Tinnitus: Is there a place for brain stimulation?

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Abstract

Tinnitus is the perception of a “phantom sound” and has a high prevalence. Although many therapies have been investigated within the last decades, there is still no effective standard therapy. Animal studies and human functional imaging studies revealed that tinnitus perception is associated with many complex changes in multiple brain structures. There is growing evidence that brain stimulation might be able to interrupt the local altered neuronal activity and hereby inhibit tinnitus perception. In this editorial review, an update is given on the most promising targets for brain stimulation. Promising structures for stimulation are the dorsal cochlear nucleus, the inferior colliculus and the medial geniculate body of the thalamus. For cortical stimulation, the auditory cortex is considered as a target. Nevertheless, the field is waiting for evidence from well-designed clinical trials, based on supporting evidence from experimental/mechanistic research, to support or discourage the application of brain stimulation in tinnitus.

Key Words: Deep brain stimulation, electric stimulation, neuromodulation, tinnitus, treatment

Currently, up to 15% of the general population suffers chronically from the perception of a “phantom sound”, also known as tinnitus. This is defined as the perception of a sound in the absence of an external source. Due to lack of awareness and an aging population, the prevalence is still rising. The most severe degree of tinnitus is experienced by 2.4% of the population and is associated with insomnia, depression, and even suicide. Although many therapies are being developed in the last years, there is still no effective standard therapy. Current therapies mostly focus on treating the distress caused by tinnitus instead of reducing the actual phantom sound. Nevertheless, many patients do not benefit from the current approaches and become severe and chronic tinnitus sufferers. In these patients, neuromodulation-based treatments can be a promising option. Several preclinical and clinical studies demonstrated beneficial effects. From coincidental findings in Parkinson’s disease patients who also had tinnitus and were treated with deep brain stimulation (DBS), we know that stimulation can alter or even completely diminish the perception of tinnitus. Since central nervous system changes especially occur in the chronic patients, it can be expected that these refractory, chronic, and often severe sufferers are the best candidates for neuromodulation. In this editorial review, pathophysiological changes associated with tinnitus and the potential of neuromodulation to interfere with these changes are discussed. Based on the latest preclinical and clinical studies, brain stimulation of subcortical...
It can be expected that modulation of Tinnitus perception is the result of dysfunction of multiple involved brain structures. The exact working mechanism of DBS is unknown, but different theories describe a combined excitatory and inhibitory effect. DBS has been shown to be able to reduce an increased spontaneous activity as this therapy inhibits the elevated bursting activity in the subthalamic nucleus in Parkinson’s disease patients. It can be expected that modulation of one arbitrary part in the complex tinnitus pathways can disrupt pathological neuronal activity and thereby alter tinnitus perception or distress caused by this phantom sensation.

Complex interactions within and between auditory and nonauditory brain structures are present in tinnitus. Every change in neuronal activity causes a cascade of changes in direct and indirect connected brain areas. An important role of the limbic system has been implied, as studies have shown that attention and emotions can influence tinnitus perception. To simplify the complex pathways, classical and nonclassical auditory pathways are distinguished, not taking descending projections into account. Following the classical pathway, the cochlear nerve fibers end in the ipsilateral cochlear nucleus (CN), further project to the central part of the mainly contralateral inferior colliculus (IC), and subsequently to the medial geniculate body (MGB) and primary auditory cortex. Brain structures in the nonclassical auditory pathway are interestingly less tonotopically organized than in the classical pathway and have additional connections with the limbic system and caudate nucleus. The central part of the IC connects to the dorsal and external nucleus of the IC, which in turn projects to the dorsal and medial part of the MGB. From these parts of the MGB, connections project to the amygdala, secondary auditory cortex, and association auditory cortex. The loudness of tinnitus does not always correlate with the burden and impact of tinnitus on life quality, suggesting a substantial role of nonauditory brain structures in the pathophysiology of chronic tinnitus. The importance of auditory-limbic interactions has been emphasized by Rauschecker et al., who propose a failing neural “noise cancelation” mechanism of (para)limbic structures as the underlying cause of tinnitus suffering.

