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Neurosurgical interventions at the cochlear nerve & nucleus for treatment of tinnitus

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General introduction and aims of the thesis

Minke J.C. van den Berge

Tinnitus – definitions, prevalence and impact

Tinnitus aurium literally means 'ringing in the ears' and is defined by the perception of sound or noise in the absence of an external physical sound source.[1] Nearly every adult experiences transient tinnitus at some point in his or her live. Persistent or permanent tinnitus is a common condition as well. In the Western population, the estimated prevalence of tinnitus is 8-20%[1], however estimations of incidence and prevalence are probably varying across studies due to lack of consistent methods to identify tinnitus. This makes it difficult to specify tinnitus and to study its epidemiology. There is however widespread consensus that tinnitus is highly common and it is anticipated that in the near future, the incidence of tinnitus will rise due to increasing amount of patients with disabling hearing loss[2], which is considered a main risk factor for developing tinnitus.[3]

Commonly, two types of tinnitus are defined: subjective and objective tinnitus. Objective tinnitus is a rare form of tinnitus and is by definition a sound that can be perceived not only by the patient, but also by an external observer. It often causes an intermittent or pulsatile sound, which in some cases can be influenced by craniocervical manipulations. Objective tinnitus may for instance be caused by (intracerebral) vascular or muscular spasms, e.g. a vascular murmur caused by a carotid stenosis; an arteriovenous malformation or myoclonic contractions of the middle ear muscles or soft palate. Treatments for objective tinnitus are regularly available and often imply an invasive treatment strategy such as surgery or embolization. Subjective tinnitus is the far more common form of tinnitus, which by definition can only be observed by the patient in the absence of an identifiable sound source. Subjective tinnitus is therefore regarded as a phantom sound.[4] It can be perceived in one or both ears, or centrally in the head. Since this type of tinnitus cannot be identified objectively, physicians can only rely on the patient's own description of his or her tinnitus. This is comparable with, for example, the symptom of pain.

Tinnitus is clinically heterogeneous and may have a severe impact on quality of life. The degree of impact varies from one to another and can also vary over time within a person. Tinnitus burden also depends on a patient's general state of wellbeing. Patients often present with various accompanying symptoms, such as psychiatric disorders (i.e. depression and anxiety), sleep disturbance and insomnia, irritability and annoyance, and cognitive impairment due to concentration disorders.[5] Tinnitus can even result in suicidal thoughts in some patients.[6,7] In addition, tinnitus is often accompanied by hearing difficulties and hyperacusis. All these factors are highly important in determining the severity of tinnitus and impact on quality of life.

With growing attention and awareness for tinnitus by different types of media and patients' platforms, together with the appearance of specialized 'tinnitus clinics', it has now become clear that the health burden from tinnitus is rapidly increasing, as is the economic burden to society.[8] It is estimated that approximately 13 million people in Western Europe and the USA seek medical advice for tinnitus.[9] Therefore, the resulting socioeconomic burden is substantial. In the Netherlands, which has 17 million inhabitants in 2019, the total mean societal costs of tinnitus were estimated €6.8 billion in 2009.[8] This amount is expected to increase as the prevalence of tinnitus is expected to increase with the rise in prevalence of hearing loss.[2]

Pathophysiology of tinnitus

Although the pathophysiologic process of tinnitus is still not fully understood, there is consensus that the central nervous system plays an important role. Tinnitus is often referred to as a phantom sound, which is the unwanted result of abnormal functioning of the central auditory system caused by deprivation of auditory input.[10]

One theory of the neural substrate of tinnitus is that cochlear hearing loss leads to a diminished cochlear nerve activity, which results in down regulation of inhibitory cortical processes. This in turn leads to spontaneous hyperexcitability of central auditory structures, such as the primary auditory cortex.[11] The abnormal cortical neuronal activity, or 'pathological reorganization', can be perceived as tinnitus. Also, neural synchrony is thought to play a role in tinnitus perception. Neural synchrony is a physiological phenomenon of nearly simultaneous firing of individual neurons, which causes synchronized oscillations of membrane potentials in a network of neurons. However in tinnitus patients, as a result of deafferentation in hearing loss, a maladaptive process in neural synchronization is thought to play a role in the perception of tinnitus.[12,13] In patients who experience tinnitus, increased or abnormal neural synchrony might occur in the absence of a physical auditory stimulus, which leads to the percept of a phantom sound.[14] Tinnitus-related activity is not limited to central auditory structures, also non-auditory structures such as the somatosensory system[13,15] and 'awareness networks' such as the cingulate cortices, thalamus, amygdala, (para)hippocampus, prefrontal and parietal cortex and anterior insula, play a role in conceiving tinnitus.[13,16]

A major issue in understanding the pathophysiology of tinnitus is that tinnitus may not be a solitary disorder with one underlying pathophysiology, but a heterogeneous disorder with various underlying pathologies, depending on the type of damage and the anatomical location (i.e. cochlear, cochlear nerve or other parts of the brain).

Overview of tinnitus treatments

In search for a treatment for tinnitus, a range of treatments has been developed and investigated over the years. Different treatments, from conventional to more experimental treatment methods, are outlined below.

Current conservative treatments
When causes for tinnitus amenable for medical treatment have been excluded after thorough examination, the recommended treatment strategy according to the Dutch tinnitus guidelines consists of: 1) counseling and explanation of tinnitus and influencing factors; 2) sound therapy (hearing aids and/or sound generators); and 3) psychological guidance in the form of cognitive

behavioral therapy. The majority of patients have sufficient benefit from counseling and conventional, non-invasive treatments. However, not all patients are sufficiently treated and a subgroup of patients still has severe complaints of tinnitus despite these first-line treatment options. For patients not responding to these standard, non-invasive strategies, treatment in the form of (neuro)surgical implants are under investigation.

Neuro-otological and neurosurgical treatments

Over the past years, several studies have been performed that investigated the role of microvascular decompression surgery and surgical placement of active implants on peripheral and central auditory level. In fact, several levels of the auditory pathway have been investigated as target for surgery or stimulation in order to decrease tinnitus (see overview in Figure 1). Below, the targeted levels of the auditory pathway are described from cochlea tot cortex.

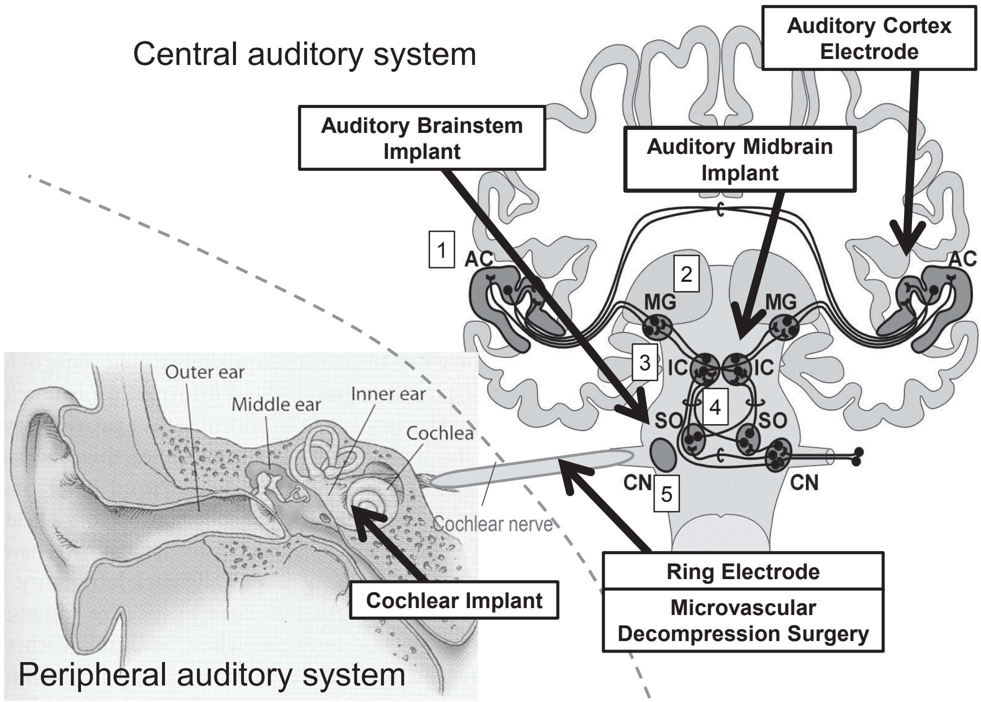

Figure 1. Overview of various surgeries or implants which are being investigated as treatment option for intractable tinnitus

AC: auditory cortex; 2) MG: medial geniculate body; 3) IC: inferior colliculus 4) SO: superior olivary complex); 5) CN: cochlear nucleus.

Cochlea

Since many forms of tinnitus are suggested to be the result of auditory deprivation, restoring auditory input might be a solution to provide relief for tinnitus. A well-known example is the use of hearing aids, which are often advised in common practice. However, for patients with severe sensorineural hearing loss and tinnitus, hearing aids are not a viable option.

For those patients with severe sensorineural hearing loss, a **cochlear implant** (CI) is a well-established treatment option for hearing rehabilitation. Studies in patients with profound sensorineural hearing loss who have been implanted with a CI in order to restore hearing, demonstrate a beneficial effect on tinnitus symptoms in 25-93% of the patients.[17] Prospective investigation in CI recipients for regular indication (i.e. severe sensorineural hearing loss) showed that 25% of patients reported tinnitus cessation after cochlear implantation and 50% reported at least partial tinnitus reduction.[18] Furthermore, in an experimental prospective study with 26 patients with single-sided deafness accompanied by tinnitus, implantation of a CI resulted in a subjective benefit on tinnitus and a significant long-time reduction in tinnitus loudness.[19] Thus, by restoring auditory input, tinnitus reduction can be achieved. Suggested mechanisms for this beneficial effect are[20]:

1) restoring input to the auditory nerve by electrical stimulation may reverse pathologic reorganization associated with peripheral deafferentation (e.g. by causing an inhibitory effect on central hyperactivity causing tinnitus);
2) a masking effect by acoustic input, comparable to sound therapy, that masks or draws the attention away from the patient's own tinnitus sound.[21,22]

Although the majority of patients in these studies were reported to have improvement in tinnitus symptoms, aggravation and new-onset tinnitus after cochlear implantation have also been described in 8.2% and 19.6% of CI patients, respectively.[23] An explanation for this finding is that the insertion of the electrode may damage intracochlear structures.[20,21] Today, a CI is only a potential option for those tinnitus patients with profound sensorineural hearing loss. Thus, only tinnitus patients without residual hearing abilities are potential candidates for CI. This means that there is a large population of tinnitus patients who have (any) hearing function left, for whom a CI is not a treatment option.

Cochlear nerve

Tinnitus has several similarities with neuropathic pain, which is also regarded as a hyper excitability disorder.[4] Direct stimulation on the spinal cord is a technique that is often successful in the treatment of severe neuropathic pain.[24,25] In analogy to this technique, the University Medical Center Groningen developed a cuff electrode for **direct stimulation of the cochlear nerve** in patients with intractable, unilateral tinnitus. Six patients had been implanted with this cuff electrode, showing a promising effect in terms of reducing tinnitus.[26,27] However, extension of this research to a larger patient group and with long-term follow-up data was warranted.

Another example of interventions at the cochlear nerve is the relief of a neurovascular conflict. A neurovascular conflict is the phenomenon of a blood vessel, either a vein or an artery, compressing a cranial nerve that may cause symptoms related to the affected nerve. Well known types of a neurovascular conflict are trigeminal neuralgia and hemifacial spasms.[28] A neurovascular conflict of the cochleovestibular nerve has been suggested to cause tinnitus, vertigo, and sometimes sensorineural hearing loss, which is also referred to as the 'cochleovestibular nerve compression syndrome'.[29] A neurovascular conflict can be diagnosed on magnetic resonance imaging (MRI), although its diagnostic value remains uncertain as not all patients with an neurovascular conflict on MRI experience tinnitus.

Conservative treatment of a neurovascular conflict such as trigeminal neuralgia or hemifacial spasms comprises treatment with carbamazepine and/or Botox injections.[30,31] Another option is surgical treatment in the form of **microvascular decompression surgery** (MVD). For trigeminal neuralgia, the long-term success rate of this type of surgery was previously reported to be 83%.[30] For hemifacial spasms, the reported success rate was even higher, i.e. 91%.[32] However for tinnitus and/or vertigo in case of a neurovascular conflict of the cochleovestibular nerve, there is however no general acceptance of MVD since its success rates vary widely. The estimated success rate of MVD for tinnitus varies between 28 and 100% and for vertigo between 75 and 100%.[33] More research on the success rate and possible predictors for success for this latter type of surgery is warranted.

Cochlear nucleus

The fibers of the cochlear nerve enter the brainstem at the cochlear nucleus. The cochlear nucleus can be divided in the dorsal cochlear nucleus (DCN) and ventral cochlear nucleus. Especially the DCN seems to play an important role in generating and modulating noise- induced tinnitus.[34,35] Hyperactivity of the cochlear nucleus has been demonstrated following damage of peripheral auditory pathways by noise-exposure.[36] This hyperactivity in turn causes reduced intrinsic inhibition and elevating excitability.[14] The DCN is the location where the auditory system converges with the ipsilateral somatosensory inputs and it has been clinically observed that tinnitus can be modulated by certain head positions or for example jaw-clenching.[15] Hence, the DCN may also play a critical role in mediating in the auditory- somatosensory interaction.[34,37]

In 1979, House and Hitselberger successfully implanted the first **auditory brainstem implant** (ABI). The ABI is an electrical active implant that is comparable to a CI, yet is specifically designed to bypass the cochlea and the auditory nerve and to directly stimulate the cochlear nucleus in the brainstem.[38] The purpose of the ABI, similar to the CI, is to improve hearing ability in patients with profound sensorineural hearing loss. The ABI was developed in extension to the CI especially for patients with neurofibromatosis type II (NF2). These patients often have severely damaged cochlear nerve(s) because of growth of vestibular schwannomas and/or surgical removal of these tumors. Therefore, cochlear implantation is usually not an option for hearing rehabilitation.[38,39]

The ABI received FDA-approval in 2000. The ABI was initially only indicated for hearing rehabilitation in adult patients with NF2 and concomitant bilateral vestibular schwannomas. More recently, the indications for ABI were expanded to patients with: total ossification of both cochleae following meningitis; severe retrocochlear otospongiosis; cochlear trauma or cochlear nerve disruption; young congenitally deaf patients with cochlear nerve aplasia or hypoplasia and/or severe cochlear malformations. However, these expanded indications are still subject of debate.[40]

With the positive effects of a CI on tinnitus symptoms in mind, it was suggested that the ABI may also have a positive effect on tinnitus. The first to report on the clinical effect of electric stimulation on the cochlear nucleus for tinnitus were Soussi and Otto. In their study in 10 ABI recipients (NF2 patients), 7 out of 10 patients reported a decrease in tinnitus loudness during stimulation.[41] More recently, this finding was also demonstrated in clinical studies from Behr et al., McSorley et al. and Roberts et al., who all described a reduction of tinnitus during stimulation with the ABI in patients who suffered from tinnitus before the implantation.[42-44] An animal study by Luo et al. demonstrated that electrical stimulation of the DCN suppressed behavioral evidence of tinnitus in rats.[45] Suppression of tinnitus was noted during stimulation in the high frequency regions, and tinnitus suppression persisted after stimulation withdrawal.[45] In conclusion, both experimental and clinical studies suggest that electrical stimulation of the DCN may play an important role in the generation and/or modulation of noise-induced tinnitus. Future experiments should be performed to examine if electrical stimulation, for instance with ABI, indeed results in suppression of tinnitus.

Inferior colliculus

The inferior colliculus is located in the midbrain, halfway up the central auditory pathway, and is an important convergence center in the auditory system, as bilateral ascending and descending input is integrated in the inferior colliculus. Also, the inferior colliculus is known to show tinnitus related activity, especially in the central nucleus.[46] The **auditory midbrain implant** (AMI) is designed to stimulate the central nucleus of the inferior colliculus in order to improve hearing in profoundly deaf NF2 patients with such a distorted anatomy that would make adequate ABI placement challenging.[47,48] The AMI consists of one or two shanks with up to 20 electrodes.[47] The implant is placed along the tonotopic axis of the central nucleus of the inferior colliculus. A clinical pilot study described 3 patients that were implanted with the AMI and these patients have shown improvement in lip-reading capabilities and environmental awareness with some speech perception in one patient.[47]

The possibility of suppressing tinnitus through deep brain stimulation of the inferior colliculus using the AMI was investigated in guinea pigs.[49] In this study, the feasibility of the AMI for tinnitus treatment was successfully demonstrated, considering that plastic changes were shown in the central nucleus of the inferior colliculus by stimulating the dorsal cortex of the inferior colliculus.[49] In another more recent experimental study, it was demonstrated that deep brain stimulation of the inferior colliculi was effective in reducing behavioral signs of tinnitus in rodents.[50] Results of the AMI on tinnitus reduction in humans have not yet been described.

