

REVIEW Article

The Pathological Mechanisms and Treatments of Tinnitus

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ABSTRACT

Tinnitus is defined as the ringing, hissing, clicking or roaring sounds an individual consciously perceives in the absence of an external auditory stimulus. Currently, the literature on the mechanism of tinnitus pathology is multifaceted, ranging from tinnitus generation at the cellular level to its perception at the system level. Cellular level mechanisms include increased neuronal synchrony, neurotransmission changes and maladaptive plasticity. At the system level, the role of auditory structures, non-auditory structures, changes in the functional connectivities in higher regions and tinnitus networks have been investigated. The exploration of all these mechanisms creates a holistic view on understanding the changes the pathophysiology of tinnitus undertakes. Although tinnitus percept may start at the level of cochlear nerve deafferentation, the neuronal changes in the central auditory system to the neuronal and connectivity changes in non-auditory regions, such as the limbic system, become cardinal in chronic tinnitus generation. At the present moment, some tinnitus generation mechanisms are well established (e.g., increased neuronal synchrony) whereas other mechanisms have gained more traction recently (e.g., tinnitus networks, tinnitus-distress networks) and therefore, require additional investigation to solidify their role in tinnitus pathology.

The treatments and therapeutics designed for tinnitus are numerous, with varied levels of success. They are generally two-fold: some treatments focus

on tinnitus cessation (including cochlear implants, deep brain stimulation, transcranial direct current stimulation and transcranial magnetic stimulation) whereas the other set focuses on tinnitus reduction or masking (including hearing aids, sound therapy, cognitive behavioral therapy, tinnitus retraining therapy, and tailor made notched musical training). Tinnitus management has focused on implementing tinnitus masking/reducing therapies more than tinnitus cessation, since cessation treatments are still lacking in streamlined treatment protocols and long-term sustainability and efficacy of the treatment.

This review will focus on concisely exploring the current and most relevant tinnitus pathophysiology mechanisms, treatments and therapeutics.

SUMMARY

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Keywords

Tinnitus, central gain control theory, thalamocortical dysrhythmia, global tinnitus network, tinnitus pathology, tinnitus treatments.

Abbreviations

tDCS (transcranial direct current stimulation); rTMS (repetitive transcranial magnetic stimulation); SFR (spontaneous firing rates); DCN (dorsal cochlear nucleus); GAD (glutamic acid decarboxylase); IC (inferior colliculus); MGB (medial geniculate body); fMRI (functional magnetic resonance imaging); MRI (magnetic resonance imaging); AC (auditory cortex); fNIRS (functional near-infrared spectroscopy); dorsal ACC (dorsal anterior cingulate cortex); OFC (orbitofrontal cortex); EEG (electroencephalogram); MEG (Magnetoencephalography); ROI (regions of interest); RSN (resting state network); BOLD (blood oxygenation level dependent response tests); sgACC (subgenual anterior cingulate cortex); pgACC (pregenual anterior cingulate cortex); TCD (thalamocortical dysrhythmia); CBT (cognitive behavioral therapy); TRT (tinnitus retraining therapy); TMNMT (tailor made notched music training); THI (tinnitus handicap inventory); TQ (tinnitus questionnaire); DBS (deep brain stimulation) TFI (tinnitus functional index); BDI (Beck's Depression inventory).

1. Introduction

Tinnitus is defined as the ringing, hissing, clicking or roaring sound in the ears (either bilateral or unilateral)¹. The individual consciously perceives a sound in the absence of any external auditory stimulus². Different classification systems have been developed characterizing tinnitus as pulsatile, subjective or objective, primary or secondary, and acute or chronic. Pulsatile tinnitus is almost always specific to causes that are vascular in origin³. Objective tinnitus is heard by the patient and the examiner whereas subjective tinnitus is only heard by the individual². Primary and secondary are on the basis of cause whereas acute and chronic indicate duration for which the patient has experienced tinnitus. Currently, tinnitus is viewed as a symptom of an underlying disease rather than a disease of its own. Therefore, multiple causes have been implicated in tinnitus including but not limited to the following: Meniere's disease, otosclerosis, otitis media, and ototoxic medications². One of the most common risk factors for tinnitus is noise induced hearing loss^{4,5}. However, cases exist in which tinnitus can occur as an idiopathic symptom⁶.

Once tinnitus develops, it is likely to be permanent. As a result, for some individuals, tinnitus can become a crippling condition to live with,

making their day-to-day tasks difficult to complete. For others, they are able to adapt to this symptom and easily integrate into their normal lives. Regardless, its potentially debilitating nature highlights the importance of understanding tinnitus outside of the condition that caused it.

Despite advancements in the causes of tinnitus and types of tinnitus that exist, there is still contention over its pathophysiological mechanism and consequently, the treatments leading to tinnitus cessation. The pathophysiology of tinnitus is characterized by different aspects. Research done at the cellular level demonstrates tinnitus as an increase in neuronal synchrony (i.e., increased firing rate of neurons simultaneously)⁷. This mechanism, by far, is one of the most studied mechanisms for tinnitus pathology. Previously, the focus was placed on auditory structures such as cochlear nerve deafferentation being the cause of tinnitus⁸. However, tinnitus research has ventured into studying the role of non-auditory structures and tinnitus networks in the brain^{8,9}. Evidently, tinnitus pathology research has undergone fundamental changes and continues to do so.

