

New Treatment Approaches in Tinnitus: The Place of Repetitive Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

Review ▶

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Abstract ▶

Tinnitus is described as the perceived sensation of sound in the absence of acoustic stimulation. According to recent studies, it is one of the most common health problems disturbing patients in their daily lives. Although previous studies have focused more on the peripheral features, such as inner ear pathologies, as the possible causes of tinnitus, accumulating evidence suggests that tinnitus is related to neuronal hyperexcitability in the auditory and non-auditory brain areas. Recent neuroscience research has shown that neuromodulation tools, such as repetitive transcranial magnetic stimula-

tion (rTMS) and transcranial direct current stimulation (tDCS), have promising effects in the treatment of tinnitus. However, the mechanisms of these observed positive effects are still far from being clear. The aim of this article is to review the pathophysiology of tinnitus and possible pathways of recovery by neuromodulation treatments and to summarize the results of recent randomized, controlled studies using tDCS and rTMS.

Key Words: Tinnitus, rTMS, tDCS, neuromodulation

Introduction

Tinnitus, which is seen in more than 10% of the adult population in the world, is defined as sound heard in the head (ringing in the ears) without any external stimulus. According to studies carried out, only a restricted response can be received to the treatment of tinnitus, leading to impaired quality of life and loss of functioning, by today's pharmaceutical treatment methods (1). Tyler (2) suggested that tinnitus caused anxiety, nervousity, irritability, cognitive dysfunction, sleep disorder, and even insomnia and depression.

Tinnitus can be examined under 2 general categories: objective and subjective tinnitus. Its objective form is felt by reaching the sound that originated from the body to the ear, and contrary to subjective tinnitus, this sound can be sometimes heard, even from outside by a stethoscope. On the other hand, in subjective tinnitus, the sound heard is not physically originated and can not be heard by others. The subjective tinnitus form, having higher prevalence than its objective form, is classified into many subgroups. The intensity and characteristics of every subgroup differ from each other. While they can be classified into two subgroups-having one- or double-sided characteristics-there are also tinnitus forms arousing a feeling of coming exactly from the middle of the head. Some researchers classified them as mild, moderate, and severe according to their intensities (3).

By the scales through which the patients assess themselves, only a subjective tinnitus perception can be achieved. Present studies increasingly seek a

solution for the treatment of this problem. According to the prevalence studies carried out by Leske (4), while the incidence of severe tinnitus in the age range of 18-24 is 3%, this incidence increases to 11% in the 65-74 age range. Similarly, Nondahl et al. (5), in their study that they conducted with individuals over the age of 50, found the prevalence as 8.2% and observed that this rate increases by age but decreases after the age of 80. We can suggest considering these findings that increasing age is a risk factor for tinnitus formation. Besides that, low education level and socioeconomic status and smoking for a long period of time are considered significant risk factors (6).

From the past to the present, many methods, such as pharmacological agents, sound therapy, and behavioral applications, have been used for treatment of tinnitus (7-9). However, as a result of empirical and clinical observation trials, it was indicated that the present applications provide only a partial response to the treatment (10). A significant reason of the low success rate of treatment response is that the methods used target developing methods to cope with tinnitus rather than reducing the perception of it (10). On the other hand, the lack of a diagnostic method to differentiate objectively the various subforms of tinnitus is considered to be among the greatest obstacles before treatment of tinnitus (10). The gamma-aminobutyric acid (GABA) agonist agents are the most frequently used drugs in pharmacological treatment (12). However, the effects of these drugs on tinnitus are restricted and still open to discussion.

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The complexity of the pathophysiology of tinnitus has brought forward interdisciplinary studies about this subject. In studies investigating tinnitus, although there were many studies in the past suggesting that the disease was connected with the degeneration of auditory neurons in the internal auditory canal, after the use of neuroscientific tools became widespread, strong current evidence has emerged about its connection with an increase in prefrontal cortex and temporoparietal neuronal excitability (1, 12-17).