Auditory cortex

The auditory cortex is usually considered to be the end station of the auditory tract and is also thought to be involved in the pathological functioning of neural networks that generate tinnitus.[51] In search of finding an optimal place for electrical stimulation, **auditory cortex implants** have been investigated as well.[51] Transcranial magnetic stimulation is a non- invasive method which causes depolarization and changes excitability of cortical neurons by delivering oscillating magnetic fields and a small electrical current from an electrical coil. When used for tinnitus suppression, the efficacy varies over different studies from 53-100% and is often temporarily.[51] An invasive alternative for this method has been investigated, in order to provide chronic stimulation, in placing an auditory cortex electrode extradurally[52-54] of intraparenchymal.[55] However, in a recent double-blind randomized cross-over study with 8 patients with severe tinnitus who underwent chronic epidural stimulation of the auditory cortex showed that this was not efficient in treating severe and resistant tinnitus.[56]

Aims and outline of this thesis

Aims

Surgical treatment may be an option for patients who have intractable tinnitus that is not manageable with conventional treatment options. The aim of this thesis is to explore the possibilities, feasibility and effect of various neurosurgical treatment options for tinnitus at the level of the cochlear nerve and cochlear nucleus.

Outline of the thesis

There is a tendency to search for an individual, patient-tailored strategy instead of a 'one size fits all' approach to tinnitus treatment.[57] It can be speculated that specific subgroups of tinnitus patients, require specific treatment. In order to design phenotype-specific treatments, more insight in the heterogeneity of tinnitus is needed. Therefore, in **Chapter 2** a cluster analysis was performed on a large database of tinnitus patients of the University Medical Center Groningen with the aim to identify recognizable subgroups of tinnitus patients.

One proposed surgical treatment for tinnitus is MVD surgery. However, general acceptance of MVD surgery for tinnitus by a neurovascular conflict is lacking and the success rates of this type of surgery for tinnitus relief are varying. In order to gain more insight in the effectiveness, complication rate and prognostic factors for success of MVD surgery for tinnitus, a systematic review and meta-analysis using individual patient data was conducted (**Chapter 3**).

The causal relation between a neurovascular conflict and tinnitus is complicated. The clinical value of a neurovascular conflict on MRI is unclear, since not all patients with a neurovascular conflict of the cochleovestibular nerve on MRI experience tinnitus. In fact, close contact between the cochleovestibular nerve and surrounding blood vessels is often observed in tinnitus patients (25-53%), but this percentage does not differ from asymptomatic patients.[58,59] In **Chapter 4**, we hypothesize that the type or degree of compression of the cochleovestibular nerve may have diagnostic value in tinnitus patients with an neurovascular conflict and may yield more insight into whether a neurovascular conflict is causative for tinnitus symptoms. Therefore, we performed a retrospective study in tinnitus patients who underwent an MRI to investigate the type and degree of compression of the cochleovestibular nerve and related this to clinical tinnitus parameters.

The remaining chapters of this thesis consider electrical brain stimulation for the treatment of tinnitus. A previous pilot study by our colleagues Bartels et al. showed that direct stimulation of the cochleovestibular nerve with an implanted cuff electrode in patients with intractable, unilateral tinnitus is a safe procedure and generated promising results in terms of tinnitus reduction.[26] In **Chapter 5**, a long-term follow-up of this study was described together with the results of an additional five patients who were implanted with a cuff electrode. Since this study showed a moderate success rate with an important unwanted complication of induced hearing loss, stimulation of the auditory tract using the ABI was suggested as a next and better step in searching for a solution. The ABI has been reported to have a positive effect on tinnitus in NF2 patients who received the implant for hearing rehabilitation.[41-44] An advantage of the ABI over a CI in tinnitus treatment might be that the ABI does not harm auditory structures. Therefore, patients with residual hearing ability and tinnitus may benefit from this option. In order to investigate the safety and effect of direct stimulation of the cochlear nucleus with the ABI in patients with intractable tinnitus, a prospective study was designed. In **Chapter 6** the protocol of this interventional pilot study is described in detail. In **Chapter 7**, the preliminary results of the first patients of this ongoing trial are presented.

Finally, in **Chapter 8** the main findings and conclusions of this thesis are discussed and future directions in the ongoing search for surgical treatment options for tinnitus are suggested.

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