

Invasive neuromodulation as a possible treatment for tinnitus

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A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine

Academic year: 2017 – 2018

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1. Abstract

Background: Tinnitus is the perception of a meaningless sound which does not originate from an external sound source. It affects a large part of our population and can have a serious impact on people's lives. Many different therapies have been suggested, but few are evidence based and none has proven to be effective for all tinnitus sufferers so far. Neuromodulation techniques for tinnitus are currently under investigation. Non-invasive neuromodulation is already implemented quite often, although a Cochrane systematic review from 2011 concludes that there is very limited support to recommend this treatment. The fact that some patients did respond well to non-invasive neuromodulation, opened the door to try more invasive techniques. As new and more detailed hypotheses for the pathophysiology of tinnitus arise, more central types of invasive neuromodulation gain interest.

Objectives: We aimed to collect and review the published studies on invasive neuromodulation techniques for the therapy of tinnitus and to assess whether these results seem promising for the future. The included techniques are deep brain stimulation, cortical stimulation, vestibulocochlear nerve and vagus nerve stimulation.

Search methods: MEDLINE and Embase databases were scanned for articles using PRISMA guidelines.

Results and conclusion: In total, 22 studies were included in this systematic review. There are 2 randomized controlled trials who found no effect of cortical stimulation during the blinded phase. Other cortical stimulation trials show more promising results, especially for unilateral, pure tone tinnitus. However, the evidence is of low quality. Deep brain stimulation studies are mostly pilot studies where some patients responded with a decrease in tinnitus loudness or severity, but there are no placebo results to compare. Invasive stimulation of the vagus nerve shows a general decrease in tinnitus severity and an improved depression score but there is no decrease in tinnitus loudness and again, these studies are not placebo controlled. Cochlear nerve stimulation transformed the tinnitus percept in a more pleasant sound in two trials, but there was no change in loudness. Due to the limited quality of literature at this moment, it is not possible to draw conclusions about the effectiveness of invasive neuromodulation techniques for the treatment of tinnitus. At this moment risk/benefit ratio is not favourable for such an invasive technique and should not be recommended in general, although some promising effects are mentioned. Further research must be encouraged to gain more insight in this matter.

Samenvatting

Achtergrond: Tinnitus is de perceptie van een betekenisloos geluid dat niet afkomstig is van een externe geluidsbron. Een groot deel van de populatie wordt hierdoor getroffen en tinnitus kan een grote impact hebben op het leven van deze patiënten. Er zijn reeds talrijke therapieën op de markt, maar slechts een klein deel hiervan is wetenschappelijk gestaafd en tot nu toe is er geen enkele therapie in staat om een voordelig effect te bieden aan de gehele patiëntenpopulatie. Momenteel worden neuromodulatietechnieken onderzocht voor tinnitus. Niet-invasieve neuromodulatie wordt al vaak in de praktijk toegepast, al blijkt uit een systematische review van de Cochrane database dat er niet genoeg bewijs is om deze therapie aan te raden. Aangezien sommige patiënten met tinnitus wel hun voordeel halen uit deze niet-invasieve neuromodulatie, heeft dit de deuren geopend om ook meer invasieve technieken te onderzoeken en uit te proberen. Er schieten steeds nieuwe en meer gedetailleerde hypothesen over de pathofysiologie van tinnitus uit de grond die een grotere focus leggen op meer centraal gerichte invasieve neuromodulatietechnieken.

Doelstelling: We hebben getracht om de reeds gepubliceerde studies omtrent invasieve neuromodulatie technieken als therapie voor tinnitus te bundelen en te evalueren of de resultaten en besluiten veelbelovend zijn voor de toekomst. De geïnccludeerde technieken zijn diepehersensstimulatie, corticale stimulatie, vestibulocochleaire zenuwstimulatie en vagale stimulatie.

Zoekstrategie: De MEDLINE en Embase databases zijn gescand op artikels en dit volgens de PRISMA guidelines.

Resultaten en conclusies: In totaal werden 22 studies geïnccludeerd in deze systematische review. Er zijn 2 gerandomiseerde controlestudies opgenomen die beide geen effect van corticale stimulatie kunnen aantonen tijdens het gerandomiseerd deel van de studie. Andere studies over corticale stimulatie tonen positievere resultaten, vooral wanneer het gaat over unilaterale, zuiver tonale tinnitus. De kwaliteit van deze studies is echter laag. Studies over diepehersensstimulatie zijn tot nu toe voornamelijk pilootstudies waarin sommige patiënten een verbetering tonen van het volume of de ernst van de tinnitus. Deze studies zijn echter niet of amper placebo getest. Invasieve stimulatie van de vagale zenuw resulteert in enkele studies in een daling van de tinnitusernst en een verbeterde depressiescore. Het volume van de tinnitus daalt echter niet of nauwelijks en ook deze testen zijn moeilijk met een placebotest te controleren. Stimulatie van de vestibulocochleaire zenuw transformeert, volgens de patiënt, de tinnitus in een aangename geluid maar ook hier was er geen verandering in de luidheid. Door gebrek aan kwalitatieve literatuur omtrent dit onderwerp op dit moment, is het niet mogelijk om conclusies te trekken over de effectiviteit van invasieve neuromodulatie als

therapeutische optie voor tinnitus. Op dit moment is de risico/batenverhouding niet gunstig voor een dergelijke invasieve techniek en kan die dus niet algemeen aangeraden worden. Toch bevatten deze studies enkele veelbelovende resultaten en moet verder onderzoek aangemoedigd worden om meer inzicht te krijgen in deze materie.

2. Introduction

2.1 Epidemiology and classification of tinnitus

Tinnitus is the perception of a meaningless sound which does not originate from an external sound source. Tinnitus affects 15 to 20% of the population, of which 1-2% suffers from a severe form (1). For some patients, it can interfere with their daily life, they report concentration problems, sleep deprivation and even anxiety or depression (2).

Two types of tinnitus can be distinguished. Objective tinnitus is usually generated inside the patient's body. It can be caused by hypertension, a vascular abnormality, muscular spasms of the middle ear or palatum. Subjective tinnitus, on the other hand, cannot be perceived by anyone else except the patient and has a distinct pathophysiology (2, 3).

Another distinction is the one between primary tinnitus and secondary tinnitus. In case of an underlying pathology other than pure auditory deprivation, the tinnitus is called secondary (2). In this case, the treatment is logically adjusted to the condition causing it. Examples are Meniere's disease, otosclerosis or more banal conditions such as a simple cerumen impaction (2). Primary tinnitus is idiopathic, although it is associated with a peripheral auditory lesion in many cases (2, 4).

Tinnitus is often classified as acute or chronic. Up until 3 to 6 months after onset, there is a good chance of spontaneous resolution of tinnitus. After this period of time, it is more likely that actual changes in the neural network are established and that the tinnitus will be persistent. Other treatment strategies will then have to be considered and discussed (2). In this paper, as from now, we will only deal with the chronic, subjective type of tinnitus.

2.2 Physiology of the auditory system

2.2.1 Classical auditory pathway

Sound is transferred from the outer ear, via the external ear canal, through a vibration of the tympanic membrane and ossicular chain, to the cochlea. In the cochlea, afferent nerve fibers from the inner hair cells extend to the ipsilateral cochlear nucleus (CN) in the brainstem. From here, neurons connect to the ipsi- and contralateral nucleus olivaris superior and the inferior colliculus (IC) (5). The IC, mainly the central nucleus (ICC), receives afferent fibers from the CN and is seen as the primary processing center. The dorsal nucleus of the IC (ICD) receives descending pathways from the auditory cortex. Intrinsic projections from the ICD to the ICC can modulate the ascending auditory pathway.

The ventral part of the medial geniculate body (MGB), which is actually the auditory sensory nucleus of the thalamus, is the relay station between ICC and the primary auditory cortex. The thalamus receives feedback from the descending auditory pathways and is responsible for the

balance between the afferent pathways and the descending inhibitory pathways. A neutral non-changing stimulus does not carry new information that can help improve our knowledge about the world around us and should therefore not reach conscious perception or should have no influence on other systems in the brain. Via the reticular nucleus of the thalamus, frequency selective thalamic inhibition can strongly influence the sensory relay neurons in the MGB and prevent certain information from reaching the primary auditory cortex, this is called 'thalamic gating' (5, 6).

The primary auditory cortex is the final station in the classical auditory pathway, where all stimuli are processed in a more analyzing, 'mathematical' way. There is a tonotopic organization throughout the classical pathway from the basilar membrane in the cochlea to the primary auditory cortex. Tonotopy means that each frequency has its own representation in the cortex, starting from the cochlea. A specific frequency of sound causes a specific vibration of the tympanic membrane and thus the endolymph in the cochlear duct. Changes in thickness of the basilar membrane depict where it is moved most easily. The lower the frequency of the vibrations, the further the maximum movement on the membrane. Hair cells located on this place of the membrane will transfer the mechanic energy into an action potential of specific neurons of the cochlear nerve. Lateral inhibition by the excited neurons prevents the spreading of action potentials to neighbouring neurons in lateral direction. In the following relay-stations (CN, ICC, and the ventral part of the MGB), this tonotopy will be respected until the frequency-specific neurons of the primary auditory cortex are stimulated (6). The primary auditory cortex is connected to the secondary associated auditory cortex, which projects to the amygdala, part of the limbic system. The sounds, recognized by the primary cortex, will be further processed by these cortices to give the sounds deeper sense (7, 8).

2.2.2 Non-classical auditory pathway

The amygdala is part of the limbic system and can be described as a sensory gateway. It receives input from the thalamic and cortical level, including auditory input. Between the lateral and central amygdala, inhibitory intercalated cells can be found. This area is responsible for the detection of relevance of the sensory input. The central amygdala is connected to the hypothalamus, which affects the autonomic sympathetic response and to the dorsal nucleus of the vagus nerve, which affects the parasympathetic response. This means that the level of relevance, detected in the amygdala, will decide upon the autonomic response of our body to sensory information.

Another part of the limbic system is the hippocampus. This part is closely connected to the amygdala. Its function is the formation of long-term memory, as well as auditory memory. When

auditory stimuli are repeated, the response in the hippocampus weakens, this is called hippocampal gating (9).

The above mentioned structures are part of the so-called non-classical auditory pathway (see figure 1). The main difference with the classical structures is the relay station in the thalamus. The inferior colliculus now fires information to the dorsal and medial nucleus of the MGB, with direct connections to the amygdala. In this way, information bypasses the higher structures of the primary auditory pathway. The amygdala receives auditory input almost unprocessed, which can influence the emotions in a different way. This pathway is particularly active in children, under normal circumstances it is no longer active in adults (7, 8).

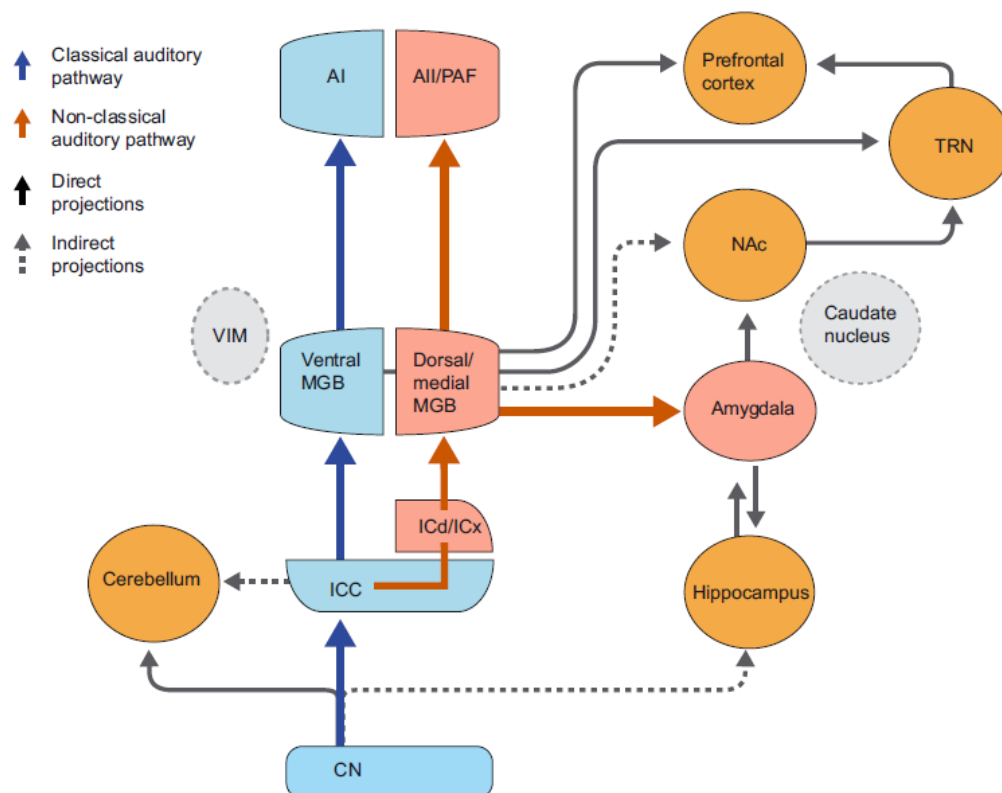


Fig 1: Schematic diagram showing connections from the classical and the nonclassical ascending auditory pathways. Adapted from Smit JV et al (7).