There is an increasing amount of scientific data about the possibility of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), which are used in clinical routine and investigation of the treatment of maladaptive brain activity changes and hyperexcitability seen in psychiatric and neurological diseases. The purpose of this review is to overview the literature about the promising neuromodulation treatments of tinnitus forms, to examine its association with tinnitus pathophysiology, and to share the future applications and limitations with the reader.

Pathophysiology of Tinnitus

The studies investigating the pathophysiology of tinnitus may be classified under two groups. While some researchers examine the structures in the internal and middle ear canals, considering tinnitus as a peripheral disorder, others consider that this disease is related with the central nervous system.

Different pathophysiological models and clinical data point to the peripheral auditory structures in tinnitus perception. According to the studies conducted, tinnitus was mostly associated with cochlea and auditory nerve damage. In some studies, dysfunction of frequency-specific auditory cells or abnormal firing of acoustic nerve cells was pointed out as potential sources of tinnitus (11, 18). Accordingly, any dysfunction in the cells responsible for hearing leads to a reduction in inhibitory inputs, in line with the emergence of hyperexcitability (17). Additionally, the studies carried out with animal models indicated the existence of a peripheral mechanism, including N-methyl-D-aspartate (NMDA) glutamatergic receptors, as well in the cochlea, for tinnitus generation. The studies performed showed that tinnitus can be prevented by NMDA receptor blockers applied to the cochlea before ototoxic drug (salicylate) application, which increases spontaneous firing in auditory nerve cells and accordingly creates tinnitus, and besides that, the NMDA receptor blockers decrease hearing loss occurring after sound trauma (19, 20).

A lot of researchers who investigated tinnitus pathophysiology in the central nervous system mentioned about a probable neuronal maladaptation. As is known to all, neuronal plasticity is generally associated with the renewability skill of the nervous system after damage or its readaptation. However, this plasticity was held responsible in some special cases for the occurrence of some diseases, like tinnitus (21, 22). For instance, Mühlnickel et al. (22), in their study, associated tinnitus with its maladap-

tive plasticity, showing itself by the hyperactivation of auditory space in the central nervous system and the simultaneous activation of nonauditory brain regions, such as the insula, anterior cingulate cortex, and dorsolateral prefrontal cortex (DLPFC). Many other studies examining and supporting the connection between tinnitus and cortical excitability were carried out (17, 21). The DLPFC, consisting of nerve cells associated with auditory memory and having a facilitative effect in the auditory memory storage process, is the most accentuated brain region in tinnitus studies in our day (23, 24). The DLPFC, with its direct connections to the auditory cortex and indirect connections to the posterior orbitofrontal cortex, plays a role in focusing on auditory signals and pressing the auditory distractor signals with its projections to the reticular nucleus of the thalamus (23).

When considered from another perspective, tinnitus that develops secondary to peripheral or central auditory processing disorders may be the corollary of inhibition, and the change in excitation balance, reorganization of neuronal circuits, change in tonotopic map, and excessive or wrong processing of sensory information result from them. There is strong evidence that the deterioration of the change in the inhibition-excitation balance in cochlear nuclei found between the bulbus and pons in favor of increased excitation or decreased inhibition forms the foundation for increased auditory sensitivity seen in tinnitus.

Thus, the applications targeting to regulate brain activities that began to be used for brain activity disorder treatments have found a place for themselves in tinnitus treatment in the pathophysiology framework above. The most common treatments among these somatic neuromodulation applications in our day are rTMS and tDCS treatments.

