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Transcranial Magnetic Stimulation in the Treatment of Tinnitus

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<http://dx.doi.org/10.5772/intechopen.73221>

Abstract

Tinnitus is a disturbing noise that is heard without any hearing stimulus, affects the quality of life of the individual, and leads to psychosocial problems. Its prevalence characteristically increases with aging. It is seen in 33% of the general population. Pathophysiology of tinnitus known to accompany nearly all disorders in auditory system has not been fully understood; therefore, there are some difficulties in evaluation and treatment thereof. Despite the restrictive factors of tinnitus treatment, progress in auditory neuroscience provides a positive view of tinnitus treatment. Transcranial magnetic stimulation (TMS) is a method based on the stimulation of neuronal tissue without depending on the transfer of electrical current by means of electrodes or the skin. TMS is used in the treatment of various diseases with developing neuroscience. In the recent years, the number of studies on TMS application with repetitive low frequency for the treatment of tinnitus has increased, and most of these studies have given successful results. Repetitive use of TMS in tinnitus is very novel; however, it is commonly used in psychiatric disorders, especially in the treatment of drug-resistant depression. The chapter shows that low-frequency repetitive TMS (rTMS) is useful in the treatment of chronic tinnitus.

Keywords: tinnitus, transcranial magnetic stimulation, tinnitus handicap inventory, rTMS, THI

1. Introduction

1.1. Tinnitus

Along with the development of technology and urbanization, there are some additional burdens along with the convenience of our lives. Increasing traffic with urbanization, increasing

use of mobile phones from early ages, and listening to loud music with headphones cause our life to become more loud and tense.

Tinnitus is a symptom thought to be heard without a voice stimulus. The presence of tinnitus also affects the quality of life of individuals and causes psychosocial problems. It is characteristic that it becomes more common with aging. It is present in one third of the general population [1].

Forty-sixty million people in the United States have a tinnitus on one occasion, and according to most of them, this does not pose any problem for any treatment. Only 1–5% of individuals with tinnitus have severe and uncomfortable ear tinnitus [2, 3].

Tinnitus occurs with 30-dB hearing loss at the rate of 75%. As the hearing level decreases, its incidence increases. It was detected that exposure to high sound or noise increases tinnitus prevalence.

Pathophysiology of tinnitus known to accompany nearly all disorders in auditory system has not been fully understood; therefore, there are some difficulties in evaluation and treatment thereof. Tinnitus is still a subject of research on neurotology. However, the etiology and physiopathology are not well known. Therefore, tinnitus treatment has not yet been clarified.

Tinnitus can also have a large economic effect. The lack of standardization of tinnitus diagnosis and treatment management increases the cost of health care [4]. Tinnitus reduces the concentration of the person, restricts their participation in professional activities, thus reducing the work efficiency of the person [5–7].

Despite the restrictive factors of tinnitus treatment, progress in auditory neuroscience provides a positive view of tinnitus treatment.

Transcranial magnetic stimulation (TMS) is a method based on the stimulation of neuronal tissue without depending on the transfer of electrical current by means of electrodes or the skin. TMS is used in the treatment of various diseases with developing neuroscience. Good news is coming from recent studies on TMS application with repetitive low frequency in tinnitus treatment. TMS inhibits abnormal cortical activities in the affected area. Tinnitus treatment is applied to auditory cortex. Positive results have been revealed during the studies [8, 9].

This chapter is devoted to evaluate the effects of transcranial magnetic stimulation (TMS) on the treatment of subjective tinnitus.

1.1.1. Tinnitus pathophysiology

The auditory system is a complex system and contains a large number of central nuclei that provide the cortical organ peripheral fibers in the spiral laminates, multiple afferent and efferent delivery channels, and complex integration in the upper centers of the central nervous system [10–12]. The pathologies that occur anywhere in these regions cause an increase in the perception of sound through unknown mechanisms. Researchers have tried to explain the formation and perception of tinnitus with many different mechanisms.