This review aims to thematically provide the current pathophysiological understanding of tinnitus and to analyze the current therapies.

For this review, the following exclusion criteria were implemented: tinnitus in children, tinnitus pathophysiology articles before 2010, tinnitus treatment/therapeutics articles before 2015. The inclusion criteria included articles testing treatments on people or animals.

2. Mechanisms of Tinnitus Generation

Previously, tinnitus research focused on the internal ear, cochlear nerves and the auditory system in the pursuit of understanding tinnitus pathophysiology. In more recent years, the focus has shifted to tinnitus networks and their interrelationship with other regions in the brain. The research for what started at the level of the ear has effectively been shifted to understanding it at higher levels in the nervous system.

The pathologies section thematically covers the different theories and conjectures regarding tinnitus pathology. The mechanisms are discussed under three categories: cellular level, system level and others (Figure 1).

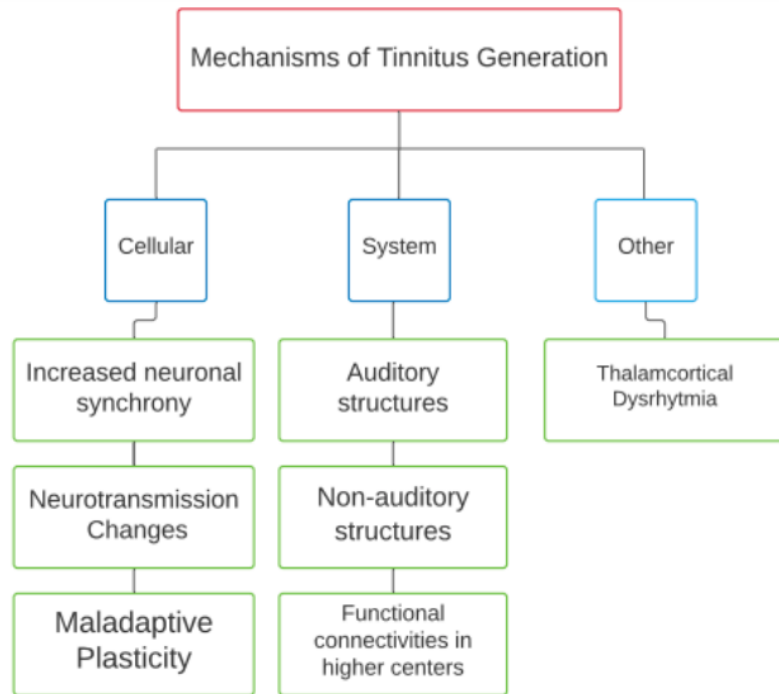


Figure 1. Overview of tinnitus generation mechanisms

2.1 Cellular level

2.1.1 Increase in neural synchrony

The most extensively studied mechanism of tinnitus pathology at the cellular level is increased neuronal synchrony.

The general mechanism starts with noise-induced hearing loss leading to reduced neural input to the central auditory system. As a result, there is increased spontaneous firing rate in the *central auditory system* despite the absence of a physical auditory stimulus^{3,8,10-13}. There are slight discrepancies in the location of hyperactivity since studies on the dorsal cochlear nucleus show an increase in neuronal synchrony evidenced by increased spontaneous firing rates (SFRs) in the fusiform cells of the dorsal cochlear nucleus (DCN)^{8,10}. Essentially, the neurons are firing action potentials in a synchronized fashion leading to the overall increase in neuronal activity. Animal studies on the medial geniculate body (MGB) demonstrated increased neuronal firing in animals with tinnitus than those without it^{8,10}. Therefore, increased neuronal synchrony has an established role in tinnitus pathology and several auditory structures

have been implicated in this mechanism. In later sections, the involvement of other auditory and non-auditory structures will also be discussed in the context of this hyperactivity.

This neuronal hyperactivity is also addressed under the “central gain control” theory which states that increased neuronal synchrony occurs in the central auditory system due to the auditory (sensory) deprivation from the cochlea¹¹. Again, the mechanism by which hyperactivity occurs is not well understood (can be a decrease in inhibitory synaptic response, increased excitatory synaptic response or altered intrinsic neuronal excitability)¹¹.

2.1.2 Neurotransmission changes

Another tinnitus generation mechanism at the cellular level includes changes in neurotransmission. It is important to note that these neurotransmission changes are intrinsically linked to increased neural synchrony which was discussed above. The basic mechanism of cause includes the loss of inhibitory drive which leads to unopposed action of the excitatory drive producing hyperexcitability that is perceived as tinnitus¹⁴. A study performed by Pilati

and colleagues demonstrated a downregulation of high voltage-activated K⁺ channels in the DCN after intense sound exposure which ultimately resulted in increased incidence of burst responses (i.e., firing rates of neurons)¹⁵. Another study demonstrated a decrease in presynaptic glutamic acid decarboxylase (GAD) levels in high frequency regions of the primary auditory cortex with a concomitant elevation in firing rates¹⁶.