Non-Invasive Brain Stimulation Treatments

Transcranial Direct Current Stimulation (tDCS)

Transcranial Direct Current Stimulation is an older and non-invasive stimulation method that regulates cortical excitability by giving low and constant current to the cerebral cortex. In this stimulation method, an anode is placed to the related brain region, and a cathode is placed opposite to the region (generally to the neck and shoulder region) to be stimulated (25). To date, tDCS protocol is generally in the form of applying 1 or 2 mA of direct current between these two electrodes. This stimulation may take up to 20 minutes. While the anodal stimulation increases the neuronal excitability by depolarizing the cell wall, cathodal stimulation lowers neuronal excitability by hyperpolarizing the cell wall (26). However, since there are many cortical cell types in the brain, the combined effect of tDCS may be complex. It affects neural plasticity by having an impact on synaptic transmission over long-term potentiation (LTP) and long-term depression (LTD) (27) by changing intracellular cAMP-mediated calcium levels (25) and by regulating neurotransmitter pathways, such as the NMDA, catecholaminergic, GABAergic, and dopaminergic pathways (27, 28). The duration

of these effects may last from minutes to hours. In the current studies, there are articles suggesting that these neural changes in tDCS-applied patients can be observed not only in the short run after the application but also in the long run (29). In the literature, some of the very seldom and mild side effects are counted as nausea, headache, intracutaneous reactivity at the time of stimulation, and tingling sensation.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive Transcranial Magnetic Stimulation is another non-invasive brain stimulation method, like tDCS. In this method, a coil is placed on the scalp, which creates magnetic pulses having a power of almost 1.5-2.0 tesla for a very short time (100-300 ms). The magnetic field that is formed does not deteriorate much while passing through the scalp and the skull, and rTMS is strong enough for creating neuronal depolarization in the cortex. The region and intensity of the electromagnetic field created depend on the physical properties, and the intensity reduces quickly as it gets further from the coil. In vitro electrophysiology and neuroimaging studies showed that rTMS can create an excitatory and inhibitor effect in connection with stimulation frequency on synaptic transmission. Accordingly, it is thought that rTMS with high frequency (≥ 5 Hz) causes LTP, and rTMS with low frequency (1 Hz) causes LTD (30). This bimodal modulation was approved in animal models (a kind of desert rat) by a study conducted on the auditory cortex. Thus, it was indicated that rTMS with 1 and 10 Hz applied to the auditory cortex created changes in the firing rate of the stimulated neuron, depending on the frequency, and that they produced LTP and LTD, respectively (13). On the other hand, there have to be many parameters affecting the cortical activity and, in turn, the clinical outcome. These parameters also include the direction of the current in the coil, phases, and the major activity of the stimulated brain region (31, 32).

Repetitive Transcranial Magnetic Stimulation, as a research method, has increasingly attracted attention, with its power to create focal changes in brain activity. Since the effect of these changes lasts longer than the stimulation moment, this method has begun to be seen as a potential method of patients showing various cortical dysfunctions, like tinnitus. One of the most common side effects of rTMS method that does not require any anesthetic premedication is the temporary pain caused by the contraction of the muscles in the region stimulated and headache, seen at a rate of 20% after stimulation. Since it seldom (1%) causes the occurrence of seizure, it has to be used carefully in the patients having a history of epilepsy. It is known generally that rTMS has more spatial and temporal solubility than tDCS. In spite of this, the effects of tDCS on longlasting LTP and LTD are remarkable.

The Treatment Mechanism of tDCS and rTMS in Tinnitus

The data about the use of the neuromodulation treatments above mentioned in tinnitus patients increase day by day. It is thought that especially prefrontal hyperexcitation found in tinnitus pa-

thophysiology can be treated or alleviated by these modulation treatments. In spite of the fact that it has been shown in studies that the effectiveness of TMS on tinnitus depends on the stimulation frequency applied and the auditory cortex hyperactivity, the mechanism of rTMS in tinnitus is not known completely yet. Besides, it is known that the current given by rTMS is only effective in superficial cortical layers and additionally that the cortical regions are far away from the surface with which the cortical regions have a functional relationship and that it can be reached to the cortical regions by synaptic stimulations. In this context, for instance, since the Heschl's gyrus is buried in the posterior side of the Sylvian fissure, the electromagnetic field and the tissue stimulation formed when stimulation is applied to the temporal cortex may indirectly affect the primary auditory cortex, with which this brain structure has a relationship. May et al. (33) have shown in their voxel-based brain imaging study conducted with normal samples that rTMS with low frequency applied to the left temporal cortex strengthened the functional relationship in the related regions by causing an increase of the gray matter volume in the contralateral homologous region and bilateral thalamus at the same time, in addition to the temporal region stimulated. Accordingly, it is possible to state that rTMS applied with low frequency also consists of the corticothalamic projections of the tinnitus mechanism. Therefore, tinnitus may be associated with thalamocortical dysrhythmia formed of high-frequency neuronal firing synchronization, and rTMS can provide the neuronal modulation again with inhibitor stimulations in this region (11).