- Damage to inner and outer hair cells
- Ion imbalance in the cochlea
- Dysfunction in the cochlear neurotransmitter system
- Heterogeneous activation in the cochlear efferent system
- Heterogeneous activation in type I and II cochlear afferents
- Cross links between the eight nerve fibrils [13]

Every nerve fiber has an electrical discharge even at rest. This is called the spontaneous activity of that nerve. There is an increase in spontaneous activity in patients with tinnitus. All of the assumptions put forward to explain the pathogenesis of tinnitus are based on this spontaneous activity increase [1, 14]. Recent studies suggest that tinnitus is an event based on hyperactivity of the auditory system, which is temporarily adjusted by TMS [15]. Theories about pathophysiology of tinnitus can be grouped as follows:

According to Moller, some of the adjacent nerve fibers are damaged for some reason, resulting in artificial synapse between the nerve fibers, and these synapses between the fibers cause pathological transmissions. This results in increased spontaneous activity and tinnitus [1, 14, 16].

Jastreboff and Hazell note that when the temporal cortex is reduced in hearing impulses, there is an increase in neuronal sensitivity in the subcortical centers. For this reason, a tinnitus patient with normal hearing is thought to be associated with subcortical centers, which we hear as weak voices in auditory cues (e.g., in quiet rooms) [13].

Tonndorf states that tinnitus can originate from all levels of the auditory system. If tinnitus is acoustically masked, it is originated from peripheral auditory system, whereas if tinnitus masking is not present, it is originated from central auditory system. There is a chemical imbalance between the tinnitus cell membrane and the stereocilia. This leads to hyperactive flickering hair or hyperactive nerve fibers. For this reason, even very low spontaneous activities are perceived by these shaky hair or nerve fibers. This condition could be likened to postamputation phenomenon [1, 14, 17, 18]. In 1965, Melzack and Wall proposed the door control theory for chronic pain. Tonndorf proposed this theory for tinnitus [19, 20]. The balance of the impulse that comes from the afferent inner hair cell and the outer hair cell to brainstem, respectively, seems to shift unilaterally when one or more of the hair cell's subsystem is damaged. Tonndorf suggests that this imbalance of warning may cause tinnitus.

Salvi and Ahroon reported that spontaneous neural activity in the area of the cochlea lesion leads to tinnitus, that acoustic trauma affects cochlea when exposed to noise, and that spontaneous discharges more frequently occur in the high-frequency region of cochlea than in other regions. This increase in spontaneous activity level is expressed as tinnitus [21, 22].

According to Kiang, there are abnormal stereocilia. In the transition between normal and abnormal stereocilia, the suppression of normal cells is lost. This leads to increased spontaneous activity. This leads to tinnitus [14]. Sellick et al. argued that the displacement of the

membrane towards to scala tympani causes hyperactivity. It is thought that tinnitus occurs in this way [14].

In 1984, Eggermont assumed that there was hypersensitivity in stereocilia. This may be due to a reduction in the inhibition applied by the central route. Thus, nerve fibers perceive sounds that would normally not be heard. That said, tinnitus may be the cause [1, 14, 23]. In addition, Eggermont suggested in 1990 that the balance between stereocilia activities and nerve fiber activities could have contributed to tinnitus [24].

Although inner ear damage occurs and the eighth cranial nerve is cut, the continuation of tinnitus in some patients supports the concept of 'central tinnitus.' Peripheral tinnitus may be localized in one or two ears, while central tinnitus is usually not localized at one point. The major causes of central tinnitus are occupied lesions, inflammations, and vascular anomalies, and often masking does not succeed. Auditory brainstem response (ABR) is helpful in the diagnosis of central tinnitus [25].

Tinnitus can be defined as objective or subjective. Objective tinnitus can be detected by another person or physician.

Objective tinnitus usually has a pulsatile or rhythmic quality. **Table 1** lists common causes of objective tinnitus.

Objective tinnitus can be caused by auditory and nonauditory disorders such as Ménière's disease, Eustachian tube disorders, intracranial hypertension, middle ear diseases etc [26].

Objective tinnitus treatment depends on the underlying disease. This subject will not be discussed in this chapter.