Multiple targets can be proposed in which DBS might have an advantageous effect on tinnitus perception, as shown in Figure 1. Within the auditory pathway, three nuclei should be considered. First, multiple preclinical and clinical studies suggest that the dorsal CN (DCN) plays an important role in the development of tinnitus and could, therefore, be a target for DBS in tinnitus. An increased bursting activity is found in both the DCN and ventral CN. Ablation of this structure in an animal study resulted in a decrease in neuronal hyperactivity in higher output structures. In a human study, patients who did not have a functioning auditory nerve received an auditory brainstem implant in the DCN. The majority of successfully implanted patients (6/10) reported a reduction in tinnitus perception or even complete suppression (1/10) during stimulation. Side effects of stimulation that have been described include facial pain and ocular vibration, although some studies do not mention any side effects. Effects of stimulation on hearing in patients with intact auditory nerves are not known. Second, IC stimulation might have an effect on tinnitus perception since studies have shown an increased spontaneous activity and neuronal synchrony in the contralateral IC in tinnitus. Almost all ascending auditory brainstem projections converge in the IC. Electrical stimulation of the IC in patients with unilateral deafness showed some side effects including the perception of unpleasant sounds, paresthesia, dizziness, facial twitches, and temperature changes.

Third, the MGB is a possible target in the...
auditory pathway. It is known that the thalamus plays an important role in tinnitus, as thalamotomies have shown attenuation of tinnitus. Integration of auditory and limbic information occurs in the thalamus and more specifically, the amygdala receives auditory input from the MGB. The MGB has an important role in tinnitus, since the ventromedial prefrontal cortex and nucleus accumbens (NAc) might be able to tune out the pathophysiological tinnitus signal by projecting to the MGB. Although the role of the MGB in tinnitus is less intensively investigated as compared to the DCN and IC, it can be expected that stimulation of this specific thalamic structure can influence tinnitus perception and distress. Side effects of electrical stimulation of the MGB are not known. Thalamic stimulation for movement disorders, however, has been proven to be safe with only a few reversible side effects. The MGB is better accessible with stereotaxy than deeper auditory structures and, therefore, the risks of surgery are expected to be relatively low.

Coincidental findings in patients with movement disorders who were treated with DBS, taught us that stimulation of nonauditory targets can attenuate tinnitus. Stimulation of the ventral intermediate nucleus of the thalamus (VIM) in Parkinson’s disease patients who also suffered from tinnitus improved tinnitus in three out of seven patients. Furthermore, two case reports described a decreased tinnitus perception after a cerebrovascular accident in the putamen and caudate nucleus and after perioperative focal vascular injury in a locus of the caudate nucleus (area LC). A clinical study where patients with movement disorders were temporarily stimulated in area LC revealed a decrease in tinnitus loudness in all patients. Although we do not know much about the role of the VIM or caudate nucleus in the pathophysiology in tinnitus, abovementioned findings are encouraging. The NAc, also known as the “reward center” of the brain, has a role in tinnitus distress according to clinical electroencephalographic findings. It is hypothesized that DBS of the NAc in tinnitus would disrupt the abnormal functioning NAc in tinnitus patients in a way that tinnitus perception would be inhibited. DBS of the NAc has been performed in obsessive-compulsive disorder patients and is associated with a risk of hypomania. Human functional magnetic resonance imaging studies and preclinical studies have demonstrated the involvement of the amygdala and hippocampus in tinnitus, and these areas could, therefore, be considered as possible DBS targets. Side effects such as negative emotions have appeared in some patients during stimulation and make these areas less suitable for the treatment of tinnitus with DBS.

Other neuromodulation-based approaches have also been suggested. In this respect, modulating the activity of relevant cortical structures has been performed. Transcranial magnetic stimulation (TMS) is a noninvasive technique in which strong magnetic field impulses can alter neuronal activity not only in cortical but also in areas connected to the cortex. Repetitive TMS can induce residual inhibition and suppress tinnitus loudness temporarily. The effect of another noninvasive therapy, transcranial direct current stimulation, has been evaluated in a meta-analysis. Overall, 39.5% of the patients responded with an average decrease in tinnitus intensity of 13.5%. This effect can last for an hour or longer. Another method of modulating the cortical activity is by extradural electrical stimulation. Stimulation of the primary auditory cortex and/or the secondary auditory cortex can be successful in suppressing severe, refractory tinnitus. De Ridder et al. implanted auditory cortex electrodes in 43 tinnitus patients who all showed benefit from two placebo controlled TMS sessions. In this technique, the electrodes are secured on the dura of the auditory cortex, which is reached via a craniotomy (2 cm × 6 cm), guided by functional magnetic resonance imaging. Despite that all patients responded to TMS, only 67% responded to cortical stimulation with an average suppressing effect of 51%. Side effects of stimulation are limited and only occurred at high frequency or high-intensity stimulation. Symptoms as a feeling of intoxication, word finding difficulties, dizziness, vertigo, hearing perception changes, feeling of “aural pressure,” and out of body experiences were described. Complications can be severe. Epileptic seizures occurred in 3 of 43 patients and of the 4 patients, who were implanted following the intradural technique, one had an intracranial hemorrhage, and one developed an intracranial abscess. In another recent study, chronic electrical stimulation of the auditory cortex was applied in nine patients. The authors did not find a general objective efficiency. Overall, cortical electrical stimulation might become a beneficial treatment option for a subgroup of severe tinnitus patients.

Besides DBS and cortical neuromodulation approaches, some other concepts have been described. Intracochlear stimulation via cochlear implantation is a viable treatment option in patients with tinnitus and unilateral of bilateral severe or profound hearing loss. In patients with bilateral hearing loss, a systematic review concluded a reduction of mean tinnitus score of 25–72% and a total suppression of tinnitus in 8–45% of patients. Standard clinical stimulation, stimulation independent of an acoustic input, and even inaudible stimulation can be effective. This suggests an effect of central neuroplastic changes besides the effect of a shift in attention from tinnitus to environmental sounds. Another technique that can indirectly influence central tinnitus-related neuronal activity is noninvasive transcutaneous electric nerve stimulation (TENS). The cochlear nuclei receive somatosensory, nonauditory inputs besides auditory inputs from the vestibulocochlear nerve.
Preclinical studies showed that transcortaneous electrical stimulation of the branches of the trigeminal nerve and parts of the dorsal column cause modulation of neuronal activity in the DCN. TENS of the median nerve, temporomandibular joint, parts of the external ear, and upper cervical nerve C2 can be used to inhibit tinnitus perception temporarily in some patients. Recently, electrical stimulation of branches of the trigeminal nerve or the trigeminal ganglion has been proposed as a potential treatment modality for tinnitus. In conclusion, developments in the field of neuromodulation are promising for patients with severe tinnitus. Several types of neuromodulation-based approaches are being investigated. The general mechanism of action is that neuromodulation interferes with pathological neuronal activity and thereby can attenuate distress or perception of tinnitus. In this respect, increased neuronal activity is found in the DCN, IC, MGB, and auditory cortex. These regions are, therefore, potential targets for brain stimulation. It is impossible to reach these regions selectively and precisely with noninvasive stimulation methods. When surgery is considered, then the MGB is a more accessible target. Furthermore, the MGB is an important relay station where the auditory and limbic structures interact. Tinnitus perception can be influenced by superficial stimulation techniques, which attenuate abnormal auditory cortex activity. Up to date, only a subgroup of tinnitus patients responded to auditory cortex stimulation. From the nonauditory structures, stimulation of the VIM, caudate nucleus (area LC), and NAc have potential to interfere with tinnitus. Using a bottom-up approach with cochlear stimulation or TENS of somatosensory inputs of the DCN, tinnitus percept can be modified in some cases. Although much is happening at the moment, the field is waiting for evidence from well-designed clinical trials, based on supporting evidence from experimental/mechanistic research, to support or discourage the application of brain stimulation in tinnitus.

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