The recent studies showed that noninvasive stimulation methods, such as rTMS and tDCS, can be used in tinnitus treatment by stimulating the frontal and auditory cortex directly. Even a single session of tDCS applied to the DLPFC of patients having subgenual, parahippocampal hyperactivation in their auditory cortexes temporarily decreased the intensity of tinnitus and eliminated the emergent stress by this means for some time. This effect is formed by tDCS stimulated DLPFC's activating the pregenual anterior cingulate cortex and inhibiting gamma waves in the parahippocampal auditory cortex. The action time of repeated sessions is naturally longer. If the gamma wave activity's being associated with the intensity of the perceived tinnitus sound in the auditory cortex and the parahippocampal field's playing an effective role in the characteristic properties of tinnitus and the stress created by the sound are considered, the use of the repeated tDCS sessions in the treatment of tinnitus by inhibitor effects in these fields may be very useful in the clinic (34, 35).

Similarly, many studies investigating the effect of rTMS method on tinnitus were conducted. A study carried out with 200 tinnitus patients showed that rTMS applied to the lateral temporal cortex, containing primary and secondary auditory cortical areas with low frequency (1 Hz), decreased the intensity of tinnitus significantly. It is known that in rTMS, which was also used for the treatment of psychiatric diseases, such as major depression

Table 1. rTMS applications with study protocols

Study	Region Stimulated	TMS Protocol	Session	Measurement	Result
Hoekstra et al. (41)	Auditory cortex	2000 pulses 1 Hz	5	Tinnitus Handicap Scale, VAS	No statistically significant result was found; however, there is a positive correlation between tinnitus intensity and rTMS effect.
Kim et al. (40)	Auditory cortex	600 pulses 1 Hz	5	Tinnitus Handicap Scale, VAS	When the opposite side of the ear having tinnitus and the auditory cortex on the same side of the ear were stimulated, a statistically significant decrease was detected.
Picirillo et al. (42)	Left TPJ	2000 pulses 1 Hz	4 weeks	Tinnitus Handicap Scale, VAS	10 median decrease (range, -20- +40) in THS; however, there is no statistical difference compared to sham stimulation.
Barwood et al. (43)	Auditory cortex (BA41)	1 Hz	10 days	Tinnitus Handicap Scale, VAS	Statistically significant recovery in tinnitus perception 1 week and 1 month after the application compared to placebo.
Lehner et al. (38)	Left frontal+ left auditory	20 Hz (left frontal, 1 Hz (left auditory cortex) combination	20 days	Tinnitus Handicap Scale, VAS	The success rate of combination application (43%); the success rate of sham application (66%)
Kreuzer et al. (39)	Right prefrontal+ left temporal	20 Hz (left prefrontal, 1 Hz (left frontal) combination	20 days	Tinnitus scale	The combination application of right prefrontal stimulation ended up with the superiority of it to the other applications.
Anders et al. (37)	Left auditory cortex	1 Hz	14 days	Tinnitus Handicap Scale, VAS	Significant recovery was found in tinnitus intensity with rTMS.
Rossi et al. (36)	Left temporoparietal	1 Hz	5 days	Tinnitus Handicap Scale, VAS	35% recovery was detected independent from rTMS mood symptoms according to basal tinnitus scores.