CN=cochlear nucleus; AI=primary auditory cortex; AII=secondary auditory cortex; PAF= Posterior Auditory cortical Field; ICd=dorsal cortex of the inferior colliculus; ICC=central nucleus of the inferior colliculus; ICx=external nucleus of the inferior colliculus; MGB=medial geniculate body; TRN= thalamic reticular nucleus; NAc= nucleus accumbens; VIM=ventral intermediate nucleus of the thalamus.

2.3 Pathophysiology of tinnitus

2.3.1. Lesion induced plasticity

A common observation in functional imaging studies of patients with tinnitus is a hyperactivity of the auditory pathway. The cause of this hyperactivity would be a loss of input to the auditory

system. In case of a sensory deafferentation, certain neurons in the central nervous system no longer receive input and thus become 'useless'. The natural reaction of the central nervous system is to assign other sensory input to these neurons. Dormant synapses can be unmasked or new connections are created by axonal sprouting. While losing the ability of sensing some specific input, the brain area assigned to other sensory information is now increased and will be more sensitive to this input. This can actually be a good thing as some functions might (partially) come back after brain injury (8). At times, however, it may lead to hypersensitivity and hyperactivity and as a consequence might cause symptoms like tinnitus. Sensorineural hearing loss (SNHL) is often observed in patients with chronic tinnitus. The finding that some patients don't reveal any hearing loss in the standard test battery, could be explained by some form of 'hidden hearing loss'. Subclinical hearing loss (e.g. synaptopathy at the hair cell – afferent fiber junction) could then still be considered as 'deafferentation'(10).

The adaptation of the nervous system in reaction to change is called neuronal plasticity. Because of auditory nerve deafferentation, reallocation of the dynamic range is achieved by tonotopic reorganization. Due to less lateral inhibition, neurons of the affected frequency region will receive input from edge frequencies. Therefore, the frequencies right beside the affected area will be overrepresented because they take over the neurons which lost their original input. More neurons will be tuned to the same frequency, resulting in an increased spike. As a result, the cortical neurons become more sensitive to this frequency (9). This sensitivity might explain the high comorbidity of tinnitus and hyperacusis (11). A larger area of the auditory cortex will correspond with the perceived tinnitus frequencies. This is indeed indicated by preliminary findings in human Positron Emission Tomography (PET) and Magnetoencephalography (MEG) studies. More detailed animal studies also show frequency-specific reorganization of the thalamus and auditory cortex (6). Animal studies show that tonotopic reorganization of the auditory cortex is visible as soon as one to three hours after it was deprived of sensory input. Reorganization is also seen in the DCN, yet this would take up to 6 months (12).

2.3.2. Functional changes

In tinnitus, multiple functional connectivity changes have been described. In deafferented neurons between the thalamus and cortex, the normal alpha activity (8-12 Hz) seen in resting state has changed to theta activity (4-8Hz, associated with reduced consciousness). Due to the reduced band activity, lateral inhibition will decrease (9, 13). This change in functional connectivity is associated with an increase of surrounding gamma activity (above 30Hz, normally indicating the processing of new information) (5). The changes in activity patterns between the thalamus and cortex is called thalamocortical dysrhythmia (5, 13).

The thalamocortical dysrhythmia model does not only describe a change in frequency of the oscillations, there is also a change to more temporal coherence. Coherence describes the relative timing of activity between different areas in the brain. When sending and receiving areas in the brain oscillate at the same frequency, with optimal phase difference, the probability of propagation of neural activity is enhanced (9, 13). The theta activity that emerges in thalamic regions shows coherent oscillations between the thalamus and cortex. This could explain the more synchronized gamma activity nested on this theta phase. Although this has not been investigated for tinnitus in particular, it is used as a basis to explain the positive effect of some forms of neuromodulation (13).

In the previous paragraphs, a bottom-up approach with deafferentation as starting point was used to explain the functional changes. There are also top-down mechanisms that could explain several changes in patients with tinnitus. The importance of ‘thalamic gating’ in the normal hearing process has already been pointed out above. When the brain senses that it receives less auditory information than before, it can not only enhance the bottom-up pathway but it could also decrease the top-down inhibition.

Reactivating dormant synapses, new axonal sprouting and other changes in existing synapses can cause redirection of information and these changes most likely result in a higher connectivity between the classical and non-classical auditory pathway, which means the limbic system becomes more directly involved. Jastreboff already understood in 1990 that changed connections with primarily the limbic system are the cause of tinnitus annoyance and related distress (see figure 2) (4).

Due to the direct connections of the amygdala to the autonomic nervous system (see figure 2), an autonomic response is often associated with chronic tinnitus. This can result in physical symptoms related to stress or anxiety, such as palpitations or sweating (4, 14).

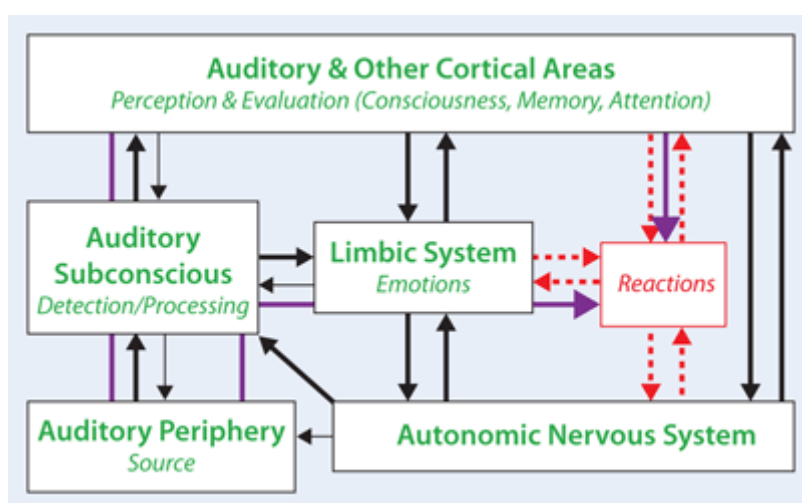


Fig. 2: diagram of the neurophysiological model of tinnitus. Jastreboff 2015 (4).

2.3.3 Brain structures involved

As deafferentation is seen as the primary cause of tinnitus, the first structures to look at are those involved in this classical auditory pathway.

Often, studies on animals are used to provide supporting evidence for certain hypothesis in tinnitus research. Both imaging as behavioural studies are used. Tinnitus is mostly induced by exposing the animals to loud noise, sometimes salicylate is used. The gap detection acoustic startle reflex is a behavioural model for the detection of tinnitus in rats. It was introduced by Turner and colleagues in 2006 and states that when a background acoustic signal was qualitatively similar to the rat's tinnitus, poorer detection of a silent gap in the background would be expected (15).

Imaging studies of animals with tinnitus show hyperactivity of the CN, more specific an increase in spontaneous bursting activity in the DCN. This is probably caused by a decrease of GABAergic inhibition in a response to the loss of input from the CN after deafferentation (7, 16). When ablation of the DCN is performed in tinnitus induced rats, this did not decrease the tinnitus. However, when ablation of the DCN on both sides happens before the tinnitus induction, it prevented the development of tinnitus. This agrees with the statement that the DCN can serve as a trigger for tinnitus, but might not be a good target for the treatment of chronic tinnitus (7).

Research by Kaltenbach argues that the DCN might play a major role in the process of attentional targeting and also the negative emotions that are often connected with tinnitus (17). Kaltenbach provides a cohesive model with the DCN playing a central role in the pathophysiology of tinnitus and its related symptoms. As the DCN receives input from other somatosensory symptoms, this could offer an explanation for somatic modulation of tinnitus, where for example clenching the jaws can modulate the tinnitus perception. A direct connection with the area of the locus caudatus (area LC), which is part of the attentional control pathways, might explain the attentional problems associated with tinnitus. Serotonergic neurons in the dorsal raphe nucleus play a central role in the pathophysiology of depression and these neurons project directly to the DCN, again providing a possible explanation for the high depression rates in tinnitus patients. This research by Kaltenbach uses mostly physiological studies on animals (rats and cats).

Where the CN is seen as simply a relay station, the IC is the primary processing center. Previous studies comparing the sound-evoked response in tinnitus patients with a control group, showed the IC had the most notable changes. These results are inconsistent with a more recent study that showed no sound-evoked activity changes in tinnitus patients. However, it did show significant changes in lateralization index involving the right IC (18, 19).

A structural MRI study showed a decrease in grey matter in the IC of tinnitus patients with normal hearing (7).

In many of the proposed theories about the pathophysiology of tinnitus, the thalamus plays a central role. Imaging studies show reduced connectivity between the thalamus and auditory cortex, supporting theories about changes in the corticothalamic feedback loops and reduced inhibitory effectiveness between the thalamus and limbic structures (5, 19, 20). Tinnitus sufferers were compared to healthy controls using high resolution MRI and voxel-based morphometry. The thalamus was the only auditory structure that showed grey matter changes. An increase of grey matter was seen especially in the area of the MGB (21).

The MGB is the part of the thalamus that seems most connected with the pathophysiology of tinnitus as integration of auditory and limbic information occurs here. In tinnitus induced rats, an increased spontaneous bursting activity is noticed (7).

While the deafferentation might affect the classical auditory pathway first, other changes in structures regulating emotions and attention have been noticed in patients with chronic tinnitus. Due to the functional changes mentioned, neuronal connections reaching the limbic structures bypass cortical structures without being processed. This stronger connectivity of the non-classical pathway can explain the mental distress that patients with moderate to severe tinnitus experience (8). This system is probably also compromised in patients with chronic pain, further underlining the similarity in both disorders (8, 22).

The caudate nucleus is connected with the auditory pathway through projections from the secondary auditory cortex and associated cortices (7). It has been implied that the basal ganglia are involved in gating and selecting cortical representation to focus attention. The selection of attention is said to be one of the key distinctions between people who suffer from tinnitus and people who don't.

A recent meta-analysis of the brain abnormalities seen in tinnitus patients shows that, although there is great diversity between the patients, there are also some common abnormalities in non-auditory brain structures (22). In this meta-analysis, 9 studies were included that compared functional imaging studies (SPECT/PET/fMRI) of chronic subjective tinnitus patients with healthy controls. Areas with consistent increased resting-state activity were identified. These areas are the insula, the middle temporal gyrus (MTG), the inferior frontal gyrus, the parahippocampal gyrus, the posterior lobe of the cerebellum bilateral and the right superior frontal gyrus. The left cuneus and right thalamus showed decreased activity.

The MTG has been suggested to be the key structure of the default mode network (DMN), a network which is most active at rest or when thinking about our own or other people's emotions

and thoughts. It shows reduced activity when a specific task is performed. fMRI shows significantly increased spontaneous activity in the right MTG and also abnormal functional connectivity between the right MTG and the left thalamus (22).

The superior frontal cortex might be responsible for receiving and integrating information from different parts of the central nervous system. The coordination happens through efferent feedback leaving the inferior frontal cortex (20, 22). In tinnitus, the frontal cortex might show more activity due to the increased negative feedback by which it tries to control the hyperactive auditory network. An increase in activity in the frontal cortex has been associated with subjective tinnitus loudness and may influence other perceptual features of tinnitus (6).

The insula is considered as a limbic-related structure and thus as a part of the central gatekeeping system for perceptual sensations. These areas would determine the affective value given to sensory information.

Suppression of unilateral tinnitus was attempted by temporally inactivating the amygdala with barbiturate injection. Significant suppression was achieved in some patients, mainly when inactivating the contralateral amygdala (7).

The parahippocampus has been suggested to play a role in memory recollection and transferring information from the hippocampus to associated areas (13).

The cerebellum, more specific the paraflocculus receives auditory input. It would also work as a gating mechanism comparing the input from the cochlea to the descending signals from the auditory cortex (22).

The changes in these non-auditory brain structures suggest multiple overlapping subnetworks involved in the pathology of tinnitus (11, 13, 21, 22). These networks are involved in defining the specifics of the tinnitus percept and burden, such as the auditory features, the emotional effect, the awareness or attention.

2.3.4 Subtypes

There is a possibility that variation in characteristics of the tinnitus symptoms are caused by subtle differences in pathophysiological mechanism. The most important factor is probably the time since the symptom has started. The instantaneous occurrence of tinnitus is likely caused by an immediate decrease in GABA surround inhibition due to damage to the afferent auditory pathway. When the loss of input lasts for a longer time, other mechanisms like axonal sprouting, synaptic changes and reorganization of the central pathways will cause more structural changes that may cause a spreading of activity to brain regions normally not involved in the auditory pathway, like those discussed above (12).

Some authors suggest that a pure tone tinnitus is related to a different pathophysiology than the noise-like tinnitus. A pure tone tinnitus would be caused by changes mainly restricted to the classical auditory pathway, whereas a noise-like tinnitus would involve changes in both the classical and non-classical pathway. This could explain why the same therapy only helps some of the patients. The networks involved might not only differ between patient groups but might also change in the same patient over time (13).

2.4 Treatment strategies

As the pathophysiology of tinnitus is complex and multifactorial, there is a wide range of therapeutic strategies. Concomitant complaints, comorbidities, extensive clinical and audiological evaluation are necessary to evaluate a new patient with tinnitus. In case of an underlying condition causing the tinnitus, the next step would logically be to treat this specific condition. However, often there are no underlying conditions identifiable, or they are hard to treat. When the tinnitus is idiopathic, a further assessment is needed to reveal the burden on daily functioning and sleep quality, and to identify possible influencing factors.

A multidisciplinary approach is warranted in the workup and treatment of tinnitus. Audiological evaluation can be very useful in case of severe hyperacusis and/or hearing loss or noise exposure. When there are severe mood disturbances, a referral to a mental health worker is advised. Also, somatomodulation of the tinnitus by neck or temporomandibular joint problems, can be approached by physiotherapy or relaxation therapy. In all cases, education of the patient is of uttermost importance. The education must involve pathophysiology of hearing, hearing loss and tinnitus. The clinician should also explain the possible factors that could influence the tinnitus, for example loud noise, attention, sleep deprivation (2, 23). Specific tinnitus approaches are described below.

Figure 5 shows the clinical practice guidelines for tinnitus assessment and treatment made in 2014 (2).

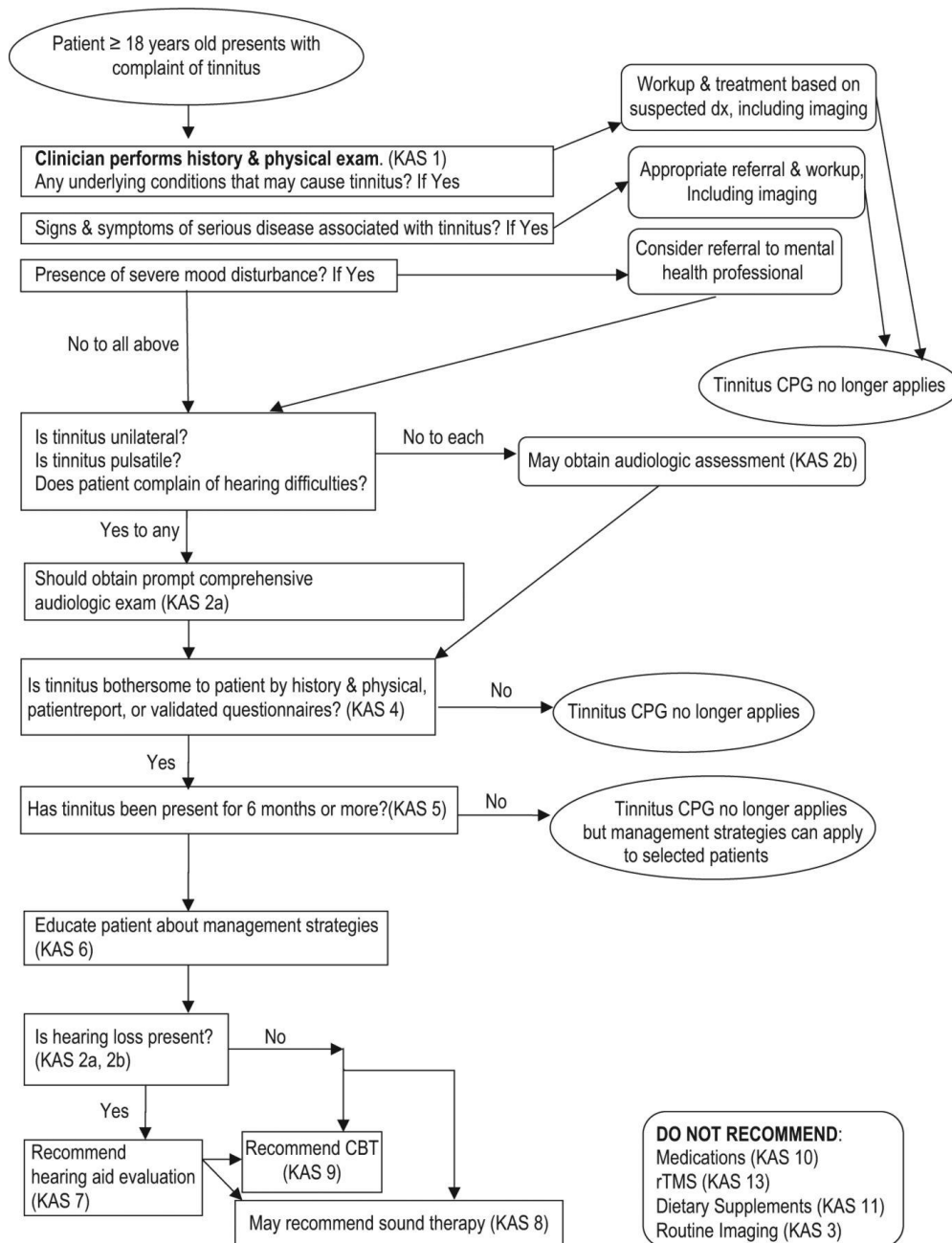


Figure 3: clinical practice guidelines from 2014, adapted from Tunkel DE et al (2)

2.4.1 Hearing aids and sound enrichment

According to a study in 2002, 90% of patients with chronic tinnitus suffer from peripheral auditory damage, which induces a process of neuronal plasticity in the central auditory system, (3, 24). A logical treatment would be to compensate the reduced auditory input with a hearing aid and restore the normal tonotopy of the auditory pathway. In this way, the auditory system no longer has the need to compensate (3, 25).

Patients with bothersome tinnitus and hearing loss could therefore potentially benefit from a hearing aid. Although the evidence only comes from observational studies, these studies are abundant and the results are quite unanimous in suggesting that a hearing aid can be beneficial to patients with tinnitus (2, 3). As these patients also suffer from hearing loss, the hearing aid will additionally improve their communication skills (3). Because tinnitus goes together with hearing loss, it is important to investigate on which aspect the hearing aid actually relieves symptoms. The patient may be less distressed merely because the problem of difficult communication is met, whereas the tinnitus itself could be perceived as equally bothersome. Literature suggests that even in patients with a mild hearing loss, a hearing aid could be helpful (2, 3).

Hearing aids are thought to work through sound enrichment (3, 14). It seems that when there is some background noise (leaving the windows open at night, listening to music), the tinnitus is perceived as less bothersome. In sound therapy, a masking sound can be used through a sound generator to relieve the tinnitus patient. The goal of the therapy is habituation to the tinnitus (2, 14). Due to the lack of qualitative studies that only use sound masking as a therapy for tinnitus, the sole effect of sound masking cannot be proven. Most of the patients get a combined therapy, many of them involving also a type of counseling as in 'Tinnitus Retraining Therapy' (TRT) (2, 4, 14).

A recommendation for a hearing aid trial should be given to all patients with bothersome tinnitus and hearing loss, even though there are no placebo trials as these are quite impossible to carry out (2). A Cochrane review concluded that hearing aids and sound generators are equally effective in tinnitus management, yet nowadays hearing aids are better accepted. (3, 25).

A special type of hearing aids are the cochlear implants (CI). Logically, the improvements made by increasing auditory input through a hearing aid, are even better with a CI. Both in bilateral and in unilateral deafness, a CI suppresses the tinnitus significantly and in some patients it even disappears during the time the implant is worn (25). The CI can be considered as a neuromodulator as well, it uses stimulation of the auditory nerve to treat symptoms. In this review, the focus is more on central neuromodulation techniques and the CI will not be discussed in detail.

2.4.2 Cognitive Behavioral Therapy

A second set of treatment options focuses on the changed connectivity between the auditory pathway and other structures of the central nervous system, most importantly the amygdala. It focuses on the mechanisms that are thought to be the cause of the mental distress in patients

with tinnitus, (see 'Pathophysiology') (26). Cognitive Behavioral Therapy (CBT) is a psychological therapy where the patient is asked to perform some cognitive and behavioural tasks that are meant to alter their response to tinnitus (2, 26). There is a significant reduction of depression score and a better quality of life, compared to controls. In a Cochrane review it was concluded that there is no significant difference in the perception of loudness of the tinnitus, after CBT (23, 26). CBT is recommended especially for people who are in distress or who suffer from feelings of anxiety or depression (2, 26). CBT has shown to be the most effective treatment in this moment, in comparison with other isolated therapies for tinnitus discussed (26).

2.4.3 Tinnitus Retraining Therapy

Tinnitus Retraining Therapy (TRT) combines fitting of hearing aids, sound enrichment and masking (2, 4, 27). It is based on Jastreboff's 'Neurophysiological Model of Tinnitus' (4). The kind of sound therapy given depends on the severity and the type of tinnitus from which the patient suffers. Follow-up is very important to ensure compliance. The goal of TRT actually is the 'extinction of subconscious conditioned reflexes connecting the auditory system with the limbic and autonomous nervous systems' (4). A Cochrane review only identified one RCT that met their criteria, in which TRT showed a beneficial effect (28). The combined therapy shows to be much more effective than other more isolated tinnitus treatments (see also under 'Cognitive Behavioral Therapy') (27). TRT is widely used as a treatment strategy for chronic debilitating tinnitus and can improve quality of life, tinnitus severity, distress and depression (4, 25, 27).

3.4.4 Medications and nutritional supplements

A third group of therapies consists of medications and nutritional supplements. In acute cases of tinnitus, intratympanic cortisone therapy is often applied. This therapy has no significant effect in chronic tinnitus compared with placebo (25). The most common medication given to patients with tinnitus are antidepressants, anxiolytics and sedatives (2, 29). It is not clear whether psychoactive drugs have a direct effect on the tinnitus or whether they merely work by treating the concomitant psychological illness experienced by some patients with tinnitus (29). There is no evidence of high quality that proves antidepressants or anxiolytics have a direct effect on tinnitus. These medications are often addictive or sedative or can even worsen the tinnitus in some cases (2, 25, 29, 30). Antidepressants should not be used as standard therapy for tinnitus. However, antidepressants are a useful completion of the therapy when the patient is struggling with accompanying depression or anxiety (2, 25, 29).

A number of studies suggest that certain nutritional supplements might have a positive effect on tinnitus, especially Ginkgo Biloba, leading to widespread use of this supplement in tinnitus

patients (2, 31). A Cochrane review concluded there is no proof that Ginkgo Biloba is better than placebo as a treatment for tinnitus (31). The general recommendation should be against using Ginkgo Biloba to treat people with tinnitus as their first complaint (2, 31). No other nutritional supplement, for example zinc, has proven to be effective as a treatment for tinnitus (2, 25, 32).

3.4.5 Neuromodulation

“The mechanism of neuromodulation for the relief of tinnitus is based on the modification of neuronal activity intimately involved in the neural circuits responsible for tinnitus processing and perception”(33). Neuromodulation can be performed in a non-invasive or an invasive manner. The most investigated non-invasive technique is **TMS** (Transcranial Magnetic Stimulation) (2, 33, 34). TMS is a procedure that induces electric currents in specific areas in the cortex of the brain (35). In this way cortical neurons are depolarized and this induces a long term potentiation or depression of cortical excitability (2, 33). When these pulses are repeated in trains of stimulation, it is called repetitive TMS (rTMS) (33). Some studies have shown improvement of tinnitus after rTMS, but there are still a lot of methodological issues (2, 34). A problem with transcranial stimulation is that good placebo trials are nearly impossible as patients can easily identify the sham stimulation (25). Reviewing 5 RCT trials that met the criteria, only one actually showed a statistically significant improvement in Tinnitus Handicap Inventory (THI), which is a questionnaire to assess the impact tinnitus has on daily life. Two small studies also showed a decrease in tinnitus loudness. The other studies that followed the same protocol showed no significant results (34). Although there seems to be some evidence in a few trials, this is not enough to advise rTMS as a standard treatment for tinnitus (2, 34). Another non-invasive technique is **tDCS** (transcranial Direct Current Stimulation). It sends electric current through the brain using two electrodes attached to the scalp. The assumption is that the increased synchrony due to the coherence of oscillations described in the TCD model could get out of rhythm or that counteracting stimuli would eliminate or influence the tinnitus symptom (25). **TENS** (Transcutaneous Electrical Nerve Stimulation) is also a non-invasive technique. Where TMS and tDCS send current through specific brain areas, TENS works by stimulating a specific nerve, in this case the C2 nerve. A combination of TENS with one of the other two might even have a better result (33). There is increasing evidence that these techniques can suppress tinnitus for a short period of time. However, non-invasive tinnitus neuromodulation seems not very promising in a longer term (33, 34).

Acoustic coordinated reset neuromodulation is a recent model based non-invasive technique that has been designed specifically to counteract the pathological synchrony seen in auditory and prefrontal areas by weakening the synaptic connectivity (36). A systematic

review included 8 studies on acoustic coordinated reset modulation for tinnitus and concluded that there is insufficient evidence for clinical implementation (37).

Invasive neuromodulation could be the permanent alternative to the non-invasive techniques. In this form of neuromodulation, there are various stimulation techniques. In **auditory cortex stimulation** (ACS), an extradural electrode is placed over the secondary auditory cortex. Other (non-auditory) areas of the cortex can be stimulated as well, such as the dorsolateral prefrontal cortex (DLPFC) or the anterior cingulate cortex (ACC). It resembles TMS, but now it is possible to constantly alter the activity in this area. **Subcutaneous occipital nerve stimulation** is the invasive alternative of TENS. An electrode is implanted subcutaneously in the C2 dermatome. **Deep Brain Stimulation** (DBS) is a technique already in use for several movement disorders and in patients with chronic pain. In some cases a co-existent tinnitus was unexpectedly treated by this mode of therapy (33). Another technique is the **Auditory Brainstem Implantation** (ABI), which is actually a subgroup of deep brain stimulation where implants are connected to structures of the brainstem. **Vagus nerve stimulation** (VNS) is one of the newest types of tinnitus treatment, it leads to a reduction of the sympathetic innervation (25). VNS would modulate synchrony and excitability in the auditory cortex probably by activation of muscarinic acetylcholine receptors (38).

2.5 Mechanism of invasive neuromodulation

2.5.1 DBS

DBS is a neurosurgical procedure, it involves implanting electrodes in a specific area in the brain. DBS is already in use to control motor symptoms of various neurological diseases, such as Parkinson's disease. Patients with chronic intractable pain can also benefit from DBS. For tinnitus and many other neurological diseases, the possible benefits of DBS therapy are currently being investigated.

The electrical stimulation is regulated by an implanted pulse generator (IPG) which is placed subcutaneously in the upper chest region. A subcutaneous wire connects the IPG with the electrodes in the brain. Stimulation parameters can be adjusted to maximize the symptom relief while minimizing the side effects. Actually, this is done through a trial and error process, adjusting one parameter after the other while observing the effect. The adjustable parameters are the pulse width (msec), the amplitude (V) and the frequency (Hz) (7).

The target site in the brain can be localized using different imaging techniques. The placement of the leads (the electrodes) is done by using a stereotactic technique with intraoperative MRI guidance. When the patient is awake during the surgery, optimal placement can also be guided by patient's feedback.

In monopolar configurations, a single electrode contact functions as the cathode and the IPG as the anode. The result is a spherical shaped field around the cathode. To create a more focused electrical field, a bipolar configuration is used. The cathode and anode are now both on the lead, generating a more concentrated electric field between them. Using varied combinations of anodes and cathodes, the shape of the stimulation field can be molded (39). In case of neuromodulation for tinnitus, a four contact stimulating electrode is most commonly used. This is placed on the contralateral hemisphere in unilateral tinnitus cases, and in the non-dominant hemisphere for bilateral tinnitus.

Table 1: Proposed mechanisms of DBS

1. Inhibition

- Hyperpolarization
- Depolarization blockage
- Glutamate depletion
- Release of inhibitory neurotransmitter (GABA)

2. Excitation

- Glutamate or cyclic GMP increase
- Dopamine release

3. Disruption of pathological oscillation

Adapted from Sugiyama K. et al, the present indication and future of deep brain stimulation (40)

Looking at how symptoms respond to DBS therapy, there are multiple proposed mechanisms. The actual mechanism is probably a combination of several theories. The different hypotheses are summarized in table 1 (40). An inhibition model was proposed as stimulation of the thalamus has similar therapeutic effects as ablation of the thalamus. High frequency stimulation could result in hyperpolarization or a sustained depolarization of the neuronal membrane, making an action potential less likely. At the level of the synaps, stimulation could result in a spillage of excitatory neurotransmitters and cause a depletion of glutamate as a consequence.

The cathode of an implanted electrode pulls away the positive charge from the outside of the axon, causing an action potential. Depending on the nature of the synapse (GABA or cyclic GMP), this will result in an inhibitory or excitatory effect (7). Axons and dendrites have lower thresholds compared to the soma of neurons, meaning neurons further away from the electrodes are sometimes stimulated instead of the closest neurons. Action potentials caused by stimulation in axons can propagate both orthodromically and antidromically (39).

The newest proposed mechanism of DBS is the disruption of pathological oscillations, described for instance in the thalamocortical dysrhythmia model (5).

Adjusting the localization of the electrodes during surgery might affect which mechanism plays the most important role, depending on the proximity of either axons or neurons and whether the synapses are predominantly inhibitory or excitatory. After surgery the different parameters can be adjusted, making further changes in the predominant working mechanism possible.

2.5.2 Cortical stimulation

Cortical stimulation was first used as a method to localize functions in the brain during neurosurgery. Later it was used for the treatment of central pain and movement disorders by stimulating the motor cortex. Concerning application of this cortical stimulation as a treatment for numerous other diseases or symptoms, one of them being tinnitus, research is still ongoing.

To know which cortex area has to be stimulated in the brain, MEG and fMRI are used often in combination with tinnitus matched sounds. It is important that the electrodes are placed where the 'symptom generating network' reaches the brain surface. The goal of electrical stimulation of the cortex is to change the functional connectivity of this network.

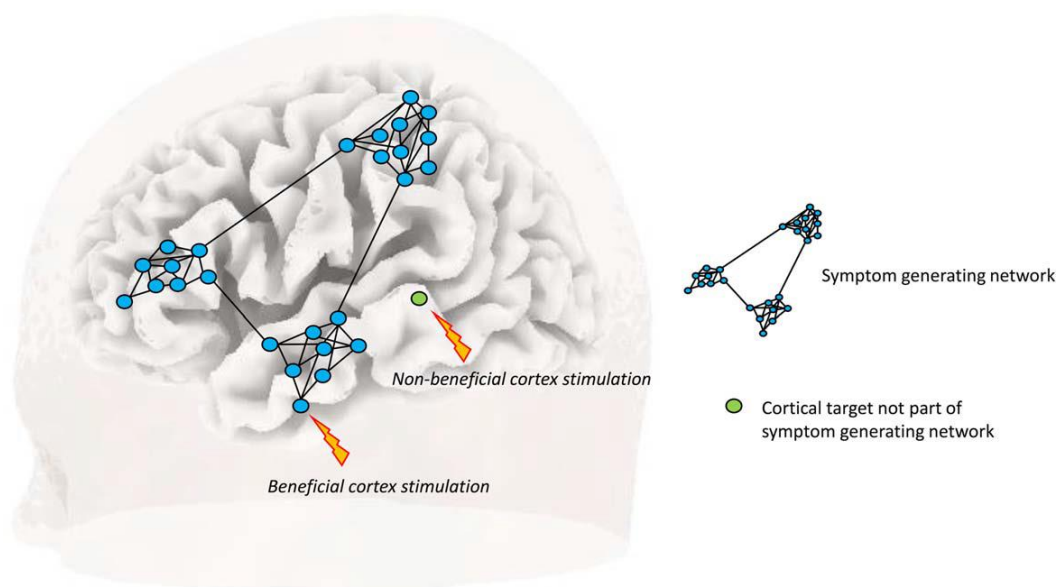


Fig. 4 'The electrode has to be positioned at a cortical target where the symptom generating network reaches the brain surface. The stimulation is thought to change the functional connectivity of the network, thereby changing its topology and its related emergent property, that is, the symptom' Figure adapted from: De Ridder et al (41)

When the electrodes are placed upon the dura mater, it is called extradural or epidural stimulation. This will stimulate quite a large area of the cortex. When the dura is opened to place the device, it is called intradural stimulation. Paddles with electrodes are used when implantation happens upon the surface of the cortex. Sometimes electrodes are implanted inside the cortex using leads as electrodes. This technique resembles DBS and enables to stimulate a smaller, more specific part of the cortex.

Stimulation of the cortex possibly suppresses tinnitus through modulating the corticocortical and corticofugal projections by affecting the neural correlates of tinnitus such as hyperactivity, hypersynchrony and tonotopic plasticity (12).

2.6 Aims and objectives

This thesis is a review of the existing literature about the invasive methods to treat tinnitus. The aim is to get a general idea of where research stands today, which methods have been successfully implemented already, which ones are promising but lack sufficient evidence and which ones show less promise. The focus will be on invasive neuromodulation techniques on a more central level than the cochlear implant.

3. Methods

Firstly, to gain insight into the general aspects of tinnitus, its pathophysiology and therapeutic possibilities, the MEDLINE and the Cochrane library were searched. As there is not yet a consensus on the pathophysiology of tinnitus, theories of multiple researchers were consulted and compared. To elaborate the different therapeutic modalities, both implemented and experimental treatments were reviewed, focusing on the effectiveness and the possible link with the pathophysiology of tinnitus.

To achieve above mentioned goals (see '2.6 Aim and objectives'), electronic databases were searched for eligible studies. The databases used were the MEDLINE and Embase. While writing this thesis, the databases were frequently searched for new articles. The last search was on 06/12/2017. Articles about invasive treatments for tinnitus were found using multiple search strategies. A list with search strategies and a PRISMA flowchart is included in respectively appendix 1 and 2.

In MEDLINE, both MeSH terms and free terms were applied. In this way, the most recent articles could be included as well. One French study was found in the references of another study.

Inclusion criteria were studies that included patients with chronic, subjective tinnitus. The therapy had to be of the invasive neuromodulation type. Because randomized controlled trials are scarce in this area, all human trials and retrospective studies of certain quality were included. The exclusion criteria were articles about non-invasive procedures or cochlear implants, articles in another languages than English or published before 2005 (except if they were of high relevance). Also, studies performed on animals were excluded, except if there was no human study available for the same technique.

The most important outcome measures looked for in studies are improvements in tinnitus severity and tinnitus disability and surgical risks like infection, brain abscess, brain hemorrhage

and severe hearing loss and also neuromodulation related side-effect such as epileptic seizure. Other outcome measures are improvements in tinnitus loudness, tinnitus related depression and/or anxiety and temporary side-effects of the therapy. The most used methods to quantify these outcome measures are summarized in table 2.

Table 2: questionnaires and scoring systems

Name	Range	explanation
Tinnitus Handicap Inventory (THI)	0-100	0-16: grade 1 (slight or no handicap), 18-36: grade 2 (Mild), 38-56: grade 3 (moderate), 58-76: grade 4 (severe), 78-100: grade 5 (catastrophic)
Tinnitus Reaction Questionnaire (TRQ)	0-100	Measure for psychological distress associated with tinnitus
Beck Depression Inventory (BDI)	0-63	0–9: minimal depression, 10–18: mild, 19–29: moderate, 30–63: severe
Structured Tinnitus Interview (STI)	0-52	multidisciplinary diagnostic approach whereby major biomedical, audiological and psychological characteristics of tinnitus are assessed
Visual analogue scale (VAS) for tinnitus severity or loudness	0-10	Used for subjective characteristics or attitudes that cannot be directly measured, patients specify their level of agreement to a statement by indicating a position along a continuous line between two end-points

4. Results

A table with the technical specifications and a summary of the results of each included study can be find in appendix 3.

4.1 Deep Brain Stimulation

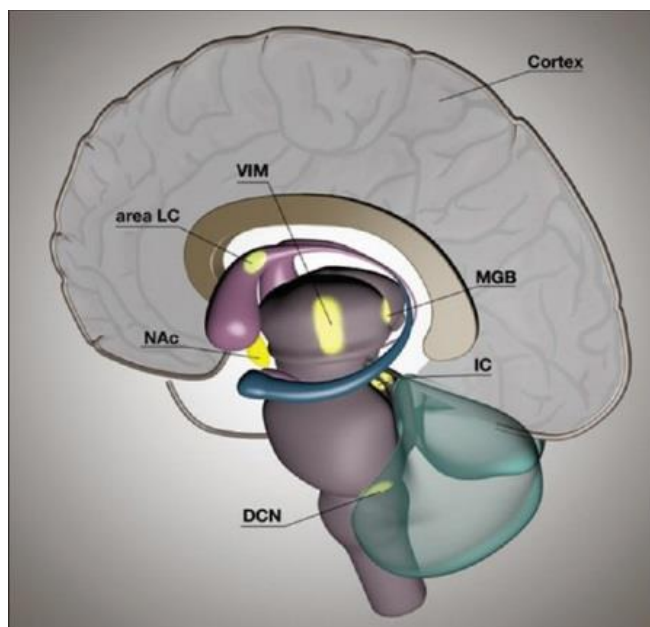


Fig. 5: Areas of interest for DBS therapy, adapted from Vanneste S. et al. (33).