Clinical studies testing for GABA_AR selective drugs have shown evidence of the link between neurotransmission change and tinnitus. A study on oral dosing of taurine (GABA_AR agonist) led to tinnitus attenuation, highlighting how taurine increases inhibition of MGB neurons specifically to decrease the hyperexcitability and thus reduce tinnitus¹⁷. Another study administered NO-711 and vigabatrin which induced increased GABA levels and again showed similar outcomes to the study above¹⁴. Furthermore, GABAergic inhibition in the central nucleus of the inferior colliculus (IC) decreased after noise exposure when measured 30 days after acoustic overexposure, leading to hyperactivity and thus tinnitus generation¹⁸. The studies outlined above illustrate that neurotransmission changes at varied structures (such as DCN, MGB, IC, auditory cortex) lead to an overall excitatory effect with decreased inhibitory effect, translating to hyperexcitability that is perceived as tinnitus by the patient.

2.1.3 Maladaptive plasticity

Neural plasticity, in the simplest terms, is the ability of the nervous system to change and adapt via reorganization of the neurons in response to new stimuli¹⁹. This phenomenon has been extensively studied in relation to memory. Thus, a review relates the plasticity of memory and tinnitus. The authors state that a NMDA receptor's 2B unit is involved during memory consolidation (a neural plasticity phenomenon) and similarly, 2B subunit antagonists in cochlear NMDA receptors eradicated long term noise-induced tinnitus in rats²⁰. Clearly, NMDA receptor antagonism causing tinnitus eradication indicates neuronal plasticity is being altered at the onset of tinnitus. The term maladaptive plasticity involves "misdirected" learning and is indicated in other neurological pathologies such as neuropathic pain²¹. In the context of tinnitus, the ringing may initially be due to hearing loss damage at the level of the cochlea, but chronic tinnitus generation is

sustained due to maladaptive changes in the auditory and non-auditory structures²¹. In later sections, maladaptive plasticity will be discussed at different levels of the auditory pathway and non-auditory structures, highlighting the key role this mechanism contributes to tinnitus generation and perception.

2.2 System level

2.2.1 Auditory structures involved in tinnitus pathology

2.2.1.1 Dorsal cochlear nucleus

One of the first physiological hallmarks of tinnitus was cited at the level of the dorsal cochlear nucleus (DCN), terming it the tinnitus generator^{8,22}. The main mechanism of DCN involvement includes increased neuronal synchrony²³⁻²⁷. For example, a rodent study demonstrated decreased synchronization of spontaneous firing due to blocked NMDA receptors in the fusiform cells of the DCN²³. Furthermore, salicylate-induced tinnitus in guinea pigs demonstrated increased SFRs, synchrony and stimulus timing dependent plasticity²⁷. The increased hyperactivity in the DCN seen as a consequence of decreased auditory nerve input is carried through to the inferior colliculus (IC), causing the IC to have elevated neuronal activity as well^{24,28}. On the other hand, a comparison study on the DCN and IC reported hyperactivity in the IC to be lower than in the DCN and explores the possibility of independent mechanisms causing hyperactivity in each structure²⁹.

Overall, as the previous section on the cellular level has established the link for hyperactivity and tinnitus, the increased neuronal activity in DCN only further supports that claim. The inter-relationship between DCN and IC needs to be investigated further to determine if preceding and/or succeeding structures in the auditory pathway impact the DCN/IC and consequently, contribute to tinnitus generation.

DCN studies have also explored the plasticity changes at this level as another cause for tinnitus. Two different studies performed on guinea pigs illustrated DCN's fusiform cells experiencing plasticity changes²⁷ and the other showed alterations in the DCN's bimodal plasticity^{5,30}.

DCN has a long-standing reputation as a tinnitus generator and, recent literature has only further proven its fundamental role. Therefore, the mechanism of DCN is largely undisputed and consistent.

2.2.1.2 Inferior colliculus

The inferior colliculus (IC) located in the midbrain of the brainstem is another auditory structure linked to tinnitus on the basis of hyperactivity^{31,32}. A review cited multiple studies that all point to increased neural activity in the IC³¹, one of which included an animal study of salicylate-induced guinea pigs and rats demonstrating increased excitability. Another guinea pigs study demonstrated increased neural gap detection thresholds in the IC³³. In contrast, one study demonstrated increased neuronal synchrony at the level of IC in guinea pigs post noise-induced trauma, but the hyperactivity was not significant between tinnitus and non-tinnitus guinea pig³⁴.

In humans, one study demonstrated that the ablation of the DCN led to reduced IC hyperactivity, implicating not only IC's role in tinnitus generation but also that its hyperexcitability is, to some extent, induced by DCN³⁵. Contrarily, fMRI study done on IC and other structures did not demonstrate increased activity in tinnitus patients³⁶. A similar sentiment is echoed by another study that states the activation of the IC was likely due to abnormal sound level tolerance rather than tinnitus³⁷.

Although the animal studies make a strong case for IC to be considered for tinnitus pathology, the recent studies on tinnitus patient's IC creates doubt. Therefore, the role of IC in tinnitus pathology is not as clear cut and requires greater investigation to verify its involvement.

2.2.1.3 Medial geniculate body

The medial geniculate body (MGB) of the thalamus is a higher center along the auditory pathway which integrates auditory and limbic information³⁸. Like DCN and IC, MGB has also been implicated in tinnitus generation³⁸⁻⁴⁰ although the current literature on it is limited. Animal models have demonstrated hyperactivity at the MGB⁴⁰ but conversely, there is evidence to prove that there is reduced neuronal excitability instead⁴¹. Consequently, MGB's role still requires more investigation to certify its significance in tinnitus generation.