TPJ: temporoparietal junction; THS: tinnitus handicap scale; VAS: visual analog scale; DLPFC: dorsolateralprefrontal cortex

and OCD, generally low frequencies (≤ 1 Hz) decrease cortical excitability and high frequencies (5-20 Hz) increase cortical excitability (6). In this framework, we can think that rTMS applied with low frequency decreases the hyperactivation in auditory cortical areas and thus the intensity of tinnitus.

Review of rTMS and tDCS Studies for Tinnitus

In this part, the methodologies and results of randomized controlled rTMS studies having a high level of scientific proof and tDCS studies (since the number of them is low) are summarized.

rTMS Studies in Tinnitus

The current scientific studies in which rTMS applications are performed with high evidence value are summarized in Table 1. Accordingly, in the placebo-controlled study realized by Rossi et al. (36), 1 Hz rTMS applied to the left temporoparietal area ended up with a significant reduction in tinnitus intensity without regarding tinnitus laterality and mood variables. Similarly, it was shown by the study of Anders et al. (37) that 1 Hz rTMS applied to the left auditory cortex caused a significant reduction in tinnitus intensity. In another study realized with 538 tinnitus patients, 1 Hz stimulation applied to the left temporal cortex and the stimulation combination of 20 Hz applied to the left dorsolateral prefrontal cortex and 1 Hz applied to the right temporal cortex were compared, and it was shown as a result of the signifi-

cant reduction in tinnitus scale that both stimulation protocols were effective in tinnitus treatment. At the same time, it was also found that the stimulation combination was more effective for patients with temporomandibular joint disorder complaints. However, the impact strengths of these differences found statistically significant were low (38). In another stimulation combination study, Kreuzer et al. (39) compared two patient groups of low-frequency (1 Hz) rTMS in the left temporal area alone and together with high-frequency (20 Hz) stimulation to the right prefrontal area, and they reported a reduction of tinnitus intensity in both groups after the stimulation. Additionally, it was observed that the group that received the stimulation combination was more inclined to recovery; however, this effect could not reach a statistically significant level. In light of these studies, it can be thought that additional stimulation applied to the right prefrontal cortex may be a promising strategy to increase the effectiveness of rTMS applied to the left temporal cortex.

Kim et al. (40) compared one-sided contralateral and ipsilateral (opposite or on the same side of the ear having tinnitus) rTMS stimulations and could not find a significant difference between the two groups. However, this study showed by the measurement 1 month after the rTMS application that there was a reduction in tinnitus intensity in both groups. In other words, it was shown by this study that regardless of laterality, 1 Hz rTMS application was effective in tinnitus treatment. As for

a current study conducted by Hoekstra et al. (41) with 50 patients, a significant difference between the rTMS-applied group and placebo group could not be found when 1 Hz stimulation was applied to the bilateral auditory cortex. However, a positive correlation was shown between the patients who benefited from rTMS and the tinnitus intensity of these patients. Similarly, in the study in which 1 Hz rTMS was applied to the left temporoparietal join by Piccirillo et al. (42), there was no significant difference between the patient and control group. But, a decrease was observed in Tinnitus Handicap Scale median score after application. Contrary to these two current studies, Barwood et al. (43) applied 1 Hz rTMS to the primary auditory cortexes of tinnitus patients for 10 days, and the decrease in tinnitus intensity of the group receiving rTMS treatment, even 1 month after the application, was statistically significant versus the placebo group.

In addition to the short-term rTMS studies reviewed above, Burger et al. (44) carried out a 4-year follow-up study in order to investigate the long-term outcomes of the rTMS method in tinnitus treatment. In this study, realized with 235 chronic tinnitus patients, some patients' left temporal cortex and some others' DLPFC, together with the left temporal cortex, were stimulated. As a result of the study, a significant decrease was found in tinnitus intensity of both groups. It was demonstrated by repeated measurements that 90 days, 2 years, and 4 years after the stimulation that the decrease in tinnitus intensity of the patients who responded positively to rTMS treatment was maintained significantly.