Pulsatile

- *Venous etiologies*
 - Venous hum
 - Hypertension
 - Pseudotumor cerebri
 - Sigmoid sinus and jugular bulb anomalies
- *Arterial etiologies*
 - Paraganglioma (glomus tympanicum or jugulare)
 - Persistent stapedial artery
 - Intratympanic carotid artery
 - Arteriovenous fistula or malformation
 - Increased cardiac output (pregnancy and thyrotoxicosis)
 - Carotid artery stenosis
 - Vascular compression of cranial nerve VII
 - Intraosseous (Paget disease and otosclerosis)
- *Tensor tympani or stapedial muscle myoclonus*
- *Palatal myoclonus*

Nonpulsatile

- *Patulous Eustachian tube*
 - *Spontaneous otoacoustic emission*
 - *Idiopathic stapedial muscle spasm*
-

Table 1. Objective tinnitus subtypes.

1.1.2. Subjective tinnitus

The most common form of tinnitus is subjective tinnitus. Unlike objective tinnitus, subjective tinnitus cannot be heard by anyone else. The prevalence of subjective tinnitus is estimated between 8% and 30% and tinnitus should be defined according to the population of the study, the severity of tinnitus, and the evaluation of the methodology [2, 27, 28].

The most important cause of tinnitus is exposure to sound. The main problem in most patients is unknown [29].

Subjective tinnitus most commonly occurs due to sensorineural hearing loss (SNHL), which is caused by the presbycusis and acoustic trauma, conductive hearing loss, endolymphatic hydrops, and cerebellopontine angle neoplasia, which are more rare causes of tinnitus. Subjective tinnitus is the most common form that affects adults, and it is the focus of this chapter. Tinnitus subtype classification schemes can be useful to identify forms of tinnitus that are responsive to specific targeted treatment programs. **Table 2** lists common causes of subjective tinnitus.

1.1.2.1. Hearing loss

Urbanization and industrialization are accompanied by increased hearing loss due to noise. Noise-induced hearing loss (NIHL) is a significant and increasing health problem. Unfortunately,

-
- **Otologic factors**
 - Presbycusis
 - Noise-induced hearing loss
 - High-frequency hearing loss
 - Outer hair cell dysfunction
 - Ménière's disease
 - **Somatic tinnitus**
 - Temporomandibular joint syndrome
 - **Typewriter tinnitus**
 - **Psychological factors**
 - Anxiety
 - Depression
 - **Pharmacological factors**
 - Aspirin compounds
 - Nonsteroidal anti-inflammatory drugs
 - Aminoglycosides
 - Heavy metals
 - **Metabolic factors**
 - Hypothyroidism
 - Hyperthyroidism
 - Hyperlipidemia
 - Vitamin deficiency
 - **Neurologic abnormalities**
 - Multiple sclerosis
 - Meningitic effects
 - Skull fracture or closed head trauma
-

Table 2. Subjective tinnitus subtypes.

many people do not care about industrial noise, fire alarms, listening to music loudly and other noises, or how unaware they are. According to a study conducted, 61% of people who went to the concert found hearing loss and temporary ringing of ears after the concert [30]. The prevalence of chronic tinnitus associated with NIHL is 50–70% [31].

Presbycusis is a sensorineural hearing loss that occurs with aging. Personal and environmental factors play a role in the development of presbycusis, but it mainly involves complex genetic factors. The best-known environmental factor is noise, and hearing is better protected in elderly people who are not exposed to high sound.

1.1.2.2. *Somatic tinnitus*

Somatic tinnitus can be modulated by maneuvers or stimulation of the head and neck region. Patients with temporomandibular joint (TMJ) disorder had higher incidence of tinnitus compared to control groups [32]. When tinnitus occurs in association with disorders of the head and neck such as TMJ dysfunction, unilateral facial pain, otalgia, and occipital or temporal headache, successful tinnitus alleviation may be possible using interventions that target the somatic dysfunction [17].

1.1.2.3. *Typewriter tinnitus*

This type of tinnitus may be confused with tinnitus that arises from a muscular source, such as spasm of the tensor tympani or stapedius muscles, or palatal myoclonus. Typewriter tinnitus is defined, as its name implies, by the characteristic sensation of a staccato quality to tinnitus, similar to a typewriter tapping, popcorn popping, or Morse code signaling. Typewriter tinnitus is distinct from these somatic sources, as illustrated by a patient with typewriter tinnitus that failed to respond to tensor tympani and stapedius resection [33].

1.1.2.4. *Psychological factors*

Emotional distress and disturbance of sleep are often associated with severe tinnitus. Stress often increases the perception of tinnitus severity, and depression frequently accentuates the complaint. In some cases, tinnitus itself may be the cause of the psychological disorder. Depression is common in patients with tinnitus, but it is not always clear whether depression is primary or secondary.

1.1.2.5. *Pharmacological factors*

The pharmaceutical industry has developed in the last 50 years. Despite the developing world, rational drug use is not yet fully established. Almost every medication can be considered as a possible cause for tinnitus. The main ones responsible are listed in **Table 3**.

The aim of tinnitus treatment is to reduce or, if it is possible, to eliminate the voice that disturbs the patients [22]. Symptomatic treatment options are important because etiologic causes are detected in 5% of the cases [34, 35].

Nonsteroidal anti-inflammatory drugs

- Ibuprofen
- Indomethacin
- Naproxen
- Phenylbutazone
- Sulindak

Amikacin

Aminoglycoside antibiotics

- Streptomycin
- Neomycin
- Gentamycin
- Tobramycin

Aspirin and aspirin-containing compounds

- Darvon
- Percodan
- Ecotrin
- Bufferin

Heterocyclic antidepressants

- Nortriptyline
 - Amitriptyline
 - Trazodone
 - Amoxapine
 - Doxepin
 - Trimipramine
-

Table 3. Medications that cause tinnitus.

1.1.3. Examination and tests

In order to be able to treat patients with tinnitus or to improve the effectiveness of treatment, detailed evaluation of the patients and the investigation of the etiology are required. We have not created a successful standard protocol for evaluating tinnitus until now. Assessment of tinnitus is medically and audiologicaly interpreted and is used to make individual plans for tinnitus treatment [36]. The transactions to be made in the evaluation can be listed as follows:

1. History: the major importance in the evaluation of tinnitus patients is anamnesis [37, 38]. A detailed history of the patient should be taken. Age at which tinnitus began, audiovestibular symptoms (hearing loss and dizziness), the nature of tinnitus (intensity and frequency) and daytime changes, family history, history of exposure to noise, smoking, alcohol use, systemic diseases, head trauma, ototoxic drug use, epilepsy, otosclerosis, and past meningitis must be questioned.
2. Physical examination: after obtaining a complete history of the patient with tinnitus, clinical management should begin with a general medical evaluation followed by a complete head and neck examination. All tinnitus patients should undergo neurological examination including a detailed ENT examination, temporomandibular joint examination and diapason tests, general medical evaluation, and cranial nerve examination [10, 11].
3. Audiologic evaluation: pure audio audiometry, speech audiometry, percentage of speech discrimination, disturbing auditory height, impedance metric evaluation, otoacoustic emission (OAE), and auditory brainstem response (ABR) can be performed [39–42].

4. Laboratory tests: complete blood cell count and extensive biochemical examinations should be performed routinely. If the patient is suspected of any metabolic or medical condition, more detailed examination should be performed.
5. Radiological evaluation: temporomandibular joint disease should be excluded by radiological evaluation. In patients with unilateral hearing loss, radiological evaluation may be needed to exclude posterior fossa tumors. Computed tomography (CT) is sufficient in the evaluation of most tumors and anomalies. MRI should be performed to exclude vestibular schwannoma or other cerebellopontine angle sister neoplasms if there is a clinical suspicion for patients with nonpulsatile tinnitus [43].

1.1.4. Tinnitus and audiologic findings

1.1.4.1. Pure sound audiogram

It has been reported that 13% of tinnitus cases have transmission-type hearing loss and 39% have sensorineural-type hearing loss. Hearing loss was more frequent in the high-frequency range of the sensorineural hearing loss group [37].

1.1.4.2. Otoacoustic emissions (OAE)

It is thought that OAE is a special evaluation method for cochlear auditory dysfunction in the light of the studies performed and objectively confirms cochlear dysfunction in patients with normal audiogram and tinnitus complaints [44].

Tyler and his colleagues reported that only one of their 25 patients had spontaneous OAEs and found no connection between spontaneous OAEs and tinnitus curtain or severity [45]. Penner and Burns investigated whether the SOAE measurement would be of an objective value in terms of tinnitus correlation, but they could not find a relationship [46]. As a result of some studies on the relationship between SOAE and tinnitus, only a small group of patients has been identified [45, 47]. Studies are underway to investigate the relationship between distortion product otoacoustic emissions (DPOAE) and tinnitus. In these studies, it was revealed that there is a significant relationship between the frequency of tinnitus emergence and DPOAE responses [48].

