviate movement disorders, the concomitant effect on tinnitus perception has been evaluated. In the first study investigating this topic, an electrode was implanted in the ventralis intermedius nucleus of the thalamus of seven patients with movement disorders and comorbid tinnitus (Shi et al., 2009). Three of these seven patients reported reduced tinnitus loudness when DBS was turned on (Shi et al., 2009). In another study (Cheung and Larson, 2010), six patients suffering from Parkinson's disease and concomitant tinnitus underwent an electrode implantation in the subthalamic or ventralis intermedius nucleus of the thalamus with the electrode lead traversing through, or being adjacent to, a locus of caudate neurons (area LC) in the body of the nucleus, which is a subsidiary of the striatal network. In five patients where the DBS lead tip traversed area LC, tinnitus loudness in both ears was suppressed (Cheung and Larson, 2010). In the one subject where the DBS lead was outside area LC, tinnitus remained unchanged (Cheung and Larson, 2010). The authors presume that the area LC, a striatal sensorimotor integration center that is not part of the classical auditory pathway, may modulate the integration of phantom sensations generated from the central auditory system to brain areas of perceptual awareness (Cheung and Larson, 2010). A recently published study (Smit et al., 2016) investigated the effect of DBS on tinnitus in a retrospective multicenter survey. The study indicated that DBS may indeed reduce the handicap caused by tinnitus. It was noted that stimulation of the subthalamic nucleus resulted in the most beneficial effect.

It must be stated that in the above-mentioned studies an electrode for DBS was implanted due to another coexisting disease. It follows that the interactive effects of these comorbidities with tinnitus are unknown. To conclude, more research of DBS in tinnitus is needed, particularly with regard to which possible brain regions show the most benefit from stimulation but also to the effects of different stimulation

characteristics, such as frequency and intensity on the neuronal level.

7 Concluding remarks

In the last two decades, different neuromodulation techniques have been developed, which enable the focal modulation of neuronal activity. The increasing knowledge regarding tinnitus-related activity changes in the brain resulted in the logical consequence that the neuronal correlates of tinnitus were directly targeted in terms of neuromodulation techniques. The innovative idea was that this influencing of the electrical activity of the involved brain networks would serve as an important diagnostic and therapeutic tool in further research. In recent years, multiple invasive and non-invasive techniques have been evaluated for the normalization of tinnitus-related brain activity as a more causally oriented treatment approach. Experimental approaches using different neuromodulation techniques have demonstrated some promising results in reducing tinnitus-related complaints, but have mostly failed in terms of a complete extinction of the tinnitus percept.

However, most of the studies mentioned have similar limitations that lower their significance. First, the treatment efficacy is elusive due to the fact that for the outcome measure of tinnitus, only subjective (and no objective) measurements exist. Moreover, different available outcome measures of tinnitus reduce the comparability between the available studies. Further limitations in most of the studies are a small sample size, a lack of adequate placebo condition or no placebo arm, the heterogeneity of the patients, possible previous treatment for tinnitus, ongoing therapy with antidepressant drugs, and no long-term follow-up. It is also important to mention the possible side effects of the different neuromodulation therapies such as seizures in rTMS or surgical risks in invasive neuromodulation techniques.

In conclusion, different neuromodulation methods provide a confident outlook to possible therapeutic options in the treatment of tinnitus. In particular, non-invasive neuromodulation techniques are promising as a treatment option for a large proportion of patients suffering from tinnitus, whereas invasive neuromodulation methods due to the neurosurgical risks will presumably be restricted to a select patient group: those with persistent severe tinnitus despite different previous treatment attempts. However, further research is needed in almost every neuromodulation procedure before the techniques can be considered as routine treatment options. The clinical heterogeneity of tinnitus leads to the assumption of the existence of different forms of tinnitus, which differ in their underlying pathophysiology (Frank et al., 2012). Therefore, it seems to be crucial to typify the different kinds of tinnitus as well as their associated involved brain networks and brain states, thus providing a basis from which to modulate these specific brain areas with different neuromodulation techniques. The hope for the future is that a better phenotypization of tinnitus (e.g. in terms of standardized EEG procedures) may enable the design of individually personalized neuromodulation strategies.

Compliance with ethics guidelines

Nicole PETER and Tobias KLEINJUNG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：神经调节方法治疗耳鸣——侵入性和非侵入性技术概述

概　要：耳鸣被定义为非外部声音产生的听觉感知，慢性耳鸣是一种影响生活质量的常见病症。目前为止，尚无任何针对耳鸣诱因的治疗方法，大部分的药理和心理治疗方法都旨在减少耳鸣对生活质量的影响。神经调节是一种新型的治疗方式，该方法通过定向刺激来改变神经活动，已经成为耳鸣治疗的一个潜在选择。本文就当前神经调节技术治疗耳鸣做了简要概述，主要目的是为相关人士提供更新的知识介绍，特别是在这个新兴医学领域的专业工作者。本文介绍了包括经颅磁重复刺激、经颅电刺激、神经反馈和经皮迷走神经刺激等非侵入性方法，以及植入的迷走神经刺激和侵入性脑刺激等侵入性方法。虽然一些研究已经展示了神经调节技术的良好应用前景，但是相关的研究还需要加强，尤其是关于神经调节的病理生理学原理，即这些神经调节技术如何发挥作用以及神经调节所引起的神经元变化。多项研究表明，不同个体的大脑活动状态和神经连接网络都参与了对耳鸣的产生和感知。因此，未来个性化定制的神经调节策略可能是一个有前景的耳鸣治疗方法，从而更显著、更持久地改善这个常见病症状。

关键词：耳鸣；神经调节；侵入性方法；非侵入性方法

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