4.1.1 Dorsal Cochlear Nucleus

A retrospective case series questioned patients with neurofibromatosis type-2 (NF2), who underwent translabyrinthine removal of VS and placement of an ABI (42). Tinnitus was reported in 83.7% (36 patients) of the responders. THI and VAS score were used to measure

the degree of tinnitus in the patients before, during and after stimulation of the CN. The average THI score before stimulation was 17.8. The ABI reduced tinnitus levels (mean VAS: Off=3.5; On 1-h=2.1; $p=0.048$). The responders reported an immediate effect after activation of the device and after one hour of stimulation (mean VAS: Off=4.8; On=2.4; On 1-h=1.8; $p<0.01$). The effect did not last after the stimulation was turned off. Audiological performance with the ABI did not correlate with tinnitus suppression.

4.1.2 Inferior Colliculus

There are no human studies with DBS of the IC for tinnitus available. Therefore, a rat study is included (43). Rats were implanted with electrodes in the external nucleus of the IC (ICx) and stimulation was applied a couple of times before the induction of tinnitus. DBS before noise trauma did not result in changes in the gap:no-gap ratio. After tinnitus was induced with a noise trauma, gap:no-gap ratios increased significantly in the 16 and 20kHz. As explained before, the ability to detect the gaps decreases in rats with tinnitus. During stimulation, the gap:no-gap ratio turned back to baseline, giving behavioural evidence for the suppression of tinnitus. No statistical significance was found when comparing hearing thresholds with and without stimulation, suggesting DBS did not damage the hearing capacity.

4.1.3 Thalamus

A study by Shi in 2009 included seven patients with implants in the Ventral intermediate nucleus (Vim) as treatment for involuntary tremors (44). These patients reported concomitant tinnitus before the surgery. The effect of the electrical stimulation on the tinnitus percept was observed by means of loudness matching and loudness rating on a visual numerical scale. Testing was done with the DBS repeatedly turned on, off and back on again. Only four out of seven patients were eventually evaluated in the clinic. Three out of seven patients reported a decrease in loudness of the tinnitus, for up to 20 minutes after stimulation, with significant reduction in two of these patients. The matched tinnitus loudness correlated with subjective impressions about the DBS-related tinnitus changes.

In 2016, a retrospective study was performed which included 61 tinnitus patients who underwent DBS treatment for movement disorders (45). A control group with tinnitus but which did not undergo stimulation was matched one-to-one to DBS patients. The electrodes were placed in the Vim, the subthalamic nucleus (STN) and globus pallidus (GPi). The patients were asked to compare the tinnitus pre-implantation with the complaints thereafter. The THI score improved significantly from 18.9 to 15.1 since the start of DBS therapy, the VAS loudness score and tinnitus burden score did not change. The STN was the only target that reached statistical significance.

4.1.4 Locus of caudate neurons

Two pilot studies investigated the effect of DBS in area LC. The first study was performed in 2010 by Cheung and Larson (46). The main focus was the possible modulation of tinnitus loudness in six male patients with Parkinson's disease and concomitant chronic tinnitus. The patients underwent surgery for implantation of the STN or Vim. The area LC is routinely traversed during this procedure, which gives the opportunity to perform these tests. The DBS lead traversed some portion of the area LC in five out of six patients and in these patients there was a modulation of loudness. In two patients there was a predominant decrease in loudness, in the other patient, there was an increase or decrease depending on the voltage. All five cases displayed decreased loudness by at least three points in one or both ears (0-10 scale). The DBS lead was positioned just lateral to the area LC in the patient without modulation of loudness. There were no adverse effects.

In the second study by Larson and Cheung in 2012, the focus was on triggering phantom percepts by electrical stimulation of the area LC (47). Again, patients in this study were undergoing surgery for Parkinson's disease or essential tremor. This time, there were three patients with chronic tinnitus and three patients without. When stimulating the area LC, the three patients without tinnitus reported phantom sounds or clicks. One of the patients with tinnitus noticed an alteration of the baseline tinnitus, changing into a higher pitch. The other two tinnitus patients reported a new phantom sound on top of their baseline tinnitus.

4.2 Cortex Stimulation

4.2.1 Anterior cingulate cortex

Two patients with severe intractable tinnitus were selected for implantation of electrodes on the anterior cingulate cortex (ACC) (48). One of the patients responded and the other one did not. Concerning the responder, TMS of the auditory cortex, tDCS of the DLPFC and TENS of C2 were tried but yielded no results. TMS of the right DLPFC resulted in a transient and marginal effect. Because the cingulate cortex showed BOLD activation, TMS targeting the dorsal ACC was tried and this resulted in better suppression than TMS targeting the DLPFC. Stimulation by bilateral implanted electrodes on the dorsal ACC resulted in large improvements in tinnitus loudness and in distress and depression score (by around 50%) with the electrodes in tonic mode. Four weeks later, the stimulation design was altered to see if even better results could be obtained. A burst stimulation design did indeed result in further improvements in terms of loudness, distress, anxiety and depression. The effect remained stable during follow up over the next two years.

4.2.2. Auditory cortex

In a pilot study in 2006 by De Ridder, electrodes were implanted extradurally in twelve patients with intractable tinnitus (49). In all these patients, TMS therapy already resulted in a tinnitus suppression of at least 50%. When no stability in tinnitus suppression could be obtained using extradural tonic stimulation, an intradural electrode was added. Significant suppression of the tinnitus percept was achieved in the pure tone tinnitus group (two patients), with an average suppression of 97%. The VAS score in this group decreased from 9.5 on average preoperatively to 1.5 postoperatively. The suppression was significant but less successful in the group who had white noise tinnitus combined with pure tone tinnitus (three patients, VAS score from 9 to 5.6) and the results were non-significant in the exclusively white noise group (five patients). There were two patients with bilateral tinnitus (one with white noise and one with combined white noise and pure tone tinnitus) and they both did not respond to the stimulation. In two other patients (both white noise tinnitus) who noticed no improvement with extradural electrodes, the intradural electrodes could not bring any improvements either. In two other patients (one with white noise tinnitus and one with combined pure tone and white noise tinnitus), intradural electrodes were added in the hope this could stabilize the tinnitus suppression. In both cases this was successful. After some time, the tinnitus reappeared in all patients. According to the authors, this could be due to habituation, reorganization or because the suppression was due to a temporary placebo effect. Reorganization of the electrode array was necessary to be effective again.

Later, in 2010, a new study by De Ridder included five patients of the previous study who had a combination of pure tone tinnitus and white noise tinnitus (50). Now, the aim was to compare tonic stimulation with burst stimulation by comparing VAS scores. The patients were blinded for which type of stimulation they were getting. For the pure tone component, no difference in results was noticed between the two types of stimulation. The white noise component was significantly affected by the burst stimulation, the VAS score decreased with 61.9% when comparing tonic and burst stimulation for this type of tinnitus.

In 2007, there was a prospective, controlled, single blinded study by Friedland to examine the feasibility of auditory cortex stimulation (51). Eight patients with predominantly unilateral tinnitus of a frequency less than 8 kHz, were followed for four weeks, after implanting auditory cortex electrodes. There was a set of tests consisting of tinnitus severity and loudness rating and measuring the minimum masking level, tinnitus frequency and hearing thresholds. Besides the tests, questionnaires were also used (THI, TRQ, BDI). During these four weeks, consisting of two weeks with actual stimulation and two weeks with sham stimulation, no significant results were noticed. This period was followed by an open-label long-term study with continuous stimulation. Now, two patients reported a persistent reduction of pure tone tinnitus. The other

six patients reported short intervals of total tinnitus suppression. It was predominantly the DBI and tinnitus questionnaires that showed significant improvements. Hearing threshold, tinnitus frequency, loudness and matched loudness remained fairly stable. No side-effects caused by the surgery or stimulation were noticed in this study.

Two case studies were described by Seidman in 2008 (52). The first case was a male with bilateral tinnitus who got an intracerebral implant in Heschl's gyrus in the dominant hemisphere. There was immediate suppression at the first stimulation. During a single-blinded test, the stimulation was turned on and off several times to rule out a placebo-effect. The tinnitus returned each time the stimulation was turned off within 30-60 seconds. After adjustments made in pulse width, frequency and intensity, a greater control was achieved. VAS scale improved from 9 to 0-2 on both sides. After two years, the improvements were stable and the suppression of the tinnitus remained for hours to days after the device was turned off. Audiometry indicated no change in hearing after surgery. The second case was a woman with unilateral tinnitus, probably linked to an accident causing hearing deficit. She got an extradural implant overlying the contralateral superior temporal region. After four months without improvements, this was replaced by extradural combined with intradural electrodes. After this, a temporary mild improvement of the symptoms was obtained, but this could not be maintained.

Litre and his group implanted extradural electrodes in one patient in 2009 (53) and again in three patients in 2010 (54). In the first patient, the stimulation led to an improvement of 80% after one year, measured by the TRQ, which evaluates the psychological distress. In the three patients in 2010, significant improvements in TRQ score were noticed (60, 40 and 100%) during the 25-month follow-up. There were no complications or side-effects.

In another study by De Ridder and his group, forty-three patients were implanted with extradural electrodes covering the secondary auditory cortex (55). These patients were selected from a bigger group of tinnitus patients by a TMS trial. If TMS therapy of the contralateral auditory cortex resulted in a suppression of the tinnitus percept of at least 20%, the patient was selected for electrode implantation. Twenty-nine patients responded to the invasive neuromodulation (results from tonic and burst stimulation combined) with an average decrease in VAS score of $53.2\% \pm 27.85\%$. Patients had better results with burst stimulation. Fourteen patients (32.56%) did not benefit from the stimulation given by the implants, although they experienced a suppression of the tinnitus percept of at least 20% on TMS. The tinnitus type (pure tone, narrowband noise or both) had a significant influence on the amount of suppression achieved, where pure tone tinnitus showed the best response. Unilateral tinnitus responded better than bilateral tinnitus, but the difference was not big enough to be clinically

relevant. No correlation was found between the amount of suppression and the duration of the symptoms.

A double-blind randomized cross-over was finished in 2014 (56). Nine patients with an average STI score of 29, were implanted with epidural electrodes. Specifics about the type of tinnitus (pure tone or white noise) were not mentioned. In a four month open label phase, the parameters were adjusted every two weeks. At the end of this setting phase the average STI score had already dropped to 22.5 (a decrease of 6.5 points). One patient was explanted before randomization due to psychiatric decompensation. The eight remaining patients were split into two equal groups, getting two weeks of real stimulation and sham stimulation in the opposite order with a two weeks wash-out. None of the patients showed a significant improvement (>35% decrease in STI score) during the blinded phase. Five patients were still stimulated in a long-term open follow-up, two of them showed a significant improvement in STI scores while four out of five patients had a subjective feeling of improvement.

4.2.3 Dorsolateral Prefrontal Cortex (DLPFC)

There is one case study involving extradural stimulation of the DLPFC (57). Noninvasive stimulation (tDSC), had already showed short-term clinical improvements and a reduction of DLPFC activity on EEG. At the time of the first activation of the extradural electrode there was an improvement of 33%, and the VAS score kept improving years thereafter. Tests after one year showed reduction of DLPFC gamma-band activity during stimulation. There was also a blinded three week evaluation containing 1 week of sham stimulation, one week of tonic stimulation and one week of burst stimulation. The best results were achieved during the burst stimulation. Tonic stimulation had better results than sham stimulation.

4.3 Vestibulocochlear Nerve Stimulation

A pilot study included six patients with unilateral, severe, chronic, refractory tinnitus and severe ipsilateral hearing loss (58, 59). Four patients were implanted with electrodes around the vestibulocochlear nerve, two patients dropped out. Stimulation resulted in a clinically significant decrease in mean THI scores from 77 to 55 after 3 months and to 38 after 42,5 months. The mean VAS score for tinnitus severity improved from 8 to 3.25. These are clinically significant results. The general success of the treatment was also rated with a VAS score by the patients and was 7.25 average. All patients would agree to undergo this treatment a second time. There was no significant change in tinnitus loudness but the original tinnitus sound was replaced by a more pleasantly perceived sound (from a combination of disturbing noises to a single noise). There were no reported side effects of the surgery or stimulation.

Another trial was performed with eleven patients with unilateral, severe tinnitus and concomitant severe ipsilateral hearing loss (over 80 dB) (60). They started off with a mean THI

score of 71 ± 18 points and it decreased by an average of 24 ± 26 points ($P = 0.016$) after stimulation of the vestibulocochlear nerve. Six patients still used their stimulator daily after the latest follow-up. None of the patients reported an increase of the intensity of the tinnitus percept. The improvements were again due to a transformation to a more bearable sound. There was cerebrospinal fluid leakage in three patients which could be treated successfully. One patient experienced temporary paralyses of the right-sided pharynx with temporary swallowing problems. For another patient, the surgery resulted in permanent vertigo.

4.4 Vagus Nerve Stimulation

A case series of 10 patients were implanted with an electrode surrounding the left vagal nerve (61). Pulses of VNS were delivered just prior to presentation of a pure tone of variable frequencies in a random order. The frequencies close to the tinnitus pitch were excluded. There was an average decrease in THI score of 11%. This even appeared to be 28% when excluding the results of 5 patients under centrally-acting drugs. Three of the patients without drug intake, had a clinically significant decrease of their THI score. The EEG results showed a decrease in delta and theta wave activity during stimulation, and this decrease strongly correlated with the decrease in THI score. One patient experienced temporary vocal cord hypomobility (for 2 weeks) and another patient had an infection during long-term follow up and had the electrode explanted.

In 2015, a case report was published of a male patient with bilateral tinnitus (62). The tinnitus arose 14 years ago after a spinal fusion surgery. The patient already had bilateral auditory cortex implants, but stimulation through these electrodes did not result in a beneficial effect. Now, he was implanted with an electrode surrounding the left vagal nerve. Daily stimulation of the vagal nerve was paired with simultaneous presentation of tones for 4 weeks in a non-placebo controlled way and resulted in a THI decrease of 48%, TRQ decrease of 68% and an improvement of BDI of 40%. The effect lasted two months after ending therapy. Three months after ending the therapy, a placebo-stimulation was performed with only tones without the stimulation. This did not result in renewed improvements.

4.5 C2 Stimulation

In a case report by De Ridder and his group, two techniques were combined (63). They implanted extradural electrodes overlying the secondary auditory cortex. This stimulation was only capable to diminish the pure tone component of the tinnitus percept, the noise-like component kept bothering the patient and could also not be suppressed by changing the stimulation to burst mode. Because extreme neck rotation, which is signaled through the C2 nerve, clinically altered the patient's tinnitus loudness, a trial test with transcutaneous electric nerve stimulation (TENS) of the C2 dermatome resulted in the reduction of the noise from 7/10

to 1-2/10 in a placebo controlled way. The patients used this therapy on a daily basis, but the effect weakened after three months. Now, they placed a subcutaneous electrode to stimulate the C2 dermatome, both the pure tone as the white noise component showed improvements. Placebo testing could not be performed as the amplitude required for highest efficacy in the C2 dermatome is supra-threshold for paresthesias. The combination of extradural electrode and percutaneous C2 nerve field stimulation resulted in complete reduction of the pure tone component and a 50% reduction of the noise-like component (from 8/10 to 4/10). The suppression remained unaltered during the 5-year follow-up.

5. Discussion

5.1 Value of review

There is a large variety in available and investigated treatments for patients with tinnitus. Until now, none of these therapies has been able to improve the symptom in a sufficient way in a broad, heterogeneous population. Invasive neuromodulation is emerging as a promising therapy for different neurological pathologies. For some diseases, it already proved to be effective and for a number of diseases, research is still ongoing, as it is for tinnitus. This study aimed to give an overview of the existing literature on invasive neuromodulation for tinnitus at this moment. To the best of our knowledge, there is no systematic review available bundling the latest studies on invasive neuromodulation. It is important to often bundle the studies that have been carried out until now and to make a general overview on how the research is progressing at the moment. Especially when there are only small studies that offer no great quality or significance on their own, combining all these studies can bring more insight by looking whether there is consensus in their conclusions or whether they are rather discordant in their results.

5.2 Limitation of study types

5.2.1 Population size

Because invasive neuromodulation as a treatment for tinnitus is a quite recent study subject, many of the included studies are still pilot or very small studies and none allows the results to be generalized to a broader tinnitus population.

Only a few possible DBS targets have been tested for the treatment of tinnitus and the number of participants is very low, being 6 or 7 at most for studies with DBS of the thalamus and area LC (44, 46, 47). In other studies, conclusions are only based on case studies or reports (64). The two randomized controlled trials about auditory cortex stimulation only include 8 and 9 patients (51, 56). Some studies on cortical stimulation have a higher patient number, but there are other issues concerning the study design that lower the quality of these studies. The trial with 43 patients, for instance, did not publish the placebo results and the effect of the treatment

was only assessed by making use of a VAS-scale (55). One has to bear in mind, however, that placebo-controlled trials for invasive, experimental therapies are difficult as surgery has a placebo effect of its own and sham therapies are often easily recognized by patients (24).

5.2.2 Study design

There are two retrospective studies on DBS that have a higher patient number but they use questionnaires, relying on the memory of the patients concerning the characteristics of their tinnitus (42, 45). Obviously recall bias will have had a strong influence on these results, especially because the patients in both studies were not actually treated for their tinnitus but for another underlying disease.

The two RCT trials published, should be of higher value, but they also raise some questions about their validity. They both conclude that the positive changes could be caused by a placebo effect and considering this, no therapeutic effect is achieved. While both studies conclude that there is probably only a placebo effect, they use subjective feedback from the patients to adjust the parameters to optimally suppress the tinnitus symptom after implantation. This 'setting time' before the actual blinded phase starts is only 2 weeks in the RCT by Friedland, which is very short. In the RCT by Engelhart, this setting time is several months, but might still not be enough to reach the full potential of the stimulation. After being stimulated for several months, a two week wash out might not be sufficient to bring back the original tinnitus symptom and might give an underestimation of the effect during the blinded period. The RCT by Engelhart uses many questionnaires for evaluation. Some of these questions can only be evaluated after some time, like influence on work and social life. However, in the trial, they need to be answered in just two weeks of stimulation which might lead to an underestimation of the effect.

5.2.3 Etiology

As mentioned in the introduction, tinnitus is a symptom and the underlying cause or disease varies between patients or is simply not known. Damage to the afferent auditory pathway might be a common pathophysiological mechanism but different causes might result in modest differences of this mechanism between patients. The fact that many methods can result in tinnitus suppression but the efficacy varies, might be due to the complex etiology of tinnitus.

5.2.4 Heterogeneity of the symptom

The type of tinnitus patients are suffering from, seems to be variable. The sound of the percept varies from having a low or high frequency, being purely tonal, noise-like or a combination or being heard centrally, bilaterally or lateralized. These different types of tinnitus might differ in pathophysiology and thus, could respond differently to the same therapy. Looking for a common target for stimulation that will work for all types of tinnitus might be unrealistic. This would mean that it could be primordial to subdivide tinnitus patients according to their clinical

characteristics, or the suspected cause and underlying pathophysiology. Moreover, as study populations are currently small in neuromodulation research, certain subgroups could be under- and/or overrepresented, which makes conclusion drawing for a general tinnitus population even more challenging.

In many studies, the authors look for a reason why some patients show a response to the therapy and others don't, linking it back to patients' characteristics or imaging studies. For cortical stimulation, some authors concluded that pure tone tinnitus seems to respond better to tonic stimulation, while narrow band noise responds almost only to burst stimulation (50, 55). Other studies suggested that there is an inverse relationship between stimulation induced tinnitus suppression and the duration and severity of the symptom (12). A wider network of brain areas could become more important in the pathophysiology of tinnitus after some time. This has been suggested in TMS trials as patients with tinnitus for a shorter time showed better results and the optimal stimulation parameters were different compared with patients with chronic tinnitus (49). In the study with DBS of the Vim, the 2 responders had had tinnitus symptoms for less than a decade, while the non-responders had had tinnitus symptoms for over 2 decades (44). In the report of two patients with stimulation of Heschl's gyrus, the authors state tinnitus should be treated as soon as possible, preferably within 5 years of onset (52). They suggest stimulation can work as long as 'reorganization has not yet reached the ultimate phase of irreversible cortical, thalamocortical and corticothalamic connectivity'. This implicates that patients with a longer history of tinnitus will need to be treated differently. Possible differences that can be tested are a longer stimulation time, different parameters or by adding additional stimulation tools such as acoustic stimulation or stimulation of the vagal nerve (12).

Different areas in the brain have been stimulated, yet it is hard to predict which patient will respond to stimulation of a certain area. It is still undetermined whether stimulation of the primary cortex differs from stimulation of the secondary auditory cortex in the suppression of tinnitus (12). De Ridder looked at variations regarding the connection with the parahippocampal area to explain the difference in results between the patients (65). He compared responders and non-responders from a previous study (55) and concluded the functional connectivity between the auditory cortex and both hippocampal and parahippocampal area is increased in the patients who responded to auditory cortex stimulation. The same observation was made in the case report of two patients with anterior cingulate implants (48). The responder showed increased alpha connectivity between parahippocampal area and ACC, while the non-responder showed decreased activity between those areas.

5.2.5 Tinnitus not the primary treated symptom

In many trials, tinnitus is not the actual reason for implantation of the stimulator. DBS of the area LC was only performed peroperatively as the actual target here was the thalamus (46, 47). This means the time of stimulation was very short and the only thing that could be tested is whether there was any immediate effect of stimulation. There could also be an underestimation of the possible effect as the parameters could not be adjusted optimally.

Almost all of the patients in the included DBS studies were actually treated for movement disorders (44-47). Patients with movement disorders often have a dysfunction in the basal ganglia or thalamus, making it hard to compare them with otherwise healthy tinnitus patients, especially as the pathophysiology of tinnitus is still unclear. The study concerning DBS of the CN includes only deaf patients with NF-2 who are getting an ABI to restore hearing capacity (42). These patients do not only belong to a specific subgroup, they are also deaf which means changes in hearing capacity, an important possible side effect of CN stimulation, cannot be predicted yet.

The retrospective studies include patients who also received DBS for other reasons than tinnitus. Because they included all patients who reported having tinnitus before the DBS treatment, the average THI starting score is low, meaning the range of possible improvement is smaller and clinically significant results are harder to achieve. A low THI score means many patients were only slightly to moderately handicapped by the tinnitus percept and did not even need therapy or might have benefitted from other less invasive therapies. Therefore this group of patients is not representative for the target population, which are patients with severe, refractory tinnitus

5.2.6 Animal studies

Many hypotheses about the pathophysiology and possible therapies are based on animal studies. Vagus nerve stimulation as treatment for tinnitus was tested in animals before it was tested in humans. In the animal tests, spectacular results were achieved, while in humans, this was not significant. This shows animal testing does not necessarily predict the results in humans. There are many difficulties in applying information gained by these studies to humans. First of all, tinnitus generation mechanisms in animal experiments might not reflect the tinnitus induction in humans. In humans, though noise trauma can be a cause, tinnitus often exists due to a long process where the symptom gradually worsens over time while in animal experiments they always induce tinnitus quickly to save time. There is a possibility that the pathophysiology of tinnitus evolves with the duration of the complaints. Therefore long-term tinnitus might benefit from a different therapeutic approach, than those investigated in animal experiments with acutely induced tinnitus complaints.

Secondly, tinnitus is a subjective symptom. Investigating tinnitus severity and its social impact is therefore not possible in a very exact way in animal experiments. In many hypotheses about the pathophysiology of tinnitus, the frontal cortex plays an important role as it is part of the attention regulating process. DLPFC stimulation is even suggested as a neuromodulation target (57). A big difference between humans and animals is their far more developed frontal cortex, which suggests that other animals do not have this complex way of processing sound. The gap detection test, frequently used in animal experiments, does not take into account the emotional repercussions of tinnitus such as distress or anxiety, which is important to estimate how much the patient actually suffers from the symptom.

5.3 Measurement of effect

A difficulty in tinnitus research is the fact that tinnitus is a subjective symptom, there is no reliable, objective way to measure the effect. The most commonly used way to quickly evaluate tinnitus loudness is by using a VAS score, in which you rely on the opinion of the patient. Research shows that the subjectively perceived loudness does not correlate with the passively matched loudness perception (66). Also, loudness is clearly not the only important factor in the evaluation. Some patients experience a lot of distress from a more silent noise, while other patients clearly hear a rather loud noise but are not that bothered by it.

Unfortunately, there is a big variety in applied effect measurement for each investigated treatment. A lot of different tests and questionnaires are in use, which makes it difficult to compare the results of studies. Many of the trials on cortical stimulation and the trial on DBS of the area LC focus only on changes in loudness (46). A decrease of the amount of distress linked to the tinnitus might be enough to reach a clinically significant result. Stimulation of the vestibulocochlear nerve did not alter the loudness but the original tinnitus sound was replaced by a more pleasant sound with a clinically significant decrease in THI score (58). Stimulation of the vagus nerve resulted mainly in an improved depression score, which raises the question whether vagus stimulation actually has an effect on the tinnitus sound or merely acts as an antidepressant (61, 62). However, a treatment that results in an antidepressant effect might be a sufficient treatment for a group of tinnitus patients.

Many of the included studies are short in duration, measuring only the short time effect. A good result at the beginning does not necessarily mean this effect will last. DBS on the vagus nerve in a case study had good results at first, unfortunately this improvement disappeared after two months and the severity of the tinnitus was the same as before (62).

5.4 Limitations of the technique

There are important risks involved with invasive neuromodulation, both during surgery and afterwards. As a foreign device is implanted, there is always a risk of infection. Especially

because implantation happens near or in the brain, the complications can be severe. In the cortical stimulation trial by De Ridder and colleagues, several patients got complications including brain hemorrhage and brain abscess (55). Other possible surgical risks are hematoma, meningitis, CFS leakage, epileptic seizure. When manipulating the auditory pathway, a logical side-effect is damage to the hearing capacity, especially when implanting a device in the cochlear nucleus or around the cochlear nerve. However, the discussed trials in these regions include only patients with severe hearing loss or even deafness, making it hard to evaluate the possible hearing damage (42, 58).

To use a technique this invasive, a successful risk-benefit ratio is primordial. Momentarily, the success rate of neuromodulation for tinnitus is very low. One has to consider the difference between statistical and clinical significance, as partial suppression of the tinnitus percept might not be satisfactory for the patient. Even if this technique proves to work, a thorough selection procedure should allow to predict which patients have a better chance of success, e.g. patients with refractory tinnitus and/or major distress. For cortical stimulation, non-invasive TMS of the targeted area is often tested before implantation but there is no evidence of a predictive value (55). The reason could be that magnetic stimulation works in a different way compared to electric stimulation. Therefore it would be reasonable to use transcranial ACS instead of TMS as selection test (25). Functional connectivity tests might prove to be more helpful in the selection of patients and especially in choosing the area that should be stimulated. While at first the primary and secondary auditory cortex was targeted, other areas like the DLPFC have gained interest as well. Most studies assume that the implants should be on the contralateral hemisphere for unilateral or lateralized tinnitus and on the dominant hemisphere in case of bilateral tinnitus, although there is no real consensus and limited evidence.

For cortical stimulation, it seems logical that intradural electrodes would be superior as they can generate more specific stimulation whereas epidural stimulation spreads out more widely and cannot access deep brain tissues. However, a comparison is hard to make due to the limited number of studies using intradural electrodes. There is also no standard protocol for the type of stimulation that should be administered and how the parameters should be adjusted. In one of his studies, De Ridder compared low frequency stimulation to high frequency stimulation and concluded that low frequencies yielded better suppression and are probably better for long-term stimulation (12, 49).

Research concerning the willingness of tinnitus patients to undergo brain surgery showed that 70% of 439 patients with severe tinnitus would accept implantation of a stimulator to reduce the distress caused by tinnitus and most patients would spend up to 5000 dollars to lose their tinnitus (25).

Up until today, DBS in general still has some limitations. It is hard to correctly focus the electrical stimulation onto the target, if the target is even identifiable with the current techniques. The adjustment of the parameters still happens through a trial-and-error process and is highly dependent on the individual, making it hard to standardize the procedure. Many potential targets for DBS have not been tested in humans yet. Until now, studies for tinnitus happen on structures that are targeted for other diseases and thus the options are limited as the risks of brain surgery for this unproved therapy are not always accepted. The MGB is a central structure in the pathophysiology of tinnitus and would be fairly easy to target in comparison with other DBS targets. However, as this structure has never been targeted in humans, the effect on tinnitus and especially, the side-effects, cannot be predicted. To treat tinnitus it might even be necessary to target multiple structures in the same patients, addressing more parts of the neuronal network responsible for the tinnitus symptom. The case study where adding C2 dermatome stimulation to cortical stimulation resulted in an even better suppression of the symptom. The hypothesis is that targeting both a central area and a compensation mechanism might improve success rates (63). Another tested multitarget strategy is the combination of vagus nerve stimulation with sound therapy (61, 62).

5.5 Future perspectives

Perspectives for the future can be divided into two groups. One focus lies on the patient selection and the division of tinnitus patients into multiple subgroups, each having their own adjusted, while the other focus is therapy on the optimization of the surgical process and the technique of neuromodulation.

Further elaboration of the pathophysiology of tinnitus will help creating subgroups of patients, who might benefit from different kinds of therapy or from targeting a different structure with DBS or cortical stimulation. Functional imaging can be used to see which brain areas are changed. If these changes can be coupled to a certain type or characteristic of the tinnitus percept, this could help in choosing the right treatment for each patient. It might also be necessary to combine different therapies in one patient to prevent compensatory mechanisms to arise that might reduce the beneficial effect of solo therapy as different pathophysiological mechanisms might give rise to the tinnitus symptom (24). Long-term trials are needed to evaluate whether the effect of neuromodulation can last.

The technique of DBS is developing fast. New multidirectional leads can improve focusing on a specific target which can help to get a better suppression of the symptom without increasing the side-effects. The problem of habituation can be helped by creating pseudorandom stimulation designs to prevent the need for frequent reprogramming sessions which are labour

intensive at this moment. Further miniaturization of the IPG and electrodes or paddles can make the technique more attractive (40).

5.6 Conclusion

The level of evidence at this moment is not sufficient to recommend invasive neuromodulation therapy for the treatment of tinnitus. Nevertheless, some of the discussed studies show promising results and the evidence against the effectiveness of neuromodulation is not strong enough to completely dismiss this technique as a possible future treatment. Especially for DBS, certain theoretically promising structures have not been targeted for tinnitus yet and thus many options still have to be explored. The technology of the equipment and of the surgery is quickly developing and keeps bringing new possibilities in this domain of medical therapy. Once the risks of this therapy can be reduced, more insight in the exact pathophysiology of tinnitus can be gained and patients can be subdivided in groups according to clinical characteristics or neuro-imaging, then larger qualitative studies will be possible.

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Appendix 1: search strategy

Selection criteria

	Inclusion	Exclusion
Type of studies	RCT, case series, case study, case report, pilot study, trials	animal studies if a human trial is available; case studies if larger studies are available
Type of participants	Subjective, chronic tinnitus	organic causes (vascular, otosclerosis, tumor)
Type of interventions	Invasive neuromodulation	cochlear implants
Type of measurements/outcomes	tinnitus severity, tinnitus disability, tinnitus loudness, depression anxiety, severe adverse effects, not severe adverse effects, complications of surgery	
Date	from 1/1/2005	

Search terms

MEDLINE database:

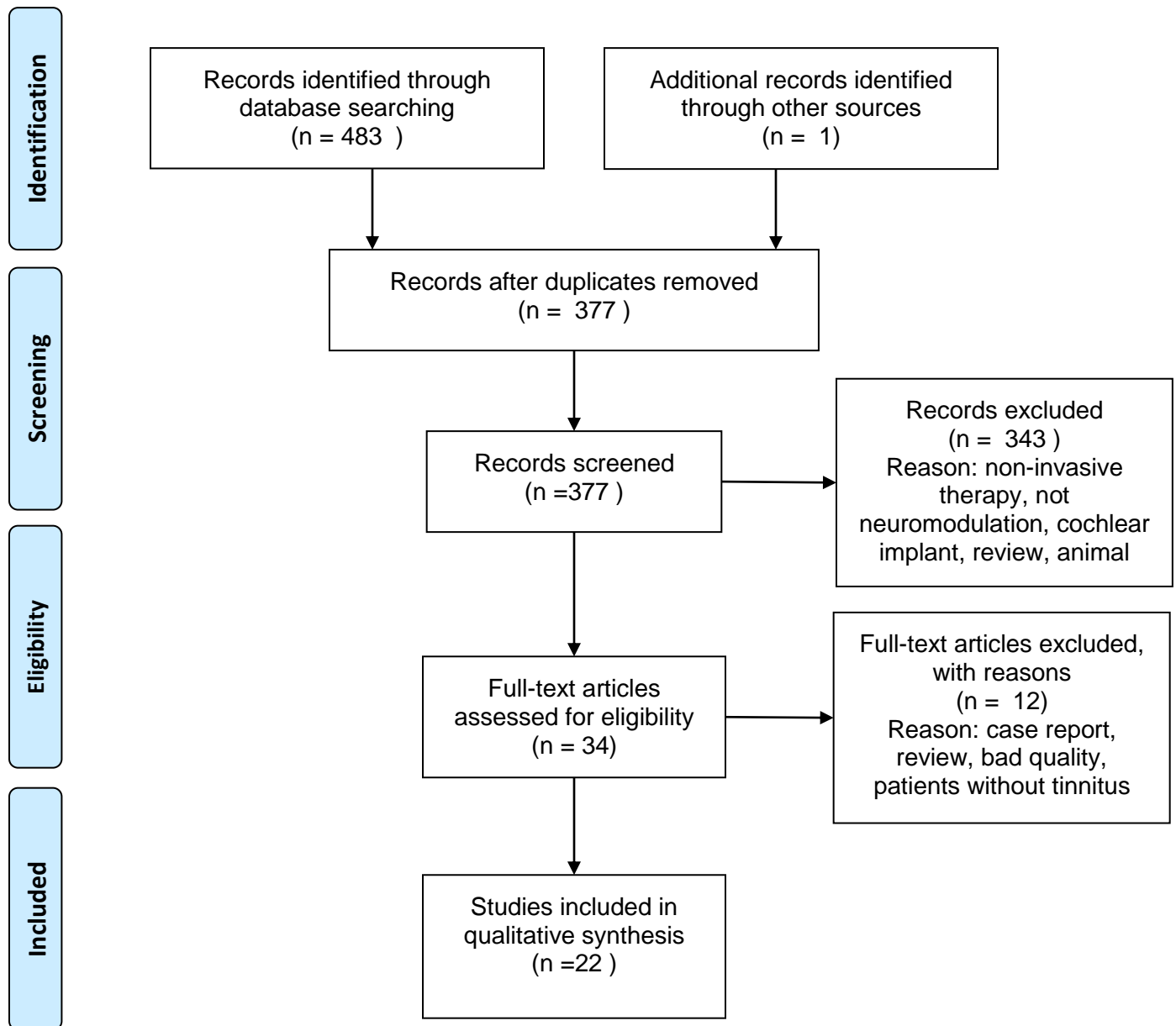
- ("Tinnitus"[Mesh]) AND "Deep Brain Stimulation"[Mesh]
- ("Tinnitus"[Mesh]) AND "Electric Stimulation Therapy"[Mesh]
- ("Tinnitus/surgery"[Mesh])
- (("tinnitus"[MeSH Terms] OR "tinnitus"[All Fields]) AND ("deep brain stimulation"[MeSH Terms] OR ("deep"[All Fields] AND "brain"[All Fields] AND "stimulation"[All Fields]) OR "deep brain stimulation"[All Fields]))
- (("tinnitus"[MeSH Terms] OR "tinnitus"[All Fields]) AND extradural[All Fields] AND ("electrodes"[MeSH Terms] OR "electrodes"[All Fields]))
- Tinnitus[Mesh] AND "Vagus Nerve Stimulation"[Mesh]

Embase database:

- ('tinnitus'/exp OR 'ear buzzing' OR 'tinnitis' OR 'tinnitus' OR 'tinnitus auris' OR 'tinnitus aurium') AND 'invasive neuromodulation'
- ('tinnitus'/exp OR 'ear buzzing' OR 'tinnitis' OR 'tinnitus' OR 'tinnitus auris' OR 'tinnitus aurium') AND ('brain depth stimulation'/exp OR 'brain depth stimulation' OR 'deep brain stimulation' OR 'electrical brain stimulation') AND [english]/lim
- ('tinnitus'/exp OR 'ear buzzing' OR 'tinnitis' OR 'tinnitus' OR 'tinnitus auris' OR 'tinnitus aurium') AND ('brain depth stimulation'/exp OR 'brain depth stimulation' OR 'deep brain stimulation' OR 'electrical brain stimulation') AND [english]/lim AND [2005-2018]/py



PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Appendix 3: Technical specifications and summary of results of the included studies

Intervention	Reference	Study design	Technical specifications	Results
DBS in area of caudate nucleus	Cheung and Larson, 2010	Pilot study, case series of 6 pts, perioperative tinnitus loudness modulation	Medtronic model 3387 (except for one: 3389).Pt 3,4,5: bilateral stimulation. Standard stereotactic technique, FrameLink software. Bipolar stimulation. 150-185 Hz, 60-90 μ s (pulse width) , 60-240s (duration), 0-10 v (amplitude). Only amplitude varied within a stimulation epoch due to time limitation.	Modulation of tinnitus loudness in 5 out of 6 patients (decrease or increase), no adverse effects.
	Larson and Cheung, 2012	Pilot study, case series of 6 pts, perioperative modulation of auditory percepts and sounds	Medtronic model 3387 (except for one: 3389). 0-10V (amplitude), 10 or 150 -180 Hz(frequency), 60-180ms (pulse width), and 60-120s (duration). Bipolar stimulation. Pts 4, 5, and 6 (without tinnitus) were presented with an external 1-kHz tone at 60-dB sound pressure level via earphones (contralateral to the side of area LC stimulation).	5 pts hears phantom sounds, clicks or sound modulation, 1 out of 3 pts with tinnitus noticed change in sound quality
DBS Thalamus (Vim)	Shi, 2009	Pilot study, case series of 7 pts	DBS electrodes were placed unilaterally or bilaterally. Stimulus settings controlled involuntary tremors (not specified).	Tinnitus percept more quiet in 3 pts up until 15 to 20 minutes after stimulation. The matched tinnitus loudness agreed with subjective impressions about the DBS-related tinnitus changes.
DBS Thalamus (Vim, STN GPi)	Smit, 2016	Retrospective study case-control	pts who received DBS treatment were questioned about tinnitus symptoms prior to the surgery and after. Control patients with solely tinnitus were matched in a matched subject design	THI improved significantly (from 18.9 to 15.1, $p<.000$), it was only significant for STN, VAS loudness and burden did not change significantly. THI in control group did not change. The incidence of newly formed tinnitus following DBS was 10.5%
DBS in Anterior cingulate region	De Ridder, 2016	Case report, 2 pts, bilateral implants	pt 1: 2 Lamitrode 44 electrodes. Alternating anodes and cathodes. Tonic stimulation at 6 Hz. After 4 weeks: eon IPG providing 6-Hz burst mode (best clinical effect compared to 2,4,8 and 10 Hz), 5 spikes at a 500-Hz spike mode, and a 1000- μ sec pulse width at 1.4 mA. Pt2: same technique	Pt 1 had large improvements with tonic stimulation in distress (9/10 to 5/10), in loudness (10/10 to 5/10 right and 8/10 to 4/10 left) With burst stimulation further improvements were made in distress (to 3/10), loudness (to 3/10 left), anxiety score (13 to 6) and depression score (13 to 8). Effect remained during 2 year follow up. Pt 2 had no significant changes.

Appendix 3: Technical specifications and summary of results of the included studies

DBS of Inferior Colliculus	Smit, 2016	Animal study (rats)	Electrode placing in the ICx. Tinnitus induction through noise trauma. DBS treatment was performed without a noise trauma an after a noise trauma, while looking a the gap:no gap ratios. Bilateral high frequency stimulation was performed using a bipolar, concentric electrode using monophasic rectangular pulses, frequency of 100Hz, amplitude of 100 mA and a pulse width of 60ms.	After noise trauma, the gap:no gap ratios increased. During DBS treatment, gap:no-gap ratios returned to baseline and did not change significantly during DBS at baseline without noise trauma.
Dorsal cochlear nucleus	Roberts, 2017	Retrospective case series and patient survey, ABI in bilaterally deaf neurofibromatosis-2 pts	not specified	The ABI reduced tinnitus levels (mean VAS: Off=3.5; On 1-h=2.1; p=0.048)
Cortical stimulation of auditory cortex	De Ridder, 2006	Primary and secondary auditory cortex stimulation in 12 pts with tinnitus (good response on TMS)	routinely implanted the electrode extradurally (Lamitrode ® 44 lead) , when no stability could be obtained, an intradural (Lamitrode ® 22 lead in sylvian fissure) approach was used as well. intradurally on the primary auditory cortex and extradurally overlying the secondary auditory cortex. Best freq: 6hz or 40-80hz. Cycle mode: 5s on, 5s off for stimulation >10Hz and the same mode or 15min on, 5min off for stimulation <10hz.	pts with selective pure tone tinnitus(n=2): VAS from 9.5 to 1.5. Pts with selective white noise (n=5): VAS from 8.8 to 6.8. Pts with combined pure tone and white noise(n=3): VAS from 9 to 5.6. Pts with bilateral tinnitus(n=2): no improvements. Follow up from 3 to 28 months.
	Friedland, 2007	prospective, controlled, single blinded study for 4 weeks, after this open-label, 8 pts	epidural electrode (2 contacts) over the posterior superior temporal gyrus (secondary auditory cortex). During the long-term evaluation, the parameters were adjusted to maximize tinnitus suppression	No results in the 4 weeks blinded period. Long-term 2 pts reported a persistent reduction of pure tone tinnitus and 6 pts reported short periods of total tinnitus suppression. Significant results in THI, BDI and TRQ in the open-label follow-up
	Seidman, 2008	2 pts, one with electrode in Heschl's gyrus, the other one with an electrode on the gyrus	pt1: quadripolar electrode intracerebral in dominant hemisphere (bilateral tinnitus), maximum therapeutic effect at 1-3V, 25Hz and 460ms pulse width. Pt 2: first an extradural quadripolar electrode, later two two-contact electrodes (one	In pt 1 the suppression was nearly complete (VAS scale improved from 9 to 0-2). All postoperative questionnaire scores showed improvement (THI, TRQ, BDI). In pt 2 the suppression was moderate and not sustained.

Appendix 3: Technical specifications and summary of results of the included studies

			directly on Heschl's gyrus, the other extradural), all in contralateral hemisphere (unilateral tinnitus)	
	Littre, 2009	extradural electrodes in 1 p	electrodes on both primary and secondary cortex (the main part on the secondary auditory cortex)	Reduction of 65 to 80% in tinnitus related distress after 1 year
	Littre, 2010	extradural electrodes between primary and secondary auditory cortex in 3 pts	2 electrodes were placed between the primary and secondary auditory cortex, contralateral. Bipolar stimulation, best results were obtained with low frequency (1 Hz).	significant improvements during 25 months follow up. TRQ improved 60%, 40% and 100%, respectively for pt 1, 2 and 3. No side-effects
	De Ridder, 2010	Burst stimulation in 5 pts	pts were already implanted with extradural electrodes (De Ridder, 2006). Pts receive tonic stimulation of 40 Hz and burst stimulation of 40hz (5 spikes of 1 msec pulse with and 1 msec interval)	For pure tone tinnitus there is no significant difference between tonic and burst stimulation. The white noise component of tinnitus is only significantly improved by burst stimulation (a reduction of VAS score of 61.90%, $p=0.04$).
	De Ridder, 2011	secondary auditory cortex implants in 43 pts	Lamitrode 44 or 88. Tonic stimulation of 40 Hz and burst stimulation of 40 Hz bursts and 500 Hz spike frequencies in random order. Trial and error programming session (multiple frequencies, pulse widths and stimulation configurations).	VAS scale. 29 pts responded to tonic and/or burst stimulation, the latter had better results. 14 pts had no suppression. Some severe side effects as seizure, brain hemorrhage, brain abscess.
	Engelhart, 2014	prospective, randomized double-blind cross-over trial and long term follow up, 9pts	single 4 contact-epidural 44 mm electrode, initial stimulation parameters: 3 V, 80 Hz, 300 msec. Bipolar stimulation between the two contacts closest to the auditory cortex. 4 months open label phase to adjust parameters. If the pt felt any sign related to the stimulation, it was reduced to the infra-laminar threshold to make blinded evaluation possible. 2 weeks wash-out before cross-over (2 weeks significant and 2 weeks sham stimulation or the other way around, with 2 weeks wash-out in between).	None of the pts achieved significant improvement during double blinded phase. 5 remained stimulated long-term, 3 felt slight to great subjective effectiveness, 2 reported benefits and still requested stimulation.
Dorsolateral prefrontal cortex	De Ridder, 2012	Case Study	two extradural eight pole electrodes (Lamitrode 44), extradural. Trial and error process to find optimal stimulation parameters	After 1st stimulation, the tinnitus improved with 33%, placebo controlled. 1 year later even further improvements were noticed.

Appendix 3: Technical specifications and summary of results of the included studies

Vestibulo-cochlear nerve stimulation	Holm 2005 and Bartels, 2007	Pilot study with 6 pts, 4 for long-term follow up	quadripolar stimulation lead, around vestibulocochlear nerve, after dissection from the facial nerve. Stimulation mode monopolar in 3 pts and bipolar in 1 pt. Stimulation leads individually adjusted ranging from: amplitude 0.15 to 2V, freq 50 to 120 Hz, pulse width 60 to 150ms	The VAS score for tinnitus severity: from 8 to 3.25 after long-term follow-up. Significant mean THI score improvement (77 to 55 after 3 months and to 38 after 42,5 months).
	Vandenbergh e 2016	11 pts, unilateral, sensineural hearing loss >80dB	quadripolar cuff electrode has a circular distal housing with a slit, 2 opening levers, and 4 radial positioned electrodes for placement around the CVN as close to the brainstem as possible. parameters: 60 to 450 msec for pulse width, 0 to 4.0 V for amplitude, and 2 to 250 Hz frequency.	mean THI score from 71 ± 18 points and decreased by an average of 24 ±26 points (P= 0.016) At the latest follow-up available, 6 patients (60%) still used their neurostimulator on a daily basis. The tinnitus transformed into a more bearable sound. None reported an increase.
C2 dermatome	De Ridder, 2015	Case report, 1 pt, still bothered by white noise component after extradural implant	Extradural electrode over secondary auditory cortex placed 3,5 years ago. Now, a percutaneous wire electrode stimulating the C2 nerve area was added. Stimulation parameters were supra-threshold for paresthesia's.	Extradural electrode: complete suppression of pure tone tinnitus, not of noise like component. TENS: Reduction of noise from 7/10 to 1-2/10, in a placebo controlled way. Effect wears off after 3 months. Implant: After 5 years the white noise component remained reduced.
Vagus Nerve	De Ridder, 2014	case series, 10 pts (5 on medication)	electrode around the left vagal nerve. Stimulation (0.8mA, 10microsec, 30Hz, every 30sec) was given 2.5 hours/day (20 days) during which the pts heard tones excl. the tinnitus-matched freq. A computer triggers to deliver electrical stimuli at the vagus nerve and after 150 msec activates the tone presentation delivered by ear phones the patient is wearing.	4 out of 10 pts showed clinically meaningful improvements (both THI and minimal masking level). Stable for at least 2 months. The 5 pts on medication showed no improvement.
	De Ridder, 2015	Case report, 1 man, bilateral tinnitus	patient already had bilateral extradural implants stimulating the auditory cortex without result. Now, an electrode was placed around the left vagal nerve.	THI was reduced by 48% and TRQ by 68%. Result lasted for 2 months after ending therapy. A placebo test with only tones without stimulation did not result in any improvements

Abbreviations: DBS: Deep brain stimulation, Pt(s): Patient(s), Freq: Frequency, Vim: Ventral intermediate nucleus of the thalamus, STN: Subthalamic nucleus of the thalamus, GPi: Globus Pallidus internus, ICx: external nucleus of the inferior colliculus

Appendix 4: abbreviations

List of abbreviations

ABI: Auditory brainstem implant	SPECT: Single-photon emission computed tomography
ACC: anterior cingulate cortex	STI: structured tinnitus interview
ACS: Auditory cortex stimulation	STN: Subthalamic nucleus of the thalamus
Area LC: locus of caudate neurons	TCD: Thalamocortical dysrhythmia
BDI: Beck depression inventory	tDCS: Transcranial direct current stimulation
BOLD: Blood-oxygen-level dependent	TENS: Transcutaneous electrical nerve stimulation
CBT: Cognitive behavioural therapy	THI: Tinnitus handicap inventory
CI: Cochlear implant	TMS: Transcranial magnetic stimulation
CN: Cochlear Nucleus	TRT: Tinnitus retraining therapy
DBS: Deep brain stimulation	VAS: Visual analogue scale
DLPFC: Dorsolateral prefrontal cortex	Vim: Ventral intermediate nucleus of the thalamus
DMN: Default mode network	VNS: Vagus nerve stimulation
fMRI: Functional magnetic resonance imaging	VS: Vestibular schwannoma
GABA: Gamma-aminobutyric acid	
GPI: Globus pallidus internus	
IC: Inferior colliculus	
ICC: Central nucleus of the inferior colliculus	
ICx: external nucleus of the inferior colliculus	
IPG: Implantable pulse generator	
MEG: Magnetoencephalography	
MGB: Medial geniculate body	
MRI: Magnetic resonance imaging	
MTG: Middle temporal gyrus	
NF-2: Neurofibromatosis type 2	
PET: Positron emission tomography	
RCT: Randomized controlled trial	
rTMS: Repetitive transcranial magnetic stimulation	
SNLH: Sensorineural hearing loss	