The effectiveness of rTMS application in tinnitus treatment was also proven by the changes in cortical alpha activity of TMS-applied patients. For example, in a study, tinnitus sound intensity, displaying a significant reduction after rTMS in chronic tinnitus patients whose magnetoencephalography records were taken before and after stimulation, was associated with increased alpha activity in the stimulated auditory cortex (45). In another study trying to explain rTMS treatment for tinnitus by electrophysiological mechanisms, the potential changes of tinnitus patients and the control group regarding the case before and after rTMS were examined (46). In the study, N1 response and ERP changes, called mismatch negativity (MMN) and late discriminative negativity (LDN), were investigated. As a result of this test, the tinnitus group responded to the standard stimulator with a higher N1 amplitude before stimulation, and besides, the MMN and LDN responses of tinnitus patients were lower. As for after the stimulation, tinnitus patients responded to the deviated stimulator with increased N1 and high MMN and LDN compared to the control group. When the brain tomographies of tinnitus patients were viewed before stimulation, global asymmetry was observed in the right and left cerebral hemispheres, formed by activities that were negative on the left and more positive on the right. On the other hand, the brain map of the tinnitus patients whose topographic map was viewed again after rTMS stimulation appeared to be more symmetrical.

A significant difference could not be found between the patient and control groups whose ERP changes after stimulation and topographical maps were compared. In light of this information, it can be stated that specific ERP changes and topographical maps of the tinnitus patients may be related with electrophysiological mechanisms in the beginning and during development of tinnitus. Thus, these parameters can be used as biomarkers in evaluating the auditory cortex of subjective tinnitus patients in future studies.

tDCS Studies in Tinnitus

The studies having high proof value regarding tDCS use are summarized in Table 2. Accordingly, the tDCS treatment approach in tinnitus first began with the study of Fregni et al. (47). Anodal tDCS applied to the left temporal region provided almost a 30% decrease in tinnitus intensity. Similarly, the study of Garin et al. (48) with a larger sample ended up with a significant decrease in tinnitus intensity and displayed the longlasting effect of tDCS in suppressing tinnitus, different from the other study. Vanneste et al. (34), who took the treating effect of bifrontal tDCS as a reference in other psychiatric diseases before, were the first group to try this method in tinnitus treatment. Vanneste et al. (34), who placed the anode in the right DLPFC and the cathode in the left DLPFC of tinnitus patients, showed statistically that bifrontal tDCS stimulation suppressed tinnitus intensity with a rate of 30%. Vanneste et al., with this study, suggested, in addition to the tinnitus intensity, that bifrontal tDCS affected the emotional process of tinnitus by modulating the activity of the pregenual anterior cingulate cortex, parahippocampal region, and the right primary auditory cortex and lowered the stress rate associated with tinnitus. In another study investigating bifrontal tDCS stimulation, it was indicated that a 1.5 mA current applied for 6 sessions with an anodal electrode placed in the right DLPFC did not create a significant change but led to a decrease in restlessness feeling related with tinnitus (49). Frank et al. (49), who also considered gender difference as a variable, reported that female patients responded more positively, compared to the male patients. Moreover, they reported that the anodal electrode placed in the left DLPFC modulated depression, and the anodal electrode placed in the right DLPFC modulated anxiety. One of the most recent studies that can be exemplified with regard to the use of tDCS in tinnitus treatment was conducted by Shekhawat et al. (50). The 1-session 2 mA current given for 20 minutes to tinnitus patients, in whom anodal electrode in the left temporal region was placed, suppressed tinnitus temporarily in 56% of the patients and led to a decrease in sleep problems in 44% of them because of tinnitus symptoms in the long run.

When all of these studies are considered, it can be stated that the left temporal and bifrontal regions are the most frequently used ones in tDCS application for tinnitus. When these two stimulation regions are compared, it is possible to reach the conclusion that the tDCS method applied to both regions leads to almost the same rate of decrease in tinnitus intensity.

