A review on developments in tinnitus treatment

Tom Wemelsfelder
student number: 4492226

***Abstract*— Tinnitus is a disorder describing the sensation of phantom sound, affecting 10-15% of the world population [1]. It can have a severe impact on mental health and quality of life depending on its severity. Although an objective form of tinnitus exists, in most cases tinnitus is a subjective experience following from hearing loss [2], which is what this review will focus on. This review analyzes literature on how tinnitus manifests in the body, how it can be evaluated in humans and animals, and most notably how it can be treated. It is concluded that a lot of progress has been made in recent years, leading to improved understanding and even commercially available solutions of tinnitus suppression. However still, the exact fundamental mechanisms behind noise-induced tinnitus cannot be described fully, and treatments only provide a reduction and not a complete abolishment of tinnitus. Long lasting treatments exist in the form of bi-modal neuromodulation, providing good results lasting for at least a year. Because such technologies are still relatively new it is not known whether effects are permanent or if the tinnitus level will slowly go back to the original intensity. Future research should further investigate the long-lasting effect of existing treatments and improve our fundamental understanding of tinnitus to allow for the development of even more effective technologies.**

I. INTRODUCTION

More than 740 million adults are affected worldwide by the effects of tinnitus [1]. For more than 120 million, or 1-2% of the world population, it has a severely negative impact on their life, causing anxiety, sleep disorders or depression [1], [3], [4]. Tinnitus is a disorder relating to the perception of sound that is not really there, and is often described as a ringing, buzzing or hissing in the ear. This sensation can affect people's lives on different levels, to varying degrees. Kaltenbach et al. describes tinnitus to have three major components - acoustic, attentional and emotional - that determine the patient's experience [5]. The acoustic component refers to the loudness of the phantom sound. This determines the masking level, the intensity of an external sound stimulus required to mask the tinnitus. The attentional component is the level of attention the tinnitus demands from the patient. Irrespective of loudness, this component signifies the ability of the patient to focus on other things in their life while not being distracted by the sensation of tinnitus. The emotional component is how the patient deals with the experienced effects of tinnitus. Tinnitus is experienced as more severe by patients of older age [4]. However high frequency hearing loss among adolescents has seen a significant increase in recent years [6], which is associated with tinnitus onset as well. To reduce the effects of tinnitus multiple forms of treatments have been developed over the years. Even though no full cure is yet available, continued research in this field may lead us there. To analyze the current state of the art and how it may be improved, this review is structured as follows: First the diagnosis and severity assessment in human and animal subjects is discussed in chapter II. Then, chapter III outlines the currently known fundamental factors playing a role in the manifestation of tinnitus due to hearing loss. Chapter IV informs the reader about the current state of the art research and development in tinnitus treatment, analyzes possible directions of improvement and contributes some new ideas. Lastly chapter V summarizes the findings in previous chapters and concludes this review.

II. DIAGNOSIS AND ASSESSMENT

To systematically analyze the effects of tinnitus and possible treatments it is necessary to accurately determine the tinnitus severity in a standardized fashion. This is required for human subjects, but also for animal models which are widely used in research. Currently there is no procedure to externally and subjectively verify tinnitus in a subject, independent of possible other factors such as hearing loss [7]. As stated before, hearing loss is the major cause of tinnitus [2], but this does not mean every patient with hearing loss develops tinnitus, and thus it should not be used as the sole indicator. A pro for human subjects is that they are able to tell you whether and to what degree they experience tinnitus. However to this day there is no consensus regarding the best questionnaire to use to assess tinnitus loudness, distress, quality of life, and treatment effect [8]. Currently, the Visual Analog Scale (VAS) is one of the most used measures for assessing tinnitus loudness, annoyance, distress, and effect on quality of life, as well as pain intensity [8]–[12], allowing the subject to evaluate their experience on the three components by Kaltenbach on a 0-10 scale accompanied by smiley faces. Several other ways of assessment exist such as the Tinnitus Handicap Inventory (THI) and the Tinnitus Handicap Questionnaire (THQ). The first is a list of twenty-five yes/no/sometimes questions, and measures the impact of tinnitus on daily life [13]. The THQ is a 27-question form where the patient can answer on a 0-100 scale [14]. It measures tinnitus in three aspects [15], somewhat similar to the components described by Kaltenbach. VAS, THI, THQ and still other forms are used in human trials, sometimes in an adapted form and sometimes in combination with eachother. This high variability in assessment makes it difficult to reach a concensus and furthermore creates problems comparing the results of studies with each other. It is important that in the future a more consistent approach is taken in terms of tinnitus assessment in humans.

In the case of animal models, they will not be able to commu-

nicate their experienced tinnitus directly, so questionnaires are of little use. In 2006, a novel method was developed to diagnose tinnitus in rats, called the gap detection method [16]. This method aims to diagnose tinnitus based on the magnitude subject's reflex response to an auditory stimulus. The subject will be presented by two types of stimuli: One startle stimulus which is preceded by background noise only, and one where the background noise is shortly interrupted (gap) before the startle stimulus. It is then hypothesized that the difference in reflex magnitude is noticeably greater for subjects without tinnitus as compared to subjects with tinnitus, as the latter will have more difficulty detecting the gap preceding the startle stimulus. For rats the gap detection method is based on the whole body acoustic startle reflex, and is also known as the gap-prepulse inhibition of the acoustical startle (GPIAS) [16]. GPIAS has been adopted and improved by many subsequent studies [17]–[19]. It must be noted however that GPIAS cannot prove its own specificity, and the change in startle reflex may in fact be coupled to other conditions that usually cause tinnitus to appear, rather than the presence of tinnitus itself. Furthermore it has been shown for human subjects that conditions such as noise over-exposure do not cause tinnitus in all cases [20], a conclusion which most likely can be carried over to animal models. Improved reliability would be demonstrated by using GPIAS on human subjects as it can directly be linked to their self-assessment. One study does indeed demonstrate a reduced gap detection rate for tinnitus patients with respect to a control group, but is not able to exclude other factors [21]. Another study concludes that the impairment in gap detection for human subjects suffering from tinnitus should not be directly attributed to tinnitus itself, but rather the abnormal auditory processing associated with it [22]. similarly according to another study, the ability of human subjects to detect gaps between sounds is not impaired by the effects of tinnitus [23]. Thus evidence seems to suggest that GPIAS is an indicator for underlying conditions often associated with tinnitus, but does not bear a direct correlation. Based on the increased understanding of the origins of tinnitus in the brain in the future, it may be possible to devise more fundamental detection and assessment methods.

III. ORIGINS

There is a general consensus that tinnitus arises in the brain due to a reduced auditory output from the cochlea [24]. This in most cases is caused by hearing loss due to noise trauma [25]–[27], but tinnitus can still develop after cochlear damage without any detectable hearing loss [24]. It has been shown that the frequency region of hearing loss is associated with the pitch of the tinnitus perception [28]. Research shows that the reduction of auditory nerve output around the spectrum of hearing loss in fact causes increased activity in the cochlear nucleus [24], located in the medulla of the brain. This is confirmed by other studies showing that the dorsal cochlear nucleus displays a significant increase in spontaneous activity in tinnitus patients, resembling the activity that would normally be caused by an auditory input, due to a decreased inhibition in the auditory system after hearing loss [29], [30]. Figure 1 shows the auditory pathway in the brain. It can be seen that after sound reception in the cochlea, the cochlear nuclei are the first auditory brain station. Then the signal travels upwards to other brain regions associated with tinnitus such as the inferior colliculus and the auditory cortex. Another neurological behaviour associated with tinnitus is the increased spontaneous activity in the inferior colliculus [32] and increased synchronous neuron firing as well as a distorted frequency map in the auditory cortex, where there is a loss of sensitivity in the spectrum of hearing loss [33]. Improved insights in the origins of tinnitus will aid the current and future developments in bio-electronic treatments for tinnitus. The auditory nerve, cochlear nucleus, inferior colliculus and auditory cortex may all serve as target areas for such developments, some of which are already being addressed in existing technologies to varying degrees of success, as will be discussed in the following section.

IV. TREATMENT

No complete cure for tinnitus is currently available anywhere. However research in this particular field is experiencing rapid growth and new methods and technologies to reduce the sensation of tinnitus are improving constantly. Some new technologies recently have even been approved for commercial use and are already providing significant reduction in the manifestation of tinnitus for patients around the world. This section will review existing technologies and developments in this field as well as contribute some new ideas, primarily but not exclusively focusing on bio-electronic solutions.

A. Behavioural therapy

Behavioural therapy is the oldest form of tinnitus treatment. Here the goal is not to alter the manifestation of the tinnitus itself but rather for the patient to learn how to live with it. In other words this method addresses only the emotional aspect. Behavioural therapy can be practised autonomously or with the help of a professional. A formal form of cognitive behavioural therapy (CBT) was first developed by Beck et al. for treatment of depression [34], but can also be applied to other disorders, such as tinnitus. The core principle of this method is to take a negative thought about a specific situation, and then converting this to a more positive thought [35]. This can help with tinnitus as worrying about and focusing will not cure it and most likely will only worsen its effects. Research shows that CBT is able to improve mood and quality of life, and reduce depression and annoyance for tinnitus patients, but is not able to reduce its effects at the level of perception [36]–[38].

B. Tinnitus retraining therapy

Tinnitus retraining therapy (TRT) goes a bit further than CBT because it aims to actively teach the brain to ignore the sensation of tinnitus. It adds treatment at a subconcious level

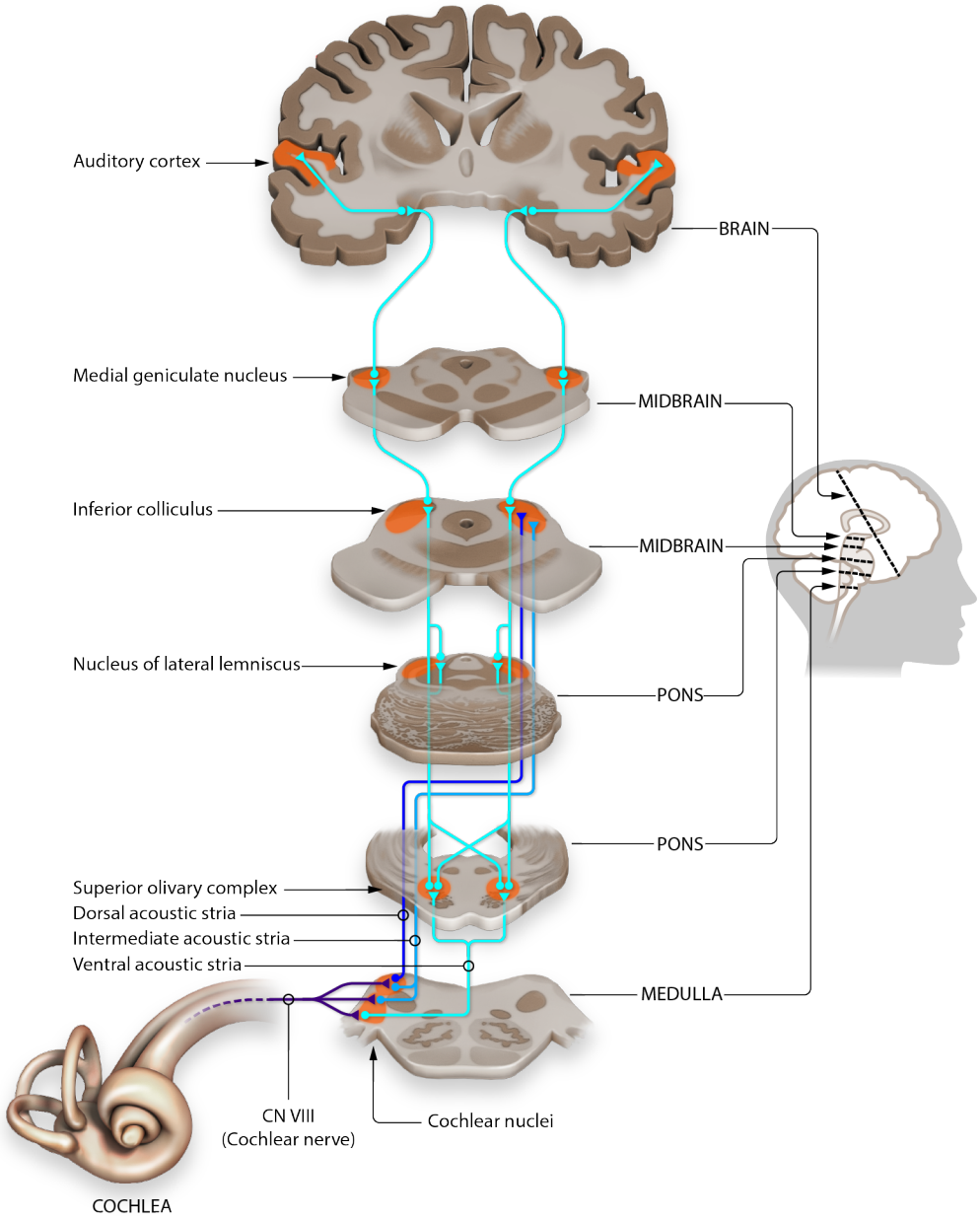

Fig. 1. Illustration of the auditory pathway from the cochlea in the ear, where sound waves are converted to electrical signals, up to the auditory cortex where you hear the sound. Regions closely associated with tinnitus are firstly the cochlea where initial hearing damage is done which can lead to noise-induced tinnitus. Secondly the cochlear nucleus and inferior colliculus display increased spontaneous activity in tinnitus patients due to missing input from the cochlea. Lastly a consistent observation in tinnitus patients is the distortion of the frequency map in the auditory cortex. *Image from [31]*

by combining counseling with sound therapy [39]. It can be said this also addresses the annoyance aspect in addition the emotional aspect. TRT is an overarching term and can be executed using different sets of techniques. One study reports that open hearing aids and sound generators can be used with equal effect [40].

C. Sound masking

To address tinnitus at the perceptive level, a straightforward approach is to attempt to mask its loudness with other auditory stimuli. On patients with impaired hearing, the tinnitus can be masked by regular hearing aids. The restoration of normal sound levels may reduce the perception of tinnitus. Otherwise, specifically tinnitus patients can use sound generators to mask it with some type of noise.

D. Cochlear implants

So far, methods have been covered that improve the patient's ability to deal with tinnitus, while not addressing the actual manifestation of tinnitus itself. By looking at the origins of tinnitus as described in section III, it is possible to devise methods which directly influence the neural signals in the nervous regions associated with it.

Cochlear implants (CI) are electrode arrays surgically im-

planted in the cochlea to allow for direct electrical stimulation of the cochlear nerve fibres. As such they can restore some of the missing input to the cochlear nucleus, and can thus target tinnitus at a fundamental level. Cochlear implantation is typically used with the purpose of restoring hearing for people with complete or severe hearing loss, as the electrode array usually will destroy any natural hearing that is left [41]. Furthermore current cochlear implant technology offers a sound quality inferior to our natural hearing [42]. Therefore tinnitus is only considered a good indicator for cochlear implantation if it follows from patient deafness [43]. Cochlear damage caused by the surgical implantation is in fact also a major factor that *causes* tinnitus in some CI users [44], similarly to what happens when the cochlea is damaged by noise trauma. One study even reports post-operative tinnitus onset after CI implantation of 19.6% [45]. Another study shows tinnitus onset or worsening for 19.8% of patients after implantation [46]. For patients with pre-operative tinnitus however, research has shown that cochlear implants in the majority of cases are able to suppress noise-induced tinnitus significantly [47], [48]. Liu et al. were able to achieve a reduction in THI score from over 80 out of a 100 points (severe) pre-operative on average, to under 30 after twelve weeks of active cochlear implant use [49]. However no complete tinnitus abolishment was achieved. After device switch-on, a significant reduction was also achieved for patients who developed post-operative tinnitus. Many other studies support the fact that CI can indeed attenuate the effects of tinnitus in most cases [50]–[55]. Most agree that the exact underlying mechanism of tinnitus suppression is not clear, which may be attributed to "habituation, acoustic masking, direct stimulation of the cochlear nerve and reorganisation of cortical area" [55] or a combination of these factors. A long term study shows that tinnitus suppression still holds after a ten year period of consistent CI use, and is the primary reported benefit for the majority of patients with single sided deafness [56]. A recent literature review states that the tinnitus inhibition can last up to 24 hours after CI deactivation [57]. Why the experienced level of attenuation is not consistent among patients is not immediately evident. Inconsistencies in exact numbers between studies can be partially explained by the lack of consensus on tinnitus assessment questionnaires, as is pressed by Olze et al. [58].

To limit the destruction of natural hearing, a partial solution is found in shorter cochlear implant electrodes [41]. They can be fabricated at a custom length and would then only stimulate the high frequency areas of the cochlea corresponding to the experienced tinnitus frequency, while not reaching further down to the apex. Thus natural hearing in the lower frequencies is preserved. This makes sense as hearing damage and tinnitus are generally more prominent in the high frequencies [59]. Still, the patient would be required to be (almost) completely deaf in these high frequency regions in order to become eligible for a cochlear implant, while tinnitus can arise long before this level of hearing damage is achieved [24]. Interestingly, one study shows that stimulation of the basal (high frequency) region of the cochlea only did not result in any tinnitus suppression, while activating a CI over the entire length of the cochlea did in fact reduce tinnitus significantly [60]. However it must be noted that all subjects developed tinnitus after complete single sided deafness (SSD), and therefore it does seem plausible that only restoring auditory signals in a narrow spectrum would not significantly suppress tinnitus. There is no obvious reason to insert a shorter electrode array if the patient is deaf over the complete frequency spectrum. One patient did have some natural hearing left in the lower frequency region, and received a shorter CI accordingly, preserving natural hearing. For this patient tinnitus suppression was comparable to the other subjects when the entire CI was activated. The study therefore seems to show that for effective inhibition of tinnitus, auditory input needs to be restored in all regions where it is missing for the patient. To apply CI technology specifically for tinnitus patients with healthy hearing, Arts et al. investigate the feasibility of pulse generating Tinnitus Implant (TI) [61], initially based on a full-length CI. Such a device is ultimately not supposed to produce any noticeable sound perception in the patient, but instead must produce repeating electrical pulses just large enough to suppress spontaneous activity further down the auditory pathway. Here, a commercially available MED-EL CI was implanted in ten patients with single sided deafness, all experiencing moderate to severe tinnitus for at least one year, as diagnosed by the VAS. The study concludes that TI and CI can accomplish similar levels of tinnitus suppression, meaning encoding of acoustic sounds is not required to suppress tinnitus via electrical stimulation in the cochlea [61]. Exact stimulus intensity is not clarified, but this study states that tinnitus suppression can be achieved with stimuli inaudible to the patient. Therefore it indeed appears to support the notion that tinnitus, for the selected group of patients, originates in the cochlear nucleus, very early in the auditory pathway before any sound is perceived in the auditory cortex.

Besides increasing electrode and channel count in conventional cochlear implant electrode arrays, an improved spectral selectivity may also be found in new innovative forms of cochlear implants, such as the use of micro-magnetic coils [62]. In this study, micro-magnetic coils were fabricated via aerosol jet printing (AJP) techniques. The microcoils are able to provide micro-magnetic stimulation of the surrounding tissue, rather than direct current injection as is the case for CI. This is beneficial because this restricts the spread in activation area to 1.5mm, whereas CI current injection will spread further around an electrode causing a reduced spatial selectivity [62]. As a proof of concept, the study shows how CI technology has the potential for further improvement by overcoming limitations in conventional CIs by switching to additive manufacturing techniques.

Overall, cochlear implants should be recommended to patients experiencing deafness or severe hearing loss in combination with associated effects of tinnitus. In all other cases, where the patient either only has tinnitus with good hearing, or severe hearing damage without tinnitus, the patient will

always have to make a trade-off. Either they will significantly reduce their hearing quality in order to reduce their tinnitus perception, or they will improve their hearing with the risk of developing tinnitus. As of now, the CI can only provide tinnitus relief for a select group of people, and the technology will need to drastically improve in terms of audio quality for it to become a reasonable option for a larger audience.

E. Ultrasound neuromodulation

To remove the need for implantation altogether, it may be worth to take a look at ultrasound neuromodulation. This technology uses focused ultrasound (FUS) waves to modulate the activity of target neurons. New developments in ultrasound neuromodulation technology [63] could make it possible to design a wearable neuromodulator, able modulate the cochlear nerve through an external device on the skin. Emphasis should be put on the fact that ultrasound can only *modulate* (inhibit or promote the generation of) neural signals, and not directly generate action potentials like the electrodes of a CI. To understand this in a better context it is important to take a brief look at how auditory signals are coded in the auditory nerve. It turns out that hair cells in fact work the same way: in rest, hair cells produce action potentials (APs) at a steady frequency, around 100Hz [64]. When the hair cell is deflected by sound, this either increases (promotion) or decreases (inhibition) this repetition frequency, and thus sound can be encoded by alternating increasing and decreasing frequencies in the cochlear nerve signals. This effect is shown in figure 2.

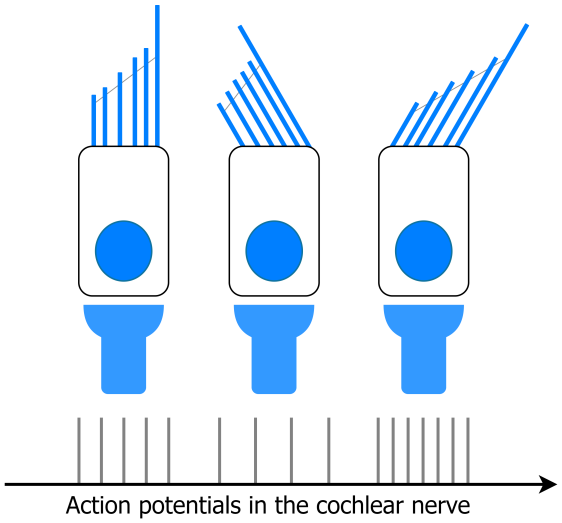

Fig. 2. A hair cell and synapse displayed in three states of activity. The generation of action potentials (APs) is shown underneath. *left*: Hair cell in passive state produces action potentials at a steady rate. *middle*: Hair cell deflection to the left inhibits AP generation and so reduces the AP frequency. *right*: Deflection to the right increases the AP frequency.

Neuromodulation of hair cells may thus in fact have the potential to encode signals which can be interpreted as sound further along the auditory pathway. This requires however that damaged hair cells still generate a steady stream of APs, and that the absence of sound encoding is caused only by the fact that the hair cell no longer deflects under the influence of sound. At the moment of writing, no research was found that shows whether after hair cell destruction there is a complete abolishment of AP generation or there is only a loss of sound encoding. It has however been shown that hair cell loss is often causes the loss of cochlear nerve fibers [65], which would make the transduction of auditory electrical signals no longer possible at that location. One study aims to find out whether or not ultrasound can restore hearing [66], but no results have been published to date. In patients where tinnitus is only caused by partial damage instead of complete deafness, it is imaginable that FUS may be able to serve a similar purpose as the TI described in the previous section by providing a minimal amount of modulation, enough to be detected by the cochlear nucleus but without the need for actual sound detection in the auditory cortex.

When talking about ultrasound neuromodulation in the ear it is important to consider its safety. The acoustic pressure required to modulate nerve signals may be damaging to hair cells in the cochlea, which is not desirable. To investigate this problem it must be known what acoustic pressures hair cells can tolerate. No research was found that directly provides this number with respect to humans. However much is known about the amplification mechanisms in the inner ear. By combining these numbers with the external sound pressures known to cause hearing damage it is possible to deduce the local pressures hair cells can endure.
Harmful sound levels as measured outside the ear, start at about $I_{ext} = 85dB$ acoustic pressure [67]. Sound pressure from outside to the eardrum is amplified about 18 times ($\sim$12dB), and is amplified another 23 dB average in the middle ear [68]. The electromechanical feedback in the cochlea amplifies the intensity experienced by the bassilar membrane by at least another 40 dB [69]. So in total this is at least a 75 dB amplification of pressure from outside the ear to the bassilar membrane:

$$I_{amp} = 12dB + 23dB + 40dB = 75dB \tag{1}$$

By multiplying the harmful acoustic pressure as measured outside the ear by all amplification factors within the ear, the hair cells in the cochlea are estimated to experience an intensity of

$$I_{hcell} = I_{ext} * I_{amp} \equiv 85dB + 75dB = 160dB \tag{2}$$

With reference sound intensity $I_0 = 10^{-12}W/m^2$, I_{hcell} can also be expressed in units of power per unit area as

$$\begin{aligned} I_{hcell} &= 10^{160dB/10} * I_0[W/m^2] \\ &= 10^{16} * 10^{-12}W/m^2 \\ &= 10^4 W/m^2 = 1W/cm^2 \end{aligned} \tag{3}$$

Low intensity focused ultrasound (LIFU) can elicit neuromodulation for intensities below $1W/cm^2$ [70]. Therefore, assuming the ultrasound frequency would not be amplified by any of the aforementioned mechanisms

in the ear, LIFU exists in magnitudes that will elicit neuromodulation while not being harmful to any tissue or hair cells when directly applied to the cochlea. Of course, this is a rough estimate and the actual intensity experienced inside the cochlea should be verified experimentally. These numbers seem to indicate at least that it would be worthwhile to test on animal models whether or at what level low intensity ultrasound will damage hearing when applied directly to the cochlea. If a safe window exists, ultrasound neuromodulation in the cochlea would be a very interesting field of research for solving hearing related issues.

F. Bi-modal neuromodulation

The CI or TI can address tinnitus at what seems to be the source, by directly restoring neural output of the cochlea over the full frequency spectrum. It has an almost immediate effect, however when the device is turned off the beneficial effects don't remain for long. Recent research shows that tinnitus can also be addressed further in the auditory pathway. By combining neuromodulation of the auditory nerve with stimulation of other neural systems, it is hypothesized that the brain will undergo some type of 're-mapping', which would reduce the tinnitus sensation. This is based on the concept of paired plasticity, where we associate meaning between to simultaneously experienced inputs [71]. Signals from the auditory nerve are integrated in the dorsal cochlear nucleus (DCN) with neural signals from other areas such as the somatosensory, vestibular and reticular system [72]–[75], which may be partially responsible for the phenomenon of paired plasticity. Especially modulation via the somatosensory pathway has been researched extensively, as somatosensory nerves are relatively easy to access [71], [72], [76]. The combination of somatosensory stimulus with auditory signals is referred to as bi-modal neuromodulation.

A popular way of accessing the somatosensory system seems to be by stimulation of the trigemenal nerve via the tongue. Conlon et al. use a 32-electrode tongue stimulation device in which electrode temporospatial activation can be coupled to the presented auditory stimulus frequency, timing and intensity [71], [76]. The treatment required device use of a total of 36 hours over a 12-week treatment period, and shows significant tinnitus reduction during the first six weeks of treatment and minimal further improvement during the second half of the treatment. Three subject arms are studied called PS1, PS2 and PS3. PS1 received pure tones over a wide bandwidth from 500 to 8kHz together with wideband noise. Electrical pulses on the tongue were provided simultaneously and were coupled to sound frequency. PS2 introduced a time delay of several tens of miliseconds, and PS3 used only low frequency tones <500Hz. PS2 and PS3 did not use spatiotemporal coupling of the electrode array to the sound stimulus. Tinnitus levels were reduced significantly for all groups during treatment, but only for patient groups PS1 and PS2 levels remained stable the following one-year follow-up measurement. It must be observed that this study displays several variations between the different arms. Because each patient group differs from the others on multiple fronts it becomes difficult to attribute any of the varying factors to the changes in outcome individually, with good confidence. Also it does not try to relate the patient's tinnitus frequency to the audio stimulus. Interestingly, no difference is reported between the efficacy for patients with short duration tinnitus versus long duration tinnitus, where patients were included with a experienced duration of maximum five years.

Another study achieves tinnitus suppression by stimulating the somatosensory system via transcutaneous active electrodes placed on the skin, targetting either the trigeminal ganglion or the cervical spinal cord [72]. Sessions of twenty minutes were held for a duration of twenty five days. Auditory stimulus was provided at the experienced tinnitus frequency and preceded the somatosensory stimulus by 5 ms. The study also shows that either the somatosensory or auditory stimulus alone does not correspond to any reduction in tinnitus.

In contrast to cochlear nerve stimulation via sounds, Sirh et al. attempts to indirectly modulate the activity in the cochlear nerve (eight cranial nerve, CN VIII) through stimulation of the trigeminal (CN V) and facial nerves (CN VII) [8]. The modulation effect is hypothesized based on the fact CN V and CN VII run close to the cochlear nerve in the body. In this study the facial nerve and trigemenal nerve are stimulated mechanically by carefull needle injection for 20-40 minutes, assumingly modulating the CN VIII. Then, nerve blocks were administered to the facial nerve and auriculotemporal nerve (a branch of CN V). Using a simplified T-VAS questionaire, the average score reduced from before treatment 7-8 to 0-2 after treatment. Tinnitus reduction level was maintained after a one year follow up study. To achieve significant long-term effects, ten to fifteen treatments were necessary per patient. Contrary to what Conlon et al. seems to have achieved, Sirh et al. states that "tinnitus should be treated as early as possible after its onset because auditory maladaptive neuroplasticity refractory to the treatment occurs $\geq$ 3 months after tinnitus onset" [8]. This study shows that combining trigemenal nerve stimulation with indirect cochlear nerve modulation can achieve similar success to the combination with cochlear nerve stimulation through sounds.

Some of the analyzed studies use auditory stimuli related to the tinnitus pitch of the patient, while others use stimuli over a broad frequency range, sometimes without any spatial mapping to the somatosensory stimulation. Sirh et al. even modulates the vestibulocochlear nerve as a whole, thus effectively targetting the entire frequency spectrum. Significant results were obtained in all cases. The broadband stimuli are likely to include the tinnitus pitch of the patient. It seems therefore likely that the auditory stimulus must indeed be in the range of the experienced tinnitus frequency, however to the knowledge of the author no conclusive research has been performed to actually verify this hypothesis specifically. If it holds true, for

somatosensory neuromodulation paired with tones to work, the patient must still have remaining hearing in the range of experienced tinnitus. However for patients where this is not the case, indirect modulation of the auditory nerve like in [8] may still prove effective nonetheless.
The combined research in bi-modal neuromodulation has led to the launch of several now commercially available products which can help people reduce their tinnitus around the world, such as Lenire [77], an electronic tongue-stimulator combined with sounds played over headphones. Bi-modal neuromodulation is also achieved in other ways, such as via a haptic wristband paired with sounds simply played over your smartphone [78]. This device is based among others on the research of Perrotta et al. [79]. Here, patients recieved ten minutes of treatment a day during a period of eight weeks. The treatment consistent of tones played in spectrum one octave above and below the tinnitus frequency 120 times per minute. Haptic stimulation of the wristband was related spatiotemporaly to the sounds played over the phone.

Another form of multimodal stimulation is tones paired with vagus nerve stimulation (VNS). A surprising contrast to the research analyzed in the previous paragraph is that bi-modal VNS is often paired with audio *excluding* the tinnitus frequency [80]–[82]. This has shown promising results on rats treated four weeks after tinnitus inducing noise exposure, according to the gap detection method GPIAS [82]. A similar experiment has been executed on human subjects [83]. However results in this case were much less convincing. A possible major cause mentioned in the paper is the fact that the human subjects all had been suffering from tinnitus for at least one year prior to the experiment. This is in contrast to the four weeks after noise exposure in [82], and reinforces the conclusion made by Sirh et al. that these types of treatments should be administered as soon as possible after tinnitus onset [8]. On the other hand Conlon et al. report significant results for a patient group including subjects experiencing tinnitus up to a 5-year period [71].
It is clear that methods, even when limited to the concept of bi-modal neuromodulation, vary greatly. Tinnitus suppression can be achieved on many occasions, but the wide variation in treatments does not necessarily help with fundamental understanding of the problem at hand. Much time and research is put into methods based on trial and error and empirical evidence. It is recommended to devise better evidence-based guidelines for more focused tinnitus treatment design, as stated by Langguth et al. [28]. For empirical improvement of proven methods it is recommended to single out a single parameter rather than trying too many variations in a single study.

V. CONCLUSION

Research on tinnitus causes, diagnosis and treatment has come a long way. Important factors playing a role in the manifestation of tinnitus have been identified. The exact mechanisms of tinnitus are slowly becoming more apparent by continued research, but a conclusive statement can still not be made. Indicators of tinnitus in animals and humans are known, but an objective method of tinnitus diagnosis does not yet exist. Evaluation in humans is inconsistent across the field and requires a consensus to be made. In the last few years, bio-electronic treatments for significant tinnitus reduction have entered the market, but complete abolishment is rare. In this report these treatments were analyzed stating up- and downsides for each. Cochlear implants are a great solution for patients seeking tinnitus reduction as well as hearing restoration, but are discouraged for use on patients with good hearing. After activation, they can provide an almost instantaneous reduction in tinnitus, but when turned off the tinnitus often returns within a day. Research has shown that the environmental sound encoding or even the sensation of sound CIs provide is not essential for the suppressing effect on tinnitus. Therefore it may be possible to modulate the cochlear nerve in other ways such as via ultrasound neuromodulation to provide similar tinnitus relief, while maintaining all natural hearing in a patient. Long-term tinnitus relief can be found in application of bi-modal neuromodulation, combining auditory nerve modulation with stimulation of other neural systems converging in the dorsal cochlear nucleus. These methods have already reached the stage of commercial deployment and can help patients in many countries around the world. A downside of this type of treatment is the time investment it requires from the patient, and the time it takes to take effect. As opposed to immediate results via direct auditory nerve stimulation as in CIs, bi-modal neuromodulation treatments take several months to provide long lasting effects. As our fundamental understanding of tinnitus continues to grow, bio-electronic treatments can improve accordingly, and one day it may be possible to achieve a permanent cure.

REFERENCES

[1] C. M. Jarach, A. Lugo, M. Scala, P. A. van den Brandt, C. R. Cederroth, A. Odone, W. Garavello, W. Schlