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Review

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Neuroscientific therapies for subjective tinnitus

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Abstract: Tinnitus, a prevalent auditory symptom, can significantly impair quality of life, yet no definitive pharmacological interventions exist despite extensive ongoing research into its pathophysiology and treatments. The advent of biomedical engineering has introduced neuromodulation as a pivotal therapeutic approach alongside conventional strategies such as pharmacotherapy and surgery. Through the deployment of invasive and non-invasive techniques, using various modalities including magnetic, electronic, and optical means, neuromodulation aims to regulate neural functions. This has not only led to the refinement of fundamental theories but has also enhanced the optimization of clinical applications. As an emerging and promising intervention, neuromodulation enriches the toolkit available for basic neuroscience inquiry and broadens the spectrum of clinical therapies for conditions affecting the central nervous system, including tinnitus. In this paper, we succinctly review the current understanding of tinnitus mechanisms, discuss the features of diverse neuromodulation technologies, explore their application in tinnitus management, and contemplate prospects for their development in treating tinnitus.

Key words: Tinnitus; Neuromodulation; Magnetic stimulation; Electrical stimulation; Light stimulation

1 Introduction

Tinnitus is a perceptual phenomenon that originates from pathologies of the auditory system or related components, and is marked by the sensation of abnormal sounds that vary in intensity (Baguley et al., 2013). It is reported that in Western societies, tinnitus affects roughly one in ten individuals. A considerable portion of these sufferers find the condition severely distressing, a situation that can escalate to include sleep disruption and suicide (Kang et al., 2021). With its increasing prevalence, subjective tinnitus has come to be recognized as a predominant auditory affliction. The effectiveness of numerous therapeutic approaches, including pharmacological and behavioral interventions, has been constrained, leading to suboptimal improvements in patient symptoms. Consequently, there is a pressing need for researchers to explore more sophisticated strategies for the treatment of tinnitus.

Neuromodulation is a cutting-edge medical technology that uses various physical stimuli, such as optical, electrical, and magnetic signals, to stimulate individual neurons or neural networks composed of diverse subtypes of neurons (Edelman et al., 2015). Its primary goal is to alleviate abnormal symptoms of the nervous system and improve neurophysiological functions (Dusan et al., 2022). As research in this field deepens, more researchers are recognizing the superiority of neuromodulation. Not only can it bring about transient and rapid functional changes in the nervous system in a reversible manner, but it can also induce long-term changes in the synaptic plasticity of local or global neural circuits (Jedlicka et al., 2015). The rapid, direct, and precise control offered by neuromodulation technology, coupled with the support of

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various national and regional brain programs, has expanded its applications from basic theoretical research to clinical practice. In addition to surgical treatment, drug therapy, and rehabilitation therapy, current neuromodulation technology has become an important tool for alleviating or improving neurological diseases (Marson et al., 2021).

Neuromodulation methods can be divided into two categories based on their mode of interaction with the body: invasive and non-invasive (Peter and Kleinjung, 2019). Furthermore, such methods can be further divided into electrical stimulation, magnetic stimulation, and optical stimulation based on their principles of action (Darmani et al., 2022). Although diverse treatment effects have been found among these methods, this does not mean that dysfunction of the central nervous system can be universally alleviated by all these interventions, some of which may have weak or even adverse effects (Krishna et al., 2018). Elucidating the mechanism and pros and cons of each technology will greatly expand the efficiency of diverse neuromodulation methods. However, few studies have focused on this aspect of neuromodulation, especially in regard to its application to tinnitus.

Therefore, in this paper, we provide a comprehensive review of the pathology of tinnitus and the features of different types of neuromodulation technology, which paves the way for the selection of appropriate neuromodulation methods. We also summarize the existing literature on the neuromodulation of tinnitus and draw a blueprint for the future development of tinnitus treatment.

2 Progress in research on tinnitus and the basis of neuromodulation

2.1 Classification and etiology

Tinnitus is differentiated into subjective and objective types (Kang et al., 2021). Subjective tinnitus is distinguished by an examiner's inability to objectively quantify the volume and tonal qualities of the patient's auditory perceptions and represents the predominant form encountered in clinical settings. Objective tinnitus, conversely, permits objective evaluation of these characteristics and is commonly associated with underlying vascular or myogenic abnormalities (Mattox and Hudgins, 2008). Vascular tinnitus typically presents as spontaneous, rhythmic pulsations, distinguishable from the non-pulsatile variety associated with muscular activity. Furthermore, tinnitus is classified into acute and chronic forms based on the duration of the symptoms. Acute tinnitus typically resolves within three months, while chronic tinnitus is defined as symptoms lasting longer than six months (Formánek et al., 2018). Tinnitus is predominantly associated with pathologies of the auditory system. Research indicates that it has a robust association with hearing impairment, aging, and exposure to ototoxic substances (Nondahl et al., 2011). Moreover, other risk factors, such as smoking, otological conditions, cardiovascular diseases, and psychological disorders, are also implicated as triggers for tinnitus within certain demographic groups, highlighting the intricate and multifactorial nature of this condition (Hinton et al., 2006).

2.2 Pathogenesis

The cochlear nucleus (CN), a pivotal center for auditory processing, plays a critical role in the onset and development of tinnitus. Comprising both dorsal and ventral components, this nucleus harbors a diverse array of neuronal types that are involved in the pathogenesis of tinnitus. Notably, within the dorsal division, fusiform cells are characterized by heightened excitability, a phenomenon purportedly involved in the mediation of tinnitus (Wu et al., 2016). The origins of this enhanced neuronal excitability can be attributed to several factors. Primary among these is the damage to cochlear hair cells due to noise exposure or ototoxic agents, which leads to a substantial reduction in auditory input to the CN. This, in turn, results in decreased activation of inhibitory neurons and increased excitability across various types of neurons (Middleton et al., 2011). Besides, it has been documented that beyond mitigating the indirect influence of inhibitory inputs on neuronal excitability, there is an enhancement in the intrinsic excitability of the excitatory neurons. Research indicates that following the disruption of auditory input, there is an upsurge in the levels of glutamate receptors and transporters within the CN, which is intricately associated with the manifestation of tinnitus symptoms (Heeringa et al., 2018). Given that the CN also receives inputs from non-auditory systems, the augmented glutamate activity may constitute a compensatory mechanism emanating from the above sources. Moreover, anomalies in potassium ion channels and hyperpolarization-activated cyclic nucleotide-gated channels can precipitate neuronal hyperexcitability, thereby facilitating the emergence of tinnitus (Li et al., 2015). Lastly, certain studies imply that long-term potentiation contributes to the enhanced excitability of neurons within the dorsal CN (DCN). A similar trend is observed within the ventral CN, where the onset of tinnitus is marked by an increase in the excitability of bushy cells (excitatory neurons) concurrent with a corresponding decrease in the excitability of D-stellate neurons (inhibitory neurons) (Gu et al., 2012). It is thought that the CN is exclusively implicated in the onset of tinnitus, with no discernible impact on the duration of the symptomatic manifestation (Brozoski et al., 2012). Speculation abounds that the chronic forms of tinnitus may arise from excitatory alterations within the superior regions of the CN.

The inferior colliculus (IC) functions as a terminal for ascending impulses transmitted from the CN along the auditory pathway and also receives descending projections directly from layer V of the auditory cortex (AC) (Winer, 2006). Observations have indicated that neurons within the IC of animals exhibiting tinnitus behavior demonstrate an elevated frequency of spontaneous discharge. Nonetheless, further investigation is needed to ascertain the degree to which this excitatory input, particularly in the context of tinnitus, emanates from the IC neurons themselves.

As a crucial nodal point within the auditory information transmission pathway, the medial geniculate body (MGB) occupies a central position in proximity to the AC. Predominantly characterized by tonic and burst neuronal firing patterns, the MGB responds with tonic activity to cell membrane depolarization and burst discharges upon hyperpolarization (Llinás and Steriade, 2006). Research indicates that tinnitus may lead to an abnormal potentiation of gamma-aminobutyric acidergic (GABAergic) inhibition, which, in turn, triggers the activation of T-type calcium channels, enhancing both the frequency and number of burst discharges within each episode (Kalappa et al., 2014). This alteration in firing patterns results in a diminished excitatory projection from the MGB to the AC, weakening the inhibitory output from regions devoid of afferent input. As a result, this intensifies the excitability of neighboring neurons and gamma oscillations, culminating in the manifestation of tinnitus. This explanation is known as the thalamocortical dysrhythmia model (Sametsky et al., 2015).

The AC, a pivotal center for sound processing, is instrumental in the onset and progression of tinnitus. Studies using magnetic resonance imaging (MRI) techniques in individuals afflicted with tinnitus have revealed that the condition is marked by an augmentation of spontaneous neuronal activity within the AC, as indicated by heightened resting-state MRI activity in this area (Isler et al., 2022). Moreover, the heightened synchrony of neuronal firing is intrinsically linked to the manifestation of tinnitus, with exposure to noise resulting in a decrease in alpha band activity and a corresponding increase in the gamma band within the AC (Lorenz et al., 2009). Given the gamma band's direct association with sensory perception, the enhancement of this frequency band is postulated to facilitate the ability to perceive the abnormal sound (Han et al., 2023). Neural plasticity generally enables the brain to adapt to hearing impairments; nonetheless, in those afflicted with tinnitus, this adaptability may give rise to abnormal neural circuitry connections and heightened neuronal excitability (Shore et al., 2016). Such an anomaly can trigger chronic gamma oscillatory activity, which, under typical conditions, might enhance signal processing during challenging auditory situations (Port et al., 2017). Nevertheless, within the context of tinnitus, potentiated gamma oscillations can selectively amplify perceived tinnitus, enabling it to overshadow ambient noise. Given that gamma activity is intrinsically tied to emotional responses and memory retrieval, it may result in the amplification of emotional reactions to the tinnitus sound in affected individuals (Meier et al., 2020). Subsequently, this enhanced gamma neural activity could consolidate the perception of persistent tinnitus and intensify the experience of distress. As the AC encompasses both excitatory neurons and GABAergic neurons, the observed phenomena extend beyond a single neuron type, instead reflecting an imbalance within the excitatory–inhibitory network. Additionally, inhibitory neurons in the AC, including those secreting parvalbumin, somatostatin, and vasoactive intestinal peptide, have the capacity to curtail the emergence of tinnitus (Harris and Shepherd, 2015). The classification, etiology, and pathogenesis of tinnitus are summarized in Fig. 1 and the neural circuitry in Fig. 2.

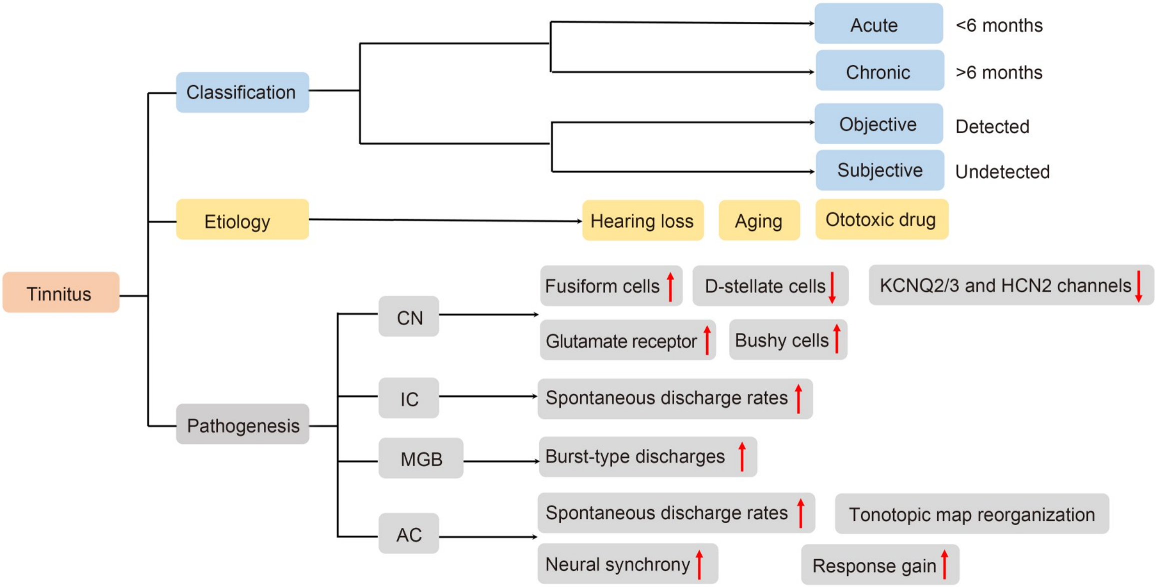

Fig. 1 Classification, etiology, and pathogenesis of tinnitus. CN: cochlear nucleus; IC: inferior colliculus; MGB: medial geniculate body; AC: auditory cortex.

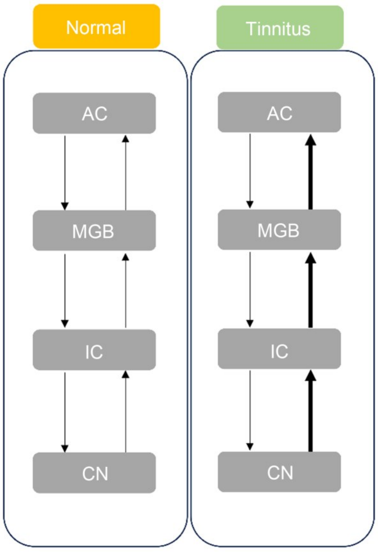

Fig. 2 Flowchart of the neural circuits involved in tinnitus generation and modulation. The bolded lines represent the increased auditory input from CN to AC. AC: auditory cortex; MGB: medial geniculate body; IC: inferior colliculus; CN: cochlear nucleus.

3 Progress in research on neuromodulation

3.1 Transcranial magnetic stimulation

Consisting mainly of stimulation coils and stimulators, transcranial magnetic stimulation (TMS) uses the principle of electromagnetic conversion, in which a coil generates a magnetic field that penetrates the skull, inducing a current that regulates brain activity (Cappon et al., 2022). High-frequency magnetic fields excite neurons in the targeted region, while low-frequency magnetic fields generate inhibitory effects (Fried et al., 2017). Additionally, different stimulation parameters yield distinct outcomes (Dougall et al., 2015). Extended sessions may yield more marked effects, although they may concurrently increase the risk of side effects. Intensified treatments can be more potent but also bear a greater risk of adverse reactions. The magnitude of the applied electrical current (commonly quantified in milliamperes) plays a pivotal role in determining the level and duration of the induced cortical excitability. Currently, it is believed that the specific mechanisms of TMS include altering the membrane potential of stimulated neurons, modifying local brain tissue blood supply, regulating the release of neurotransmitters and neurotrophic factors between neurons, and modifying brain network connections and synaptic transmission (Kumar et al., 2023).

Based on its intricate and diversified mechanism, researchers are now applying TMS to other appropriate disorders. For patients with dysfunction of the motor system, such as in Parkinson’s disease, continuous and repeated TMS can significantly enhance abnormal walking speed, possibly through the restoration of cortical inhibition (Chung et al., 2020). For other subtypes of neurodegenerative diseases such as multiple sclerosis, Huntington’s disease, and Alzheimer’s disease, TMS also showed a therapeutic effect on manual dexterity and global cognition (Wei et al., 2022). Although the therapeutic effects were partial, which may be caused by the limited number of patients, this paves the way for the enrichment of TMS application. In addition to its regulatory effect on physical motor behavior, TMS has shown promise in treating psychiatric disorders. By stimulating brain regions associated with emotions, TMS has alleviated symptoms and reduced the recurrence rate of depression (Perera et al., 2016). Besides, the symptoms of schizophrenia were shown to be alleviated by TMS, most efficiently at a frequency of 1 Hz (Bais et al., 2017). In addition, there is increasing evidence suggesting that TMS can be used in the treatment of neurological disorders such as stroke, migraine, and epilepsy (Iglesias, 2020).

Without direct interaction with the brain tissues, TMS induces no complications such as bleeding, pain, or inflammatory response, unlike invasive neuromodulation. Besides, even during the treatment process, no intolerable adverse effects were found, which makes TMS a much safer alternative curative method. Similar to the limitations of invasive magnetic stimulation, TMS lacks clear therapeutic parameters in clinical practice. Furthermore, patients exposed to high-frequency magnetic fields may experience adverse reactions such as epilepsy, hearing loss, and headaches (Sommer, 2022). The effects of magnetic stimulation on neurons are highly intricate, making it challenging to evaluate the accompanying effects. Therefore, the exact efficacy of TMS remains to be further explored. Additionally, magnetic stimulation experiences significant attenuation and dispersion after being applied transcranially, resulting in relatively low spatiotemporal resolution, which should also not be ignored (Dugué and Vanrullen, 2017).

3.2 Deep brain stimulation

Deep brain stimulation (DBS) equipment consists of three main components: a pulse generator, an electrode, and a subcutaneous wire (Giordano et al., 2023). A high-frequency current generated by the stimulation electrode, connected to the pulse generator, is used to modulate the excitability of the target brain area, which improves the function or treats the disease (Parker et al., 2020). The mechanism underlying DBS involves the ability of high-frequency current to inhibit neuronal excitability, thus downregulating the function of the targeted region (Chiken and Nambu, 2016). Moreover, DBS not only has a simple inhibitory effect but also promotes the release of neurotransmitters and upregulates the function of specific regions (Eser et al., 2024). DBS also interacts with astrocytes, which influence the regional blood flow, as well as adenosine triphosphate (ATP), inducing an indirect effect on the whole neuronal network (Lezmy, 2023). DBS modulates the function of both neurons and astrocytes in the central nervous system, which might explain its quick and efficient modulation.

As the most widely used implantable neuromodulation technique in clinical practice, DBS has been extensively used in the treatment of essential tremors and Parkinson's movement disorders (Asimakidou et al., 2024). However, not all patients report alleviation, suggesting a demand for personalized DBS in clinical practice. Moreover, with the advancement of brain precision localization technology, DBS has been applied to various conditions, including multiple tic disorders and dystonia (Poulen et al., 2024). Apart from physical movement disorders, DBS has been used in the management of chronic refractory diseases like epilepsy and chronic neuropathic pain, as well as psychiatric disorders such as depression, anorexia, obsessive-compulsive disorder, and neurodegenerative diseases like Alzheimer's disease (Acevedo et al., 2024; Zhang et al., 2024).

Unlike previous disfiguring operations such as thalamectomy and pallidectomy, DBS does not require the removal of the brain area with abnormal discharge of firing, thereby improving patient safety. With an electrode implanted in the target area, DBS accurately focuses on the dysfunctional region without affecting adjacent structures, which greatly decreases adverse effects. Although an invasive method, it is minimally invasive due to the advancement of operation procedures with the assistance of robotics. In addition, by combining improved stimulation programming, DBS can realize personalized modulation, which achieves better treatment effects. Despite the advantages of DBS in treating diseases, it is important to note its limitations. Firstly, there are potential side effects associated with the treatment, including hallucinations, cognitive dysfunction, hypersexuality, and euphoria (Zarzycki and Domitrz, 2020). Secondly, due to the surgical placement of the electrodes, there is a risk of stimulating adjacent brain areas resulting from patient head movements during or after surgery, leading to serious side effects (Fytagoridis et al., 2013). The close contact between the implanted electrode and the brain tissue increases the risk of infection and bleeding in patients (Xue et al., 2022). Additionally, the inflammatory response caused by the interaction between the electrode and the brain tissue may also impact the therapeutic effect, necessitating further attention from researchers and clinicians (Evers and Lowery, 2021). Lastly, how to make patients more willing to accept the acute implantation without stress and pressure should also be emphasized.

3.3 Vagus nerve stimulation

The vagus nerve stimulation (VNS) system consists of three main components: a pulse generator, a spiral electrode, and a subcutaneous wire (Panebianco et al., 2022). Research has shown that when the spiral electrode stimulates the vagus nerve, it leads to increased neural transmission from the nerve to the nucleus tractus solitarius and the ascending reticular structures, which subsequently increases the release of adrenaline and serotonin, and decreases the release of dopamine (San-Juan et al., 2019). The variation of these neurotransmitters in turn induces neural plasticity and network balance dynamics, which mediate the regulatory effects. Furthermore, VNS has been found to inhibit the inflammatory response in the brain through interaction with microglia, as in DBS (Kaczmarczyk et al., 2017). Additionally, VNS can enhance the permeability of the blood–brain barrier and facilitate the clearance of toxins and pathogens in the brain (Cheng et al., 2020).

Currently, the most common application of VNS is in the treatment of drug-resistant epilepsy (Suller Marti et al., 2020). Similar studies have demonstrated that improving the electrode stimulation system can significantly reduce the frequency of seizures in epilepsy patients (Fitchett et al., 2021). Previous research has shown that VNS can effectively alleviate depressive symptoms in patients, possibly due to the anatomical characteristics of the vagus nerve (Marwaha et al., 2023). Additionally, VNS has shown promising therapeutic effects for various other diseases, including migraine, Parkinson’s disease, Alzheimer’s disease, anxiety disorders, autism, and stroke (Wang et al., 2021). However, many studies focused mainly on the short-term and non-selective effects, and further research may be needed to verify the function of VNS based on the anatomical organization.

Like DBS, VNS also has the advantage of being a precise treatment with limited effects on other regions. With the development of technology, VNS can now realize non-invasive modulation through transcutaneous application. This reduces risks such as infection or peritracheal hematoma, without affecting treatment efficiency. Despite the remarkable efficacy of VNS in these diseases, there are still some unresolved problems and challenges. Firstly, it remains unclear which types of diseases are suitable for VNS. Secondly, the appropriate stage of disease development for VNS treatment is still uncertain. Additionally, the optimal stimulation parameters of VNS for treating specific diseases are currently unknown. Lastly, further confirmation is needed to determine whether the effects of VNS are attributed solely to the stimulation itself or if they are due to a compound effect. Both DBS and VNS involve invasive surgical interventions, each accompanied by inherent risks, including the potential for infection, hemorrhage, or adverse reactions to anesthesia. Patients are compelled to meticulously weigh the potential benefits against these hazardous factors. The prospect of enduring side effects or complications poses significant ethical challenges regarding the post-implantation quality of life for the patients. Ongoing monitoring and supportive care may prove indispensable, potentially affecting patients’ autonomy and long-term health strategies.

3.4 Transcranial electrical stimulation

In contrast to implantable electrical stimulation, non-implantable electrical stimulation does not require electrodes to be surgically implanted into the brain tissue. Instead, low-intensity currents (1–2 mA) are generated by positive and negative electrodes in close contact with the scalp to regulate neuronal activity in the brain (Chase et al., 2020). Research has shown that transcranial electrical stimulation (TES) can modulate neuronal firing through indirect effects, rather than directly stimulating neuronal activity. This is achieved by influencing hydrogen ions and transmembrane proteins in a non-synaptic manner, thereby altering the membrane potential of neurons. Typical intensity levels for TES range from 1 to 2 mA. Modest intensities may exert nuanced effects, whereas higher intensities could potentially induce more robust, yet possibly nonspecific, outcomes. The standard duration of stimulation ranges from 10 to 30 min. Prolonged stimulation may augment the induced plastic changes in the brain, although this is subject to a law of diminishing returns, with excessive durations running the risk of adverse reactions. Positive electrode stimulation produces an excitatory effect, while negative electrode stimulation produces an inhibitory effect. In addition to these acute effects, TES can also have long-term effects by regulating synaptic plasticity and facilitating the formation of long-term depression or long-term potentiation (Stagg and Nitsche, 2011). Positive stimulation enhances synaptic activity in the long term by acting on GABAergic or glutamatergic synapses, while negative stimulation inhibits long-term activity by suppressing the function of glutamatergic neurons.

For the modulation of neuroplasticity, TES can be applied to numerous abnormalities related to the neural network. The repetitive TES of the dorsolateral prefrontal cortex (DLPFC) has a slight relieving effect on depression (Brunoni et al., 2016). Stimulation of the middle frontal lobe has been shown to significantly improve the adaptive ability of patients with schizophrenia (Reinhart et al., 2015). Additionally, a daily 20-min 2-mA stimulation of the left temporoparietal lobe and DLPFC has been found to significantly alleviate tinnitus symptoms (Mondino et al., 2016). Furthermore, electrical stimulation has shown promising therapeutic effects for stroke, Alzheimer's disease, and epilepsy (Longo et al., 2022; Simula et al., 2022).

Unlike other forms of neuromodulation such as TMS, TES is affordable since the apparatus and materials are simply manipulated and easily acquired. In addition, the transient effects induced by TES mean that researchers are more likely to assess the effects clearly and in a timely manner. Besides the non-invasive property, the paradigm of TES can be conveniently adjusted, which satisfies the demand of personal treatment. However, there are still some constraints in the use of TES. Firstly, it is important to note that TES is still in the exploratory stage, and the specific clinical parameters, such as the number of electrodes, current strength, and stimulation duration, have yet to be determined. Secondly, due to the limited scope of TES, it is not suitable for treating diseases highly related to the dysfunction of the deep brain (Wunder et al., 2018). Lastly, it remains unclear whether TES can be combined with medication or other treatments to maximize therapeutic benefits.

3.5 Light stimulation

Optogenetics represents a sophisticated method that harnesses light to modulate cellular function, specifically in neurons, through the introduction of light-sensitive proteins. These proteins are capable of being activated or suppressed by distinct wavelengths of light, thereby enabling researchers to exert precise control over cellular activities. In conjunction with optogenetics technology, photosensitive proteins are expressed on the surface of neuron cell membranes. Specific wavelengths of visible light are then used to activate ion channels on the cell membrane surface, enabling a stimulation method that regulates neuronal excitability by altering the ion concentration on both sides of the membrane (Mitroshina et al., 2023). Photosensitive ion channel proteins are categorized into two main groups: rhodopsin channel protein 2 and halophil violet channel protein. Rhodopsin functions as a cation transport channel protein, allowing cation flow and causing depolarization of the neuron's membrane potential, thus stimulating neuronal electrical activity. The halophil violet protein, on the other hand, acts as a chloride ion transport channel protein, facilitating the flow of chloride ions inward and resulting in hyperpolarization, thereby inhibiting neuronal electrical activity.

Currently, light stimulation technology is used mainly in the analysis of neural circuits associated with diseases and physiological states. Specific activation of GABAergic neurons in the zona incerta of the brain can enhance feeding behavior (Zhang and van den Pol, 2017). Additionally, the specific regulation of midbrain dopaminergic neurons can influence depressive behavior (Chaudhury et al., 2013). Moreover, the specific inhibition of GABAergic neurons in the dorsal horn region of the spinal cord can alleviate mechanical pain (François et al., 2017). Light stimulation technology also plays a crucial role in the analysis of neural circuits related to addictive, social, learning, and memory behaviors (Josselyn and Tonegawa, 2020).

With the development of this technology, the current expression of ion channel proteins has transitioned from non-specific neuron clusters to specific types found in neuron subsets. Additionally, the types of ion channel proteins have evolved from ordinary to specialized forms (such as hyperspeed photosensitive proteins and step photosensitive proteins), enhancing the specificity and efficiency of regulation (Yizhar et al., 2011). In addition, the visible observation of neurons will facilitate real-time recording for researchers to clarify the structural and functional changes in physiological and pathological status. However, light stimulation still has limitations. Most current studies are based on rodents, making it impossible to determine the impact of exogenous light-sensitive protein genes on the safety of humans. To streamline the introduction of "exogenous light-sensitive protein genes" into human cells, researchers habitually use viral vectors—modified viruses adept at delivering genetic material into the designated cells. This procedure comprises the following several distinct stages. This initial stage is gene selection, in which investigators meticulously identify genes encoding light-sensitive proteins, such as channelrhodopsins or halorhodopsins, responsive to specific light wavelengths. This is followed by vector construction, in which these genes are incorporated into a viral vector, commonly derived from lentiviruses or adeno-associated viruses (AAVs), which can infect human cells without precipitating pathological symptoms. The subsequent delivery phase entails the application of the viral vector to the target tissue, such as the brain, through injection or infusion. Following infection, the vector integrates light-sensitive protein genes into the cellular genome. Subsequent to integration, expression occurs, resulting in the synthesis of light-sensitive proteins that can be activated by external light stimulation. Optical interface implementation is typically performed immediately above the target brain region following viral injection. The implanted fiber optic is then connected to an external laser source, and stimulation parameters are configured to record the animal's behaviors or neural electrophysiological activities. Nevertheless, ethical and technical concerns present challenges, particularly regarding safety, long-term consequences, and the potential for unforeseen complications in human subjects. Ongoing studies are focused on confirming the safety and effectiveness of these techniques before their more widespread use in humans. Additionally, the introduction of exogenous photosensitive proteins into the body necessitates some minimally invasive surgeries, resulting in corresponding damage to brain tissue. Also, the penetration range of visible light is limited, rendering it impossible to use light stimulation technology to stimulate deep brain tissue (Gong et al., 2020).

While the existing clinical trials provide valuable insights into diverse diseases, several limitations must be acknowledged to understand the robustness of the findings and to identify areas for future research. (1) Study design limitations: many trials use small sample sizes, which may limit the generalizability of the results. For instance, studies conducted on specific demographics (age, race, or gender) may not accurately represent the broader population, leading to biased results. This is particularly important in neurological disease, where variations in response to treatment are evident. (2) Short duration of follow-up: numerous trials assess outcomes only over a brief period. Long-term effects, including potential side effects or the sustainability of benefits, remain largely unexplored. Future research should prioritize long-term follow-up to assess the durability of treatment efficacy and safety. (3) Heterogeneity in outcomes: different studies often use variable definitions of success or endpoints, complicating direct comparisons. A standardized outcome measure is essential to better evaluate and synthesize findings across studies. The establishment of consensus guidelines for outcome measures in both clinical practice and research is recommended. (4) Insufficient reporting of adverse events: the documentation of adverse events in many trials has been inconsistent. A more rigorous and comprehensive reporting framework is necessary to fully understand the risk-benefit profile of treatments. (5) Limitations in population diversity: there is often a lack of diversity in study populations, which can impact the translation of results to real-world settings. Research needs to include a broader spectrum of participants to ensure that findings are applicable across different demographic groups. The clinical, mechanism, and parameter details extracted from the studies are reported in Table 1.

4 Neuroscientific interventions for tinnitus

Given the AC's crucial role in tinnitus, several studies have focused on modulating the left AC. Langguth et al. (2014) administered 1 Hz repetitive TMS (rTMS) at 110% of the motor threshold, with a regimen of 2000 stimuli over 10 d, and reported no significant benefits in tinnitus patients after an 11-week follow-up period. However, Lorenz et al.

Table 1 Neuromodulation methods

Category	Type	Mechanism	Advantage and disadvantage	Application in clinical trials
TMS	Non-invasive	Alteration of the membrane potential Alteration of the local brain tissue blood supply Alteration of neurotransmitter release	Advantage: easy operation and few complications Disadvantage: large attenuation	Yes
VNS	Invasive	Alteration of neurotransmitter release Inhibition of the inflammatory response Alteration of the permeability of the blood–brain barrier Facilitation of the clearance of toxins and pathogens	Advantage: accurate stimulation Disadvantage: operative difficulty and more complications	Yes
TES	Non-invasive	Influence of hydrogen ions and transmembrane proteins Regulation of synaptic plasticity	Advantage: easy operation and few complications Disadvantage: low precision	Yes
DBS	Invasive	Inhibition of neuronal excitability Promotion of neurotransmitter release	Advantage: accurate stimulation and individualized treatment Disadvantage: operative difficulty and more complications	Yes
Light stimulation	Invasive	Alternation of ion channels	Advantage: modulation of specific neurons and real-time recording Disadvantage: limited penetration range of visible light and exogenous light-sensitive protein genes	No

TMS: transcranial magnetic stimulation; VNS: vagus nerve stimulation; TES: transcranial electrical stimulation; DBS: deep brain stimulation.

(2009) observed a significant reduction in tinnitus symptoms with a protocol of 110% motor threshold and 1000 stimuli over 10 d. This discrepancy may stem from demographic differences, as the study population of Langguth et al. (2014) was older and potentially less responsive to rTMS than younger individuals. Anders et al. (2010) demonstrated a notable improvement using a lower number of stimuli with rTMS (110% motor threshold and 1500 stimuli over 10 d), which was also effective with a reduced stimulation duration (1800 stimuli over 5 d). These findings suggest that the left AC is a viable target for tinnitus treatment. Furthermore, the DLPFC has emerged as another significant target, as evidenced by Noh et al. (2020), who reported alleviation of tinnitus symptoms using a protocol of 1000 stimuli over 4 d. Notably, due to the penetration of rTMS being limited to superficial brain regions, other areas, such as the thalamus and the DCN, are not amenable to this method.

DBS has emerged as a significant advancement in the treatment of tinnitus, particularly due to its capability to target deep brain structures. For instance, bilateral stimulation of the caudate nucleus (with a pulse width of 90 microseconds, a frequency of 150 Hz, and an amplitude ranging from 0 to 10 V) has been shown to reduce both tinnitus functional index (TFI) and tinnitus handicap inventory (THI) scores (Cheung et al., 2020). Furthermore, DBS applied to the nucleus accumbens and the ventral anterior lateral infralimbic cortex has also shown notable improvements, using a frequency of 130 Hz and a pulse width of 90 ms, with amplitudes ranging from 3.5 to 5.0 V (Dijkstra et al., 2018). As a pivotal structure in auditory processing, stimulation of the MGB has also shown enhancements in the TFI scores (Devos et al., 2023). DBS offers a broader range of treatment targets compared to other neuromodulation techniques due to its distinct features.

VNS, currently used in the management of refractory epilepsy, is also being explored as a possible treatment modality for tinnitus (Clancy et al., 2014). The application of transcutaneous VNS (tVNS) to the tragus has been shown to mitigate beta and gamma synchrony, which is associated with the intensity of tinnitus symptoms. Conversely, the application of sham tVNS has negligible effects on normalized spectral measures at the frontal alpha and beta frequencies, with no discernible impact on indices of synchrony. Research has demonstrated that the degree of gamma-band synchronization within the human AC is indeed linked to the perceived loudness of tinnitus (Yakunina and Nam, 2021). Regarding invasive VNS, de Ridder et al. (2014) showed that 20 d of stimulation (2.5 h) significantly reduced THI scores by 11.78%, although the improvement rate was only 40%. However, other studies have shown that extended stimulation periods can enhance the efficacy to 50% in the tinnitus group, following six consecutive weeks of daily stimulation (Tyler et al., 2017). Additionally, when combined with tonal music, tVNS not only diminishes tinnitus by reducing the THI scores but also ameliorates related disorders such as stress and handicap (Ylikoski et al., 2020). Nonetheless, there is a lack of compelling and definitive evidence to suggest that tVNS in isolation effectively mitigates symptoms associated with tinnitus. This deficiency does not negate the potential of tVNS as a therapeutic intervention for tinnitus relief; rather, it underscores the need for more rigorous research to substantiate its efficacy.

Investigations into transcranial direct current stimulation (tDCS) have yielded mixed findings. For instance, dual-site stimulation of the left temporal area and the right DLPFC, administered in two sessions of 15 min each, did not produce a significant effect on tinnitus, as indicated by unchanged TFI scores and levels of anxiety (Cardon et al., 2022). Conversely, a more extensive protocol involving daily 20-min sessions of bilateral tDCS, delivering a 2-mA current for five consecutive days per week over two weeks, targeted at the AC, significantly reduced THI scores (Yadollahpour et al., 2024). Additionally, single-blind 2-mA tDCS sessions of 20 min duration were associated with increased cerebral blood flow and functional connectivity, which corresponded to a marked reduction in tinnitus intrusiveness (Leaver et al., 2024). Beyond the AC, the left temporal area has emerged as a promising target for tinnitus intervention, with 2-mA, 20-min stimulation proving more effective than other stimulation paradigms, including those using 10- and 15-min stimulation periods and a 1-mA stimulation amplitude (Bae et al., 2021). Regarding transcranial alternating current stimulation (tACS), stimulation modes using 1.5-mA, 20-min sessions targeting the AC, as well as 2-mA stimulation on the DLPFC and AC, were found to have an adverse effect on tinnitus relief (Vanneste et al., 2013a, 2013b; Claes et al., 2014). Combination with other types of stimulation, such as tDCS and transcranial random noise stimulation, appears to elicit a more comprehensive amelioration of tinnitus symptoms. Further research is imperative to elucidate the treatment effects of tACS. Concurrently, an inventory tailored for tinnitus patients should be developed, given the current absence of clinical experiments focusing specifically on this patient population.

Regarding the use of light therapy for tinnitus management, research has shown that transmeatal low-level laser therapy, administered for 6 to 15 min with a 100-mW laser at 660 nm, significantly reduces the THI score (Panhóca et al., 2023). Additionally, photobiomodulation therapy in tinnitus patients has been associated with increased levels of satisfaction (Silva et al., 2022). Nevertheless, the limited sample size precludes the recommendation of photobiomodulation for clinical use in tinnitus treatment.

Carrick et al. (1986) conducted a survey, in which forty patients from the Swansea Tinnitus Association volunteered to participate. They underwent a 10-min session of treatment, administered with an ultrasound generator or an identical placebo device, during two separate appointments. The results revealed that 40% of the participants who completed the trial experienced improvement with ultrasound therapy, as opposed to 7% in the placebo group. Low-powered ultrasound showed a statistically significant advantage over the placebo in fostering improvement ($P<0.02$, binomial test). Despite the scarcity of research on the use of focused ultrasound for tinnitus treatment, its impact on neuronal mechanisms suggests a promising potential for future studies targeting the AC to alleviate this condition.

Malfatti et al. (2021) have shown that the DCN is a pivotal region of focus for auditory and tinnitus research. Following activation by the calcium/calmodulin-dependent protein kinase 2α (CaMKIIα) promoter, channelrhodopsin 2 (ChR2)-mediated light stimulation induced action potentials in select neuronal units, yet the firing rates were mitigated when coincident with auditory stimuli. The expression and activation of CaMKIIα-eArchaerhodopsin 3.0 within the DCN exerted inhibitory effects on certain units, while the onset of sound-driven spikes was postponed under concurrent light stimulation. Conversely, stimulation of Chrna2+ cells augmented the firing activity in the DCN. These findings suggest that cortical molecular manipulation could be a viable approach for modulating DCN activity, particularly in the context of tinnitus research. This study thereby lays a foundational pathway for the application of optogenetic techniques in the exploration and potential treatment of tinnitus, encompassing the AC and additional brain regions. The clinical and parameter details extracted from these studies are reported in Table 2.

Table 2 Neuromodulation for tinnitus

Study	Stimulation	Region	Stimulation parameter	Follow-up time	Conclusion
Langguth et al. (2014)	rTMS	Left AC	110% motor threshold, 2000 stimuli	11 weeks	Insignificant
Lorenz et al. (2009)	rTMS	Left AC	110% motor threshold, 1000 stimuli	Unclear	Significant
Anders et al. (2010)	rTMS	Left primary AC	110% motor threshold, 1500 stimuli	6 months	Significant
Noh et al. (2020)	rTMS	Left primary AC and left DLPFC	110% or lower motor threshold, 1000 stimuli	8 weeks	Significant
Cheung et al. (2020)	DBS	Bilateral caudate nucleus	1–2 V increments, 90 ms	6 months	Significant
Dijkstra et al. (2018)	DBS	NAc and vALIC	0.5 V increments, 90 ms	12 months	Significant
Devos et al. (2023)	DBS	MGB	1.0 V, 60 μs	12 months	Significant
de Ridder et al. (2014)	VNS	Left vagus nerve	0.8 mA, 100 μs	2 months	Significant
Tyler et al. (2017)	VNS	Left vagus nerve	0.8 mA, 100 μs	12 months	Significant
Ylikoski et al. (2020)	VNS	Auricular branch of the vagus nerve	0.3–3.0 mA, 250 μs	12 months	Significant
Cardon et al. (2022)	tDCS	Left temporal area and right DLPFC	2 mA, 15 min	(8±2) weeks	Insignificant
Yadollahpour et al. (2024)	tDCS	Left AC	2 mA, 20 min	1 month	Significant
Leaver et al. (2024)	tDCS	Left AC	2 mA, 20 min	1 month	Significant
Souza et al. (2020)	tDCS	LTA	2 mA, 20 min	5 d	Significant
Bae et al. (2021)	tDCS	DLPFC	1 mA, 10 min	5 d	Significant
Vanneste et al. (2013b)	tACS	AC	1.5 mA, 20 min	1 d	Insignificant
Vanneste et al. (2013a)	tACS	DLPFC	2 mA, 20 min	1 d	Insignificant
Claes et al. (2014)	tACS	AC	2 mA, 20 min	1 month	Insignificant
Carrick et al. (1986)	FUS	Mastoid	500 kHz, 10 min	1 d	Significant
Panhóca et al. (2023)	LLLT	Transmeatal application	100 mW, 6–15 min	15 d	Significant
Silva et al. (2022)	LLLT	Right and left lingual veins	100 mW, 20 s	6 weeks	Significant
Malfatti et al. (2021)	Optogenetics	DCN	5–7 mW, 10 ms	1 d	Significant

rTMS: repetitive transcranial magnetic stimulation; AC: auditory cortex; DLPFC: dorsolateral prefrontal cortex; DBS: deep brain stimulation; NAc: nucleus accumbens; vALIC: ventral anterior limb of the internal capsule; MGB: medial geniculate body; VNS: vagus nerve stimulation; tDCS: transcranial direct current stimulation; LTA: left temporoparietal area; tACS: transcranial alternating current stimulation; FUS: focused ultrasound; LLLT: low-level laser therapy; DCN: dorsal cochlear nucleus.

5 Prospects

The future direction of the development of neuromodulation for tinnitus can be seen in two main aspects. For invasive neuromodulation, the main emphasis should be put on enhancing technology with the aim to minimize tissue damage and even achieve non-invasiveness while maintaining the effectiveness of existing regulatory treatments. For non-invasive neuromodulation, the main emphasis should be put on improving regulatory parameters, with the purpose of enhancing the precision and effectiveness of existing neuromodulation while preserving the non-invasive therapeutic effects. Due to the advancement of engineering, the advantages of neural modulation combined with artificial intelligence technology have increasingly emerged (Patel et al., 2021). The integration of artificial intelligence and neural modulation not only enhances the spatio-temporal resolution of stimulation but also enables real-time detection and precise intervention to evaluate the regulatory effect.

Artificial intelligence has the potential to assist in localizing areas for DBS treatment (Wong et al., 2009). Moreover, it can not only provide further assessment of the disease progress but also be used to develop personalized treatment plans for patients (Castaño-Candamil et al., 2020). By combining electrical stimulation with artificial intelligence algorithms to stimulate the striatum and internal capsule, there is a significant improvement in patients' cognitive function, surpassing the effectiveness of traditional open-loop stimulation (Basu et al., 2023). The emergence of tinnitus is attributable not only to structural changes in a single brain region but also to changes in the connectivity between different brain regions. Therefore, traditional neural regulation targeting a single brain region struggles to effectively control the entire network. When artificial intelligence is incorporated, real-time neural regulation of brain networks will no longer be challenging. Consequently, the prospects for combining artificial intelligence with neural modulation in treatments are extensive and promising for tinnitus treatment.

Author contributions

Conceptualization: Fangyuan WANG, Xiaoming LI, and Shiming YANG. Writing – original draft: Peng LIU, Xinmiao XUE, and Zhixin ZHANG. Visualization: Hanwen ZHOU, Cong XU, Lijun ZHANG, Zhen LI, Yongqing ZHOU, Shanwei SONG, and Yameng TIAN. Writing – review & editing: Peng LIU, Xinmiao XUE, and Zhixin ZHANG. All authors have read and agreed to the published version of the manuscript.

Compliance with ethics guidelines

Peng LIU, Xinmiao XUE, Zhixin ZHANG, Hanwen ZHOU, Cong XU, Lijun ZHANG, Zhen LI, Yongqing ZHOU, Shanwei SONG, Yameng TIAN, Fangyuan WANG, Xiaoming LI, and Shiming YANG declare that they have no conflicts of interest.

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

Declaration on the use of generative AI tools

During the preparation of this work, the authors used ChatGPT in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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