1.1.4.3. Auditory brainstem response (ABR)

It is a diagnostic measure to help determine the type of tinnitus. There was no difference in the ABR test of the tinnitus patient group in the study of all normal hearing individuals [49].

1.1.5. Evaluation of findings

There are many questionnaires to evaluate the severity of tinnitus and its negative impact on the patient. A standard assessment is needed to document and report the results of clinical trials. Tinnitus, which is defined and graded on this scale, is standardized, and the common denominator in the treatment approach is unified.

Various methods can be used to evaluate the findings of the patients. Tinnitus handicap inventory (THI) is an easily applicable test that is not affected by age, sex, and hearing loss of the patient [50]. A confidence interval of 95% for THI is 20 points, which suggests that a difference in scores of 20 points or greater represents a statistically and clinically significant change.

1.1.6. Tinnitus treatment strategies

Tinnitus is a complex, multifactorial problem with many potential options that can help the patient cope with the condition. You cannot cure tinnitus without understanding tinnitus. We try to approach some treatment modalities for subjective tinnitus after excluding organic causes. Currently, there are some treatment options for patients with tinnitus. Based on the 2014 tinnitus guidelines, the treatment options are shown in **Table 4** [26].

1.1.6.1. Education and counseling

Patient education should instead emphasize that tinnitus itself is a symptom and not a dangerous disease, and a comprehensive assessment can exclude any associated medical conditions that require prompt treatment.

When counseling the patient, it is absolutely necessary to explain the importance of avoiding noise. The relationship between noise and tinnitus should be reminded.

1.1.6.2. Sound therapy

Acoustic stimulation has an important place in the treatment of tinnitus. Sound therapy can decrease the subjective loudness of tinnitus, which can significantly decrease the annoyance, but this may require weeks to months of daily application. Acoustic stimulation can be achieved in many ways. Masking of tinnitus is based on the principle of suppressing the inner voice from the outside. Masking can be applied with various methods such as hearing aids, tinnitus instruments, and maskers.

A hearing aid is a simple method that can be used in patients with hearing loss who have tinnitus. The hearing aid reduces tinnitus by masking the annoying sound the patient perceives by increasing the volume of the sound coming from the outside.

The tinnitus instrument is a device that includes both the properties of the hearing aid and the masking device. Hearing aid input and masking device input are independent of each other,

-
- Education and counseling
 - Sound therapy
 - Cognitive behavioral therapy
 - Medical therapy
 - Dietary supplements
 - Acupuncture
 - Transcranial magnetic stimulation
-

Table 4. Tinnitus treatment options.

which can only increase the masking volume at night or in quiet environments where tinnitus is intensified. Masking is only a substitute solution for tinnitus and not a cure.

1.1.6.3. Cognitive behavioral therapy (CBT)

Cognitive behavioral therapy has been shown to be effective in the treatment of tinnitus-related disorders. In many patients, stress or depression is a major factor in the intensity and severity of their complaints. Cognitive behavioral therapy (CBT) is a psychotherapy based on identification and modification of maladaptive behaviors using therapist-mediated cognitive restructuring techniques. Andersson and Lyttkens analyzed 18 studies of psychological treatments for tinnitus and concluded that CBT was more effective than behavioral treatments alone [51].

1.1.6.4. Medical therapy

With the development of the pharmaceutical industry, in the last 50 years, pharmacological treatment for tinnitus has come to the forefront. Drugs used in the treatment of tinnitus are used as useful medicines in terms of improving the emotional state of the patient, reducing anxiety, and improving sleep. Anesthetics (lidocaine, tocainide, and mexiletine), anticonvulsants (carbamazepine and gabapentin), and tranquilizers (diazepam, clonazepam, and oxazepam) have been investigated as tinnitus treatments.

At this time, there are no medications approved by the US Food and Drug Administration (FDA) for treatment of tinnitus.

1.1.6.5. Dietary supplements

Tinnitus appears to be a disease that is unlikely to be treated for most patients. This situation forces the physicians and patients to try other treatment methods. *Ginkgo biloba* and melatonin are the products of recent use that is increasing. *G. biloba* extract contains multiple compounds with vasotropic, potential neuroprotective, and antioxidant effects. Several other dietary supplements have been used for tinnitus, including lipoflavonoids, garlic, homeopathy, traditional Chinese/Korean herbal medicine, honeybee larvae, and other various vitamins and minerals. Evidence for efficacy of these therapies for tinnitus does not exist.

Further study is needed to investigate the side effects that may occur in the use of *G. biloba*, melatonin, or dietary supplements, as well as the use of such products in the treatment of patients with primary tinnitus.

1.1.6.6. Acupuncture

Acupuncture is a form of alternative medicine in which thin needles are inserted into the body. It is a key component of traditional Chinese medicine. The role of acupuncture in tinnitus patients is still controversial. Although unblinded studies have suggested positive results, they have not been reproduced in blinded studies [52]. There is general consensus that acupuncture is a relatively safe treatment when administered by well-trained and experienced practitioners [53–58].

The objective of the current chapter is to evaluate the effect of TMS on the treatment of subjective tinnitus, so you can find detailed information about other treatments of tinnitus in the literature.

2. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a method based on the stimulation of neuronal tissue without depending on the transfer of electrical current by means of electrodes or the skin. Magnetic stimulation causes transient disturbances of neural activity in different regions of the cortex. The depth of penetration is limited to less than 2 cm [59]. With stimulation, it forms a temporary lesion in the region. This reversible lesion allows the investigator to provide information about whether the cortical region contributes to a particular perception or behavior [60]. To better understand motor responses and corticospinal mechanisms to deep brain stimuli in Parkinson's patients [61, 62], phantom muscle contractions were used for cortical silent period studies [63]. In 1980, Merton and Morton have shown that motor neurons can be stimulated by a single, high-voltage, short-duration electrical stimulus applied to a rigid scalp with an electrical stimulator [64]. In 1985, Barker and colleagues began to use transcranial magnetic stimulation, which is transmitted through tissues like the same electrical stimulator and applied with a magnetic stimulator that stimulates the cerebral motor cortex and is more painless [65]. Since then, transcranial magnetic stimulation became widely used in areas such as clinical neurophysiology, neurology, and psychiatry. In the following years, transcranial magnetic stimulation became widely used in the evaluation of many other cerebral functions as well as studies in the developing peripheral nerves and muscles that stimulate magnetic stimulation producing coils to stimulate a small area of the cortex [66–68]. Today, advanced TMS machines can deliver up to 60 stimuli.

The magnetic field affected by a single pulse is measured for milliseconds for a short time. Repeated stimuli cause superficial cortex to change from a few seconds to a few minutes of neuronal depolarization. Repeated stimuli produce different responses depending on the frequency of the region. The application of repetitive stimuli is termed repetitive TMS (rTMS). Low-frequency (<1 Hz) repetitive TMS decreases cortical excitability [69], whereas high-frequency (5–20 Hz) repetitive TMS increases cortical excitability [70]. 1 Hz or slower is called slow rTMS; faster than 1 Hz is called fast rTMS. In the practice of TMS, when the head piece was placed on the scalp corresponding to the projection of the motor cortex and stimulated, the opposite extremities were seen to move painlessly [65]. The diameter of the electrodes used for magnetic stimulation is the most important factor affecting the magnetic field configuration. Electrodes are divided into “circular” or “butterfly” type. Those in butterfly type are called “double shape” or “eight shaped.” Their difference from the circular types is that the maximum current intensity is below the center point. These electrodes are more suitable for selective excitation by producing more localized currents [71, 72]. A magnetic exciter consists of a high-capacity series capacitor and a copper winder. With the discharge of the capacitor, a sudden and high-power (1–4.3 T) magnetic field exchange occurs around the coil. With this effect, ion currents emerge in the neural tissues adjacent to the region where it is placed on the

coil and stimulate the neural tissue. If enough magnitude and a rapidly changing magnetic pulse are generated at a sufficient depth, this pulse will cause a secondary ion current in the neuronal tissue [68]. This leads to depolarization of the membrane in the stimulated region of the neuronal tissue. Magnetic stimulation reaches the neuronal tissue without being hindered by intervening tissues such as skin and bone, which does not cause any obvious pain because it does not stimulate the surrounding tissues [73].

The therapeutic response of magnetic stimulation has been observed to be more pronounced with frequent repetitive stimulation (repetitive magnetic stimulation) and studies have shifted to this direction. For this purpose, it was most commonly used in psychiatric disorders [74]. In drug-resistant depressions, repetitive transcranial magnetic stimulation resulted in improvements of 40–50% [75]. TMS has been studied and is still being studied in psychiatric disorders such as schizophrenia, obsessive-compulsive disorder, posttraumatic stress disorder, and mania even though it is not the same size as depression. TMS is one of the safest and painless methods used in the evaluation of the nervous system and in the treatment of the mentioned psychiatric disorders [76–79]. It is not recommended to be applied in patients who have clips with neurosurgical operation and patients with heart pace because they can stimulate an epileptic seizure on the stroke [80, 81]. Although the use of repetitive TMS (rTMS) in tinnitus is very recent, there are many studies on the efficacy [8, 9, 82]. TMS has opened a new vision into investigating the causes and associations of tinnitus-related cortical activity, and it may provide an effective tinnitus therapy for some patients.

Imaging methods can show asymmetric metabolic activity in the hearing cortex of patients with tinnitus. Functional magnetic resonance imaging and fluorodeoxyglucose positron emission tomography provide it [83, 84]. The fact that rTMS has an inhibitory effect on the area it is applied to suggests that it may also be effective in the treatment of tinnitus [8, 9, 85].

2.1. TMS in the treatment of tinnitus

Tinnitus is still a subject of research on neurotology; however, recent studies in literature are not sufficient enough to enlighten the etiology or pathophysiology of tinnitus, and because of this uncertainty, treatment options are limited. Success rate of medical treatment of tinnitus according to the literature is between 30 and 80%, and most of these studies underline the effectiveness of placebo [86, 87]. TMS application for tinnitus treatment is a relatively new subject, studies are providing very little information, but the results seem promising.

It is important to determine the frequency and loudness of tinnitus because these are correlated with affects of tinnitus on the patients' life [88, 89]. Tinnitus is present in 65% of the population with hearing problems, and tinnitus in 50% of them is a serious problem [90]. According to one study, tinnitus is a serious problem for 2.6% of the local population [91].

The probability of tinnitus is increasing in patients with hearing loss [92]. If external hair cell damage is not up to 30%, the hearing thresholds do not get affected. This could explain tinnitus in patients who do not have hearing loss [20]. The loudness and frequency of tinnitus must be determined for rehabilitation [93]. In Yilmaz et al.'s study, the mean (SD) scores in the TMS group before the treatment was 7.069 (1.42) and 7.073 (1.52) points in the placebo group,

and these results were higher when compared with the literature [44, 50]. In general literature, THI is used in the evaluation of tinnitus before and after the treatment [16, 50, 94–96].

Detection of the frequency at which tinnitus is occurring is almost always difficult [93]. It has been determined that the frequency of tinnitus changes in 60% of cases according to the studies [97]. According to general opinion, tinnitus frequency is above 2000 Hz and mostly at 4000 Hz [86]. In Yilmaz et al.'s study [50], the mean (SD) frequency of tinnitus in the TMS group before the treatment was 7234 (2818) and 5626 (2494) Hz in the placebo group. The mean frequency of tinnitus of all patients before the treatment was 6450 Hz.

Good news is coming from recent studies on TMS application with repetitive low frequency in tinnitus treatment. TMS inhibits abnormal cortical activities in the affected area. Tinnitus treatment is applied to the auditory cortex. Positive results have been revealed during the studies [8, 9]. Animal models and functional human brain imaging studies, which were designed to investigate the pathophysiology of tinnitus, suggest that there is increased signals and activity in the central auditory pathways and also nonauditory brain areas [98].

Many studies suggested radiological findings were used to determine the coil positioning in order to increase efficacy. One suggested method is using positron emission tomography (PET) to determine the hyperactive auditory cortex [99]. Electroencephalography (EEG) also suggested resting state auditory gamma activity as a marker for tinnitus [100]. However, no association was demonstrated between tinnitus loudness and auditory gamma band. Also Langguth's study showed no superiority of EEG over PET, and this study could not demonstrate PET-guided coil positioning's superiority over standard-positioned coils [101]. Anatomical magnetic resonance imaging (MRI) is used as a guide in recent studies to position the coil to the primary auditory cortex [102–104]. Functional MRI activity could demonstrate tinnitus-matched sounds' effect on specific cortex areas, but evidence of this kind of navigation for tinnitus is not available [105]. Noh et al.'s recent study showed that there was no significant difference between EEG-guided or neuronavigation-guided coil placement [106].

Functional magnetic resonance imaging and F-18 fluorodeoxyglucose positron emission tomography have shown asymmetric metabolic activity in the hearing cortex of patients with unilateral or bilateral tinnitus [83]. Coactivation of prefrontal areas was detected in imaging studies. This may be related to the affective components of tinnitus [107–109]. Frontothalamic gating system may be formed by limbic and paralimbic structures for tinnitus [110]. James et al.'s study demonstrated with functional MRI that left superior dorsolateral prefrontal cortex had a greater role in predicting tinnitus awareness [111]. Combined prefrontal and temporal cortex rTMS was found to be more effective than temporal cortex rTMS alone [101, 112–114].

rTMS's antiapoptotic mechanism was demonstrated in Yoon et al.'s recent animal model [115]. Repeated stimulation induces neuroplastic changes. Single session effects seem to be short and immediate, and daily treatment over 4 weeks seem to have longer results that last over months to years [116–118].

Kleinjung et al. reported that, after rTMS application to the patients with chronic tinnitus, the mean score of tinnitus decreased at the rate of 7.5% [8]. De Ridder and colleagues found

positive results in half of the patients with rTMS in unilateral tinnitus treatment in 114 patients [9]. Kleinjung and colleagues found that application of low-frequency rTMS for 5 days had significant effects on tinnitus treatment [8]. In another study, 3 patients were treated with 1 Hz rTMS (2000 stimulus/day) for 5 days and 2 of the patients had a positive result [99]. In Langguth et al.'s study, 28 patients were treated with 1 Hz rTMS (2000 stimulus/day) for 10 days and 67.8% of the patients had a positive result [119]. Folmer et al.'s study demonstrated that 1 Hz rTMS for chronic tinnitus is an effective treatment method. The application of rTMS daily for 10 days had significantly better outcomes of chronic tinnitus patients [120].

In order to suppress tinnitus, various stimulation patterns have been reported as effective such as 1 Hz, 10 Hz, and burst stimulation [82, 103, 121–124].

A new TMS protocol was introduced by Huang et al. in 2008 [125]: the protocol named theta burst stimulation [TBS], which is a repeated application of triplets of 50 Hz pulses with 200 ms (5 Hz; theta) pulse interval [125]. Huang et al. suggested that this protocol is superior to tonic rTMS [125]. However, literature findings are controversial. De Riddler et al., Lorenz et al., and Poreiz et al. showed the efficacy of TBS but Chung et al.'s and Plewnia et al.'s studies did not find the same efficacy [103, 126–130]. Many studies showed low-frequency 1 Hz rTMS to be effective for tinnitus. Khedr et al. suggested that 10 or 20 Hz stimulation could also be effective [123]. James et al.'s study demonstrated that 1 Hz rTMS seemed to significantly decrease the awareness, loudness, and annoyance of tinnitus, but 10 Hz stimulus seemed to decrease only the awareness of tinnitus [111].

Kreuzer et al.'s study suggested that individualized rTMS sessions' outcomes were better, since tinnitus is a personal symptom and hard to generalize [131]. In Yilmaz et al.'s study, THI score decreased by 8 points after the application of low-frequency rTMS, and also a statistically significant decrease was observed in tinnitus loudness and subjective score after the application of rTMS [50]. Park et al. studied the difference between 6000 pulse and 12,000 pulse rTMS to temporal and prefrontal cortex. Patients who received 12,000 pulses of rTMS seemed to have better outcomes. This study seems to be the first in literature that underlines the importance of pulse rate, at least 12,000 pulses of rTMS seems to achieve a favorable outcome [132].

The chapter showed that low-frequency rTMS is useful in the treatment of chronic tinnitus.

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