Table 2. tDCS applications with study protocols

Study	Anode	Cathode	Duration	Session	Measurement	Result
Fregni et al. (47)	Left temporal	Right supraorbital	3 minutes	2	VAS Tinnitus decrease scale	30% decrease was detected in tinnitus intensity.
Faber et al. (35)	Left DLPFC	Right DLFPFC	20 minutes	3	VAS intensity; VAS disorder	Decrease in tinnitus disorder degree was found, regardless of anodal position.
Garin et al. (48)	Left temporal	Right VLFPC	20 minutes	1	VAS Tinnitus decrease scale	Short- and long-term effect was found in suppressing tinnitus.
Vanneste et al. (34)	Right DLPFC	Left DLFPFC	20 minutes	1	VAS disorder	It was found that the bifrontal tDCS stimulation suppressed tinnitus intensity with a rate of 30%.
Frank et al. (49)	Right DLPFC	Left DLPFC	30 minutes	6	Tinnitus Handicap Scale, Tinnitus Scale, Beck depression scale	The response of females better than males. Decrease in discomfort and restlessness; however, no change in subjective tinnitus intensity.
Shekhawat et al. (50)	Left temporal	Right supraorbital	20 minutes	1	VAS Tinnitus Decrease Scale Sleep Assessment (Long term)	tDCS for 20 minutes was effective in the short and the long run.

TPJ: temporoparietal joint; VAS: visual analog scale; DLPFC: dorsolateralprefrontal cortex

Limitations

There are also some limitations of neuromodulation applications in tinnitus, the effectiveness of which is displayed by many studies. The neuromodulation treatment's being affected from individual sensitivities may result in their having an effect of different intensity and side effects in every individual. Such a result, while pointing to the complexity of tinnitus etiology on the one hand, suggests the necessity of investigating brain stimulation mechanisms in more detail on the other hand.

There are limitations in the determination of brain regions to be stimulated in neuromodulation applications, since there are many questions about the primary pathology of tinnitus etiology. For instance, the question of whether to stimulate the regions excluding the auditory cortex of the other group of patients while stimulating the primary auditory cortex of a group of patients is one of the major limitations that future researchers are expected to respond to (27). In fact, these limitations, leading to the need for organizing individual treatment, remind us about the study of Tyler et al. (51), recommending the determination of subgroups for tinnitus patients and organizing the clinical treatment according to these subgroups. For Tyler et al. (51), it is possible to separate tinnitus into subforms with a statistical approach. Tyler et al.'s (51) way of approach, reaching homogeneous tinnitus subforms from certain covariates by using cluster analysis method, encourages the need to develop certain treatment strategies for some tinnitus types by solving the complexity of the etiology of tinnitus. Examination of the treatment effectiveness of neuromodulation in different subgroups after such an approach will be enlightening.

On the other hand, the promising results obtained by the brain stimulation methods encourage researchers to develop clinical research and treatment strategies. For instance, there is strong evidence supporting that the auditory cortex stimulation activates and directs the corticocortical and corticofugal projections—in other words, that the auditory cortex stimulation modulates the neural connections of tinnitus in different levels of the brain. These types of modulations may also affect the neural mechanisms, such as hyperactivity, hypersynchronia, and tonotopic plasticity. In fact, it was observed that the stimulations applied to the auditory cortex suppressed tinnitus by decreasing the most important neural substrates, such as hyperactivity and hypersynchronia.

Future Applications

Recent studies point to the fact that tinnitus, which was seen as just an auditory disorder for years and the pathophysiology studies were conducted on the ear, is a more complex disorder and mainly arises out of abnormal functions in the central nervous system.

Randomized controlled trials with a high number of samples will shed light on questions, such as whether specific rTMS treatment protocols are superior to other protocols in certain tinnitus subgroup patients and whether the effectiveness of the treatment will increase or not, by using the most effective personal stimulation frequencies. Especially, the theta burst TMS protocol, which was shown by case studies to suppress tinnitus, may be one of the methods to be used in studies with many samples for finding the most effective rTMS treatment protocols in tinnitus. The next step is the measurement of the effect of different treatment protocols on neuronal functions by electrophysiology or neuroimaging methods.

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