On another note, the MGB projects to the amygdala which is a component of the limbic system involved in processing negative stimuli and emotions⁴². As discussed later on, tinnitus has an emotional component to its pathology therefore the link between the MGB and amygdala should be explored further to understand long-term tinnitus perception.

2.2.1.4 Auditory cortex

The auditory cortex (AC) is another well-established structure in tinnitus pathology as it is the final higher center at which auditory stimuli is processed. One study showed increasing intensity of perceived tinnitus with increased gamma band activity of the contralateral auditory cortex⁴³ whilst another study demonstrated increased gamma band activity in the left and right primary and secondary auditory cortex of tinnitus patients⁴⁴. An innovative functional near-infrared spectroscopy (fNIRS) approach demonstrated increased hemodynamic activity in the AC indicating plasticity changes⁴⁵ whereas another fNIRS illustrated increased resting state functional activity in the AC of tinnitus patients vs. non tinnitus individuals⁴⁶. A rat model illustrated augmented cortical excitability post- salicylate induced tinnitus⁴⁷, again reiterating the cellular mechanism of hyperactivity⁴⁷ discussed previously but now in the context of the AC. In conclusion, the AC has cemented its role in tinnitus pathology, likely through hyper-neuronal activity^{47,48}, as it is the final center at which auditory stimuli are processed.

2.2.2 Non-auditory structures involved in tinnitus pathology

2.2.2.1 Parahippocampus

The parahippocampal area plays a role in auditory habituation and since tinnitus perception is continuous (i.e., there is no habituation of the sound that is perceived), the role of the parahippocampus in perpetuating tinnitus and preventing its habituation becomes clear⁴⁹. Recent literature supports its role in tinnitus, particularly, individuals with unilateral tinnitus showed increased high frequency activity in the right parahippocampal area with increased gamma band activity of contralateral parahippocampal area⁴⁹. Another study recorded grey matter reduction in the parahippocampus³². The parahippocampus has also shown increased connections with non-auditory areas in chronic tinnitus⁵⁰. Lastly, a meta-analysis mentions multiple fMRI's that have been conducted, implicating the parahippocampal role in tinnitus pathology⁵¹. Overall, the parahippocampus' role is evidently significant in tinnitus perception.

2.2.2.2 Dorsal anterior cingulate cortex

The dorsal anterior cingulate cortex (dorsal ACC) has evidence to support its role in tinnitus distress networks. A blind source separation analysis on

tinnitus networks and tinnitus distress compared resting state electrical activity of tinnitus patients with controls and compared low vs. high distress tinnitus patients⁵². The results of the study showed two anatomically specific networks (termed IC5 and IC6) with distress related differences in tinnitus patients when compared to the controls. Specifically, tinnitus distress created abnormal alpha and beta activity in the subgenual ACC extending to the pregenual and dorsal ACC and the ventromedial prefrontal cortex/orbitofrontal cortex, insula and parahippocampal area⁵². The implications of these results stresses upon the link between a tinnitus distress network playing a role in tinnitus pathology. Therefore, how important is the tinnitus distress network to tinnitus pathology itself? As of yet, more research in regard to the psychological aspect of tinnitus, in this case a distress network, needs to be conducted. The distress network is discussed in another section below.

2.2.2.3 Ventral prefrontal cortex

A 3-part MRI studies that used voxel-based morphometry identified a decrease in gray matter in the subcallosal regions (specifically in the ventral prefrontal cortex) in tinnitus patients compared to controls⁵³. An article on frontostriatal gating cites multiple studies that have also shown gray matter reduction in this same region⁵⁴. The ventromedial prefrontal cortex (vmPFC) determines the extent to which the abnormal auditory activity is perceived consciously as tinnitus. This function suggests that gray matter reduction here indicates that the tinnitus suppression mechanism that the vmPFC should carry out is hindered, and thus tinnitus perception can occur.

The frontostriatal system (includes vmPFC and nucleus accumbens) assigns subjective value to external or internal sensory signals⁵⁴. In the case of tinnitus, changes in the input to this system can cause dysfunction in the valuation process and lead to a neutral stimulus becoming a negative stimulus and thus cause tinnitus perception⁵⁴.

2.2.2.4 Insula

The insula, like the dorsal ACC, has been implicated in tinnitus distress^{49,55}. Insula plays a role in the autonomic nervous system therefore, the tinnitus distress correlated with sympathetic activation proves the insula as a strong candidate for being involved⁴⁹. Furthermore, the alpha activity in the left

and right anterior insula was seen in patients with severe tinnitus distress⁴⁹. The altered alpha activity seen in the insula as evidence for tinnitus pathology also strengthens the claims given in the paragraph above about altered alpha and gamma activity in the dorsal ACC.

A meta-analysis states that neuromodulation of the insula of tinnitus patients was the strongest compared to other regions (amygdala, parahippocampus, ACC), indicating that it is likely involved in auditory processing which is impaired in tinnitus⁵⁰.

The insula is also considered in a salience network responsible for sensory integration⁵⁶. This network becomes relevant in the context of tinnitus in which there is sensory processing of a sound that is not actually elicited by an auditory stimulus.

2.2.2.5 Orbitofrontal cortex

Like the insula, the orbitofrontal cortex (OFC) is involved in the emotional processing of sounds and is indicated in tinnitus distress networks^{49,55}. These findings are further supported by a study that found tinnitus patients (especially females) were more emotionally responsive to tinnitus distress and had increased synchronized connectivity between the OFC and insula⁴⁹. Therefore, the role of the OFC in tinnitus generation is indicated by the role it plays in the tinnitus distress network.

2.2.2.6 Posterior cingulate cortex and precuneus

There is the concept of a network termed the brain default network which consists of the following structures: parahippocampal area, posterior cingulate cortex and precuneus⁴⁹. In the case of tinnitus patients, these 3 regions are more active during tinnitus perception.

2.2.3 Functional connectivity in the higher centers

This section of the review covers how different functional connectivities in the higher centers causes tinnitus generation and tinnitus perception. It is important to note the distinction between generation and perception; the former is at the level of the auditory system and the latter occurs due to the abnormal coupling of higher order centers of the brain with regions outside the auditory system⁵⁷.

2.2.3.1 Alterations in RSFC

With the shift towards understanding that non-auditory regions are involved in long term tinnitus

perception, the concept of altered RSFC has been investigated. FMRI, EEG and MEG studies of the resting state in tinnitus patients have been studied but clarity in terms of which structures are involved still requires more research⁵⁸. A specific study done on RSFC measured via fNIRS demonstrated increased hemodynamic activity in the auditory and selected adjacent non auditory cortices in tinnitus patients after sound stimulation and 5/9 non regions of interest (ROI) exhibited an increase in connectivity to the rest of the regions that were measured, suggesting that non-auditory regions contribute to chronic tinnitus perception⁵⁹. An fMRI study compared the auditory resting state network (RSN) connectivity in tinnitus patients vs. healthy individuals. The study demonstrated that chronic tinnitus patients had increased connectivity in the brainstem, cerebellum, right basal ganglia, parahippocampal areas, right frontal and parietal areas, left sensorimotor areas and left superior temporal region⁵⁸. Another fMRI study found an atypical RSN in tinnitus patients consisting of the medial Heschl's gyrus (i.e., the AC), inferior colliculus, mediodorsal nucleus, striatum, OFC, and lateral prefrontal cortex⁵⁸. Some of these structures (AC, IC, OFC) have been discussed in previous sections, providing credibility to the presence of this RSN in tinnitus.

2.2.3.2 Auditory - limbic association

A study using blood oxygenation level dependent response tests (BOLD) illustrated that functional connectivity of the brain was altered in bothersome tinnitus but not in non-bothersome tinnitus which indicates that the emotional and attentional aspect plays an important role in chronic tinnitus perception⁶⁰. This relationship between auditory and limbic regions (which are the hubs for emotional and attentional processes) dates back to 1990, described by Jastreboff in his neurophysiological model of tinnitus⁶¹. A more recent article outlines the “noise cancellation” process of the limbic system which eliminates unwanted sound signals by sending it to the *inhibitory* thalamic reticular nucleus, which removes the sound signal from reaching the auditory cortex⁶². However, in tinnitus, this noise cancellation system is impaired leading to the sound signal reaching the AC and causing cortical reorganization at this level that translates to tinnitus perception⁶². Evidently, the limbic system plays a cardinal role in tinnitus pathology, especially chronic tinnitus

generation in which the functional connectivities shift from the auditory system to a more diffused location throughout multiple auditory and non-auditory regions (i.e., limbic system) of the brain.

On a different note, the limbic system is involved in tinnitus distress networks as well, since a MRI-based study confirmed that tinnitus patients suffer from psychological distress which is strongly associated with the limbic system³². Furthermore, the study cites another functional research that linked the parahippocampus (part of the limbic system) to distress³².

2.2.3.3 Global tinnitus network

Up until now, it has become clear that the initial onset of tinnitus affects the auditory system primarily (usually in the form of hyperactivity) however, chronic tinnitus generation mechanisms shift towards integrating non-auditory higher centers with changed functional connectivities.

Therefore, the development of a global tinnitus network has become prevalent in recent tinnitus research. This network consists of long-range cortical connections that are outside of the central auditory system. A particular study relates the global workspace model of Dehaene-Changeux to a global tinnitus network. Dehaene-Changeux's model explains that what one experiences consciously is a consequence of selective amplification and global broadcasting of the specific piece of information to multiple distant areas⁶³. The study attempts to probe this tinnitus network via sound stimuli resembling the tinnitus tone of the patient and then observing the effect on the functional connectivity of the network⁹. Eight regions were studied yielding the following results: anterior cingulate cortex (ACC) with right frontal and ACC with right parietal showed meaningful correlation indicating tinnitus intrusiveness (i.e., how bothersome the tinnitus is)⁹. These correlations were only found in tinnitus subjects and not in control conditions further supporting that these specific connectivities within the brain are likely related to a global tinnitus network. While their results provide some evidence of such a network existing, it is possible that a general salience network (consisting of anterior insula and dorsal ACC⁶⁴) was activated instead by the perceived importance of the tinnitus sound. Thus, more studies are needed to evaluate if there is a clear distinction between the general salience network and a specific tinnitus network. If a specific tinnitus

network does exist, then more investigation on the structures involved needs to be explored.

2.2.3.4 Depression and distress networks

One study aimed to separate depression and distress networks caused by tinnitus from the neural changes i.e. tinnitus intensity networks. A source analysis of resting state EEG activity was done which demonstrated a positive correlation between those who had a higher score for tinnitus-related distress (measured via the Tinnitus Questionnaire) and increased activity in the frontopolar, OFC, sgACC and pgACC⁶⁵. There was also a positive correlation between increased BDI (Beck Depression Inventory-II) with the frontopolar, OFC, and sgACC regions⁶⁵. As discussed before, ACC plays a role in the emotional processing network thus the positive correlation between tinnitus distress and ACC further supports this statement (see dorsal ACC section for its role in tinnitus distress networks). Further, the OFC is involved in the pathophysiology of depression and it is positively correlated in this study of tinnitus patients, again demonstrating the presence of a potential depression network in tinnitus⁶⁵. The paper concludes that the parahippocampal area showed increased activity in those with higher BDI scores and this region is likely the link between a tinnitus network and the attention-emotion circuit related to tinnitus distress, underscoring this region's role in tinnitus pathology.

2.3 Others

2.3.1 Thalamocortical dysrhythmia (TCD)

TCD claims that in a state of deafferentation, the dominant alpha band activity in the thalamus reduces to theta band activity with gamma band activity surrounding the theta area⁶⁶. The increased gamma band activity is due to reduced GABA_A-mediated lateral inhibition⁶⁷ while on a molecular level, the deinactivation of T-type Ca channels at the thalamic relay cells are involved⁶⁶. This switch from alpha activity to theta and gamma activity is a feature of tinnitus thus implicating TCD mechanisms in tinnitus pathology^{66,67}.

3. Treatment and Therapeutics

Current treatments and therapeutics can be divided into two categories: tinnitus masking/ reduction and tinnitus cessation (Figure 2). Currently, tinnitus masking treatments play a greater role in the first line

treatment of tinnitus as they are more effective and easier to implement for tinnitus patients, allowing the patient's long-term outcome to be improved.

3.1 Tinnitus masking/reduction

3.1.1 Hearing aids

Hearing aids are useful in tinnitus patients with or without hearing loss. In the case of the latter, the hearing aids can augment the peripheral noise as a means to mask the tinnitus sound and help the patient focus on the ambient noises rather than their tinnitus². In the case of concurrent hearing loss and tinnitus, the hearing aids serve a dual purpose².

3.1.2 Sound therapy

This therapy involves sound production that stimulates the auditory system causing the patient to focus on that sound rather than their tinnitus thereby reducing their intensity and perception of tinnitus temporarily. This can be achieved through hearing aids or through any system that can produce sound (ex. musical player)². There is evidence in support of sound therapy being a beneficial treatment for tinnitus⁶⁸⁻⁷⁰. One study positively correlates tinnitus relief with sound therapy⁶⁸, while another study found that customized sound therapy (i.e., sound production catered to the individual's tinnitus type) improved tinnitus loudness⁶⁹. However, a meta-analysis on sound therapy concludes that there is no evidence to support the therapeutic effect of this therapy⁷¹. Currently, the use of sound therapy is criticized for not having sufficient evidence to prove its efficacy. Therefore, sound therapy is not a first line treatment for tinnitus and instead the preference of the patient is considered for choosing to avail this treatment option⁷¹. See TRT section below for its uses in that therapy.

3.1.3 Cognitive behavioral therapy

Oftentimes, the onset of tinnitus leads to emotional disturbances such as anxiety and depression in the patient as they attempt to grapple with this new condition in their lives. Thus, CBT is beneficial in reducing the patient's negative response to tinnitus via counseling and relaxation techniques aimed at their anxiety/depression⁷². Notably, a recent systematic review on CBT illustrates that although CBT is more beneficial than no treatment at all for tinnitus management, it is still not highly efficacious⁷³. The review compared CBT to other therapies (e.g., tinnitus retraining therapy),

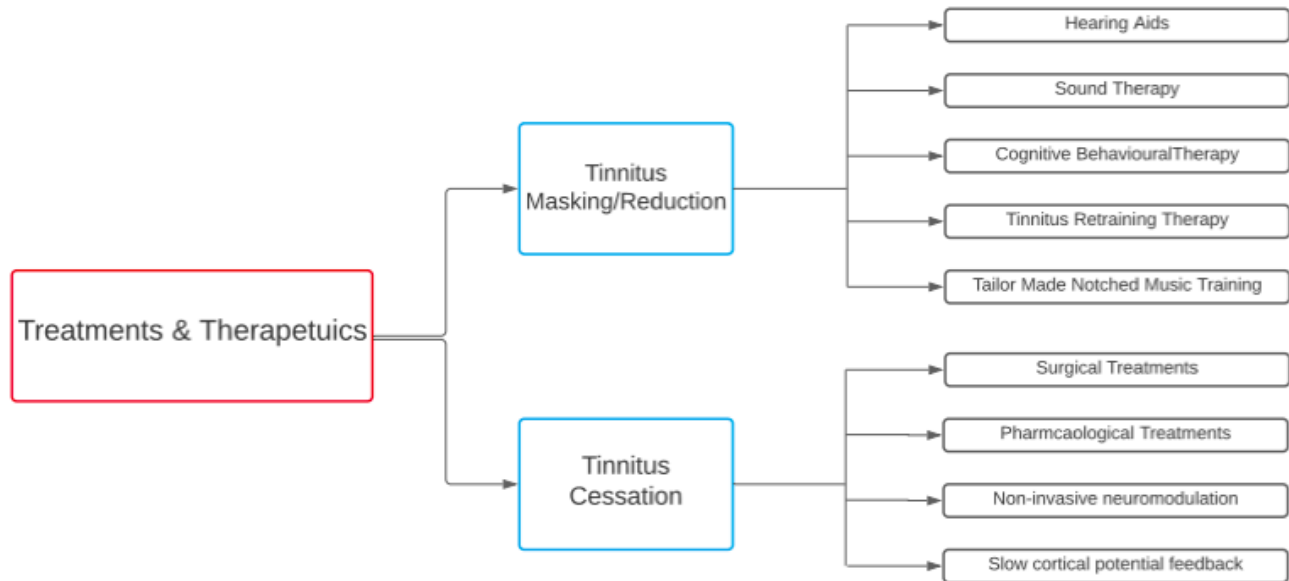


Figure 2. Treatments and therapeutics flowchart

establishing that it can relieve some depression symptoms and reduce tinnitus impact on quality of life but there is no evidence of this 6-12 months post-treatment⁷³.

Although CBT may not hold extreme efficacy on its own, a recent study showed promising results by combining CBT with music therapy^{73,74}. The CBT-Music group showed significant improvement in their tinnitus perception relative to the CBT and Music groups^{73,74}.

In conclusion, implementation of CBT is not harmful for tinnitus patients, but its efficacy and benefits are minimal.

3.1.4 Tinnitus retraining therapy (sound therapy type)

TRT was described by Jastreboff's neuro-physiological model back in the 1990s⁷⁵. The therapy itself is twofold: counselling is given to convert tinnitus stimuli into a neutral stimuli and sound therapy is provided to reduce hyperactivity of the tinnitus related neurons overall aiming to habituate one to their tinnitus⁷⁶. There is evidence to support the efficacy of this therapy⁷⁶⁻⁷⁸ and with continued treatment, TRT may prove to be one of the best treatment options for tinnitus⁷⁶.

3.1.5 Tailor made notched music training (TMNMT)

It is an acoustic neuromodulation method in which the notched music excludes one octave width of the frequency band centered at the individual's tinnitus frequency range (i.e., the notched range)^{7,79}. Therefore, the frequency in the tinnitus range is not stimulated but the neurons situated adjacent to this area are stimulated and due to lateral inhibition, they exert an inhibitory influence on the neurons in the 'notched' range. A double-blind study demonstrated significant decreases in tinnitus loudness in the tinnitus group⁸⁰. Furthermore, MEG results showed decreased synchrony of neurons in cortical areas contributing to tinnitus perception after using TMNMT⁸⁰.

3.2 Tinnitus cessation

3.2.1 Surgical treatments

3.2.1.1 Cochlear implants

Surgical placement of cochlear implants is a beneficial treatment in individuals with concurrent sensorineural loss and tinnitus^{81,82}. A longitudinal prospective study done on 142 cochlear implant patients assessed their tinnitus handicap inventory (THI) before and after implantation⁸². The results were statistically significant indicating that the implants had a suppressive effect on tinnitus thereby reducing tinnitus perception. In 37% of the

individuals, there was complete tinnitus suppression⁸², validating it as a potential tinnitus cessation treatment.

3.2.1.2 Deep brain stimulation

A Phase 1 trial conducted deep brain stimulation (DBS) of the caudate nucleus in treatment-resistance tinnitus patients. The study showed promising results in which patients indicated lower Tinnitus Functional Index (TFI) and tinnitus handicap inventory scores post-DBS. Currently, this surgical neuromodulation is one of the newest treatments present for tinnitus cessation⁸³.

DBS has been used at other targets for tinnitus cessation such as the subthalamic nucleus, globus pallidus internus and ventral intermediate nucleus of the thalamus. The study itself demonstrated that the subthalamic nucleus proved to be the most beneficial target for tinnitus⁸⁴.

Overall, more research is required to test the feasibility of DBS treatment's long-term efficacy and which DBS targets in the brain are most effective in eliminating tinnitus.

3.2.1.3 Microvascular decompression

A review on surgical treatments for tinnitus covers microvascular decompression of the cochlear nerve to relieve tinnitus in patients that were experiencing chronic compression of this nerve. The review cites a study that reported the improvement of tinnitus in 7 out of 13 patients with improved scores on the TQ (Tinnitus Questionnaire)⁸¹.

3.2.2 Pharmacological treatments

Currently, there are no pharmacological treatments available for tinnitus loudness or distress⁸⁵. This review aimed to look at treatments in the past five years and unfortunately no sustainable treatment has been found as of yet for tinnitus. One promising treatment from 2015 indicates NMDA receptor antagonism in rat cochlea led to tinnitus reduction⁸⁶ however, further trials have yet to be conducted.

Despite the presence of tinnitus distress networks and the causal link between tinnitus and depression, current guidelines advise against antidepressant, anticonvulsant or anxiolytic medication for patients with bothersome tinnitus⁷². However, patients with pre-existing anxiety and depression can use antidepressants/selective serotonin reuptake inhibitors to manage tinnitus symptoms⁷².

3.2.3 Non-invasive neuromodulation

3.2.3.1 Transcranial direct current stimulation (tDCS).

Mechanism behind tDCS method constitutes modulation of cortical excitability via anodal and cathodal stimulation in which the cathodal tDCS is usually placed over the auditory cortex to reduce tinnitus related hyperactivity^{7,79}. A double-blind placebo-controlled crossover design demonstrated a beneficial short-term effect in tinnitus intensity for 7 out of 20 patients when tDCS was applied over the left temporoparietal area⁸⁷.

Contrarily, a bifrontal tDCS therapy in distressed patients with *severe* tinnitus caused alleviation of tinnitus related distress but treatment did not correlate with reduction in tinnitus loudness⁸⁸. Furthermore, a combined therapy of tDCS over auditory cortex with tailor made notched music training in tonal tinnitus with concurrent severe hearing loss indicates there was reduction in tinnitus related distress^{7,79}.

Majority of the benefit of tDCS has been in the form of reducing tinnitus distress rather than reducing tinnitus loudness itself. Regardless, the treatment still needs more investigation to establish general treatment protocol.

3.2.3.2 Repetitive transcranial magnetic stimulation (rTMS)

rTMS has been a controversial treatment option due to conflicting results, evidence of high placebo effect, and variability in the treatment's effectiveness and longevity⁸⁹.

In earlier repetitive transcranial magnetic stimulation (rTMS) studies, the focus was on stimulating auditory cortices but recently, the focus has shifted to stimulation of non-auditory cortices⁹⁰ with the advent of tinnitus networks involving non auditory structures. A blinded randomized control study demonstrated improved tinnitus handicap inventory and VAS scores (visual analogue scores) after dual-rTMS of the frontal and auditory cortex⁹⁰. Furthermore, a systematic review confirmed the efficacy of rTMS for chronic tinnitus, citing that rTMS treatment showed efficacy at the one-week mark and continued to do so 6 months post-treatment⁹¹. On the contrary, another systematic review shows conflicting results, indicating that rTMS had little benefit in reducing the psychological issues of the patient, since there was no change in

KEY POINTS

- ◇ *Tinnitus is a heterogeneous condition, considered as a symptom that is almost always associated with an underlying disease.*
- ◇ *Investigations regarding a global tinnitus network, tinnitus-distress and depression networks are relatively newer in tinnitus research. Therefore, this domain of research requires further exploration to develop solid evidence of these network's existence in tinnitus pathology.*
- ◇ *Neuromodulation treatments, such as tDCS, rTMS and DBS, are being tested and show some promising results. However, further testing and trials are required to establish a standardized protocol and long term efficacy of the treatment.*

Tinnitus Questionnaires (TQ) and BDI (Beck's depression inventory)⁹².

Overall, there is still contention over using tDCS or rTMS as a first line of treatment and more research is required to establish streamlined guidelines on treatment protocol that will prove to be effective long term for the patient.

3.2.3.3 Slow cortical potential neurofeedback

A case report of a 50-year-old male with chronic tinnitus underwent this treatment involving slow cortical potentials (regulate excitation thresholds that might be impaired in pathological conditions such as tinnitus)⁹³. The patient reported a decrease in tinnitus loudness and pitch and these findings were supported by an EEG analysis showing close to normal changes in resting state activity of cortical areas implicated in tinnitus generation⁹³. However, this case report is not substantial in indicating the efficacy of the treatment for the general population of tinnitus patients thus, more research with this treatment is required to establish its role as a viable treatment option.

4. Conclusion

Overall, tinnitus pathology is multifaceted as the disease is heterogeneous in nature. Thus, the mechanisms highlighted in the cellular level section should be considered together, in a stepwise fashion, for an in-depth understanding. The initial onset of tinnitus is considered at the cochlea, due to cochlear nerve deafferentation, leading to decreased auditory input to the auditory system. Consequently, the auditory system (and non-auditory structures) attempt to compensate leading to neurotransmission changes that result in hyperactivity. As discussed in the system-level section, hyperactivity is seen in

auditory and non-auditory structures and is implicated in potential tinnitus networks which demonstrate a change in functional connectivities. The long-term consequence of these neuronal changes leads to more permanent neuronal plasticity changes in the auditory/non-auditory structures, leading to chronic tinnitus generation and perception.

Regarding treatments, no current tinnitus cessation treatments can guarantee tinnitus eradication. Pharmacological treatments have had a long history in tinnitus treatment research however, even currently, no such drug has prevailed to show benefit in tinnitus reduction or cessation. Consequently, tinnitus masking/reducing treatments *relatively* show better efficacy (e.g., TRT, TMNMT).

Some promising results in efficacy of DBS, tDCS and TMS treatments are met with issues regarding the absence of a standard treatment protocol nor having long-term efficacy. In conclusion, the shift towards understanding changes in functional connectivity and tinnitus networks has allowed treatment research to also shift towards targeting structures in the brain to reduce tinnitus perception. Although the current treatments are still being developed and refined, they still hold potential in eliminating tinnitus altogether.

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Conflict of Interest

The authors declare no conflicts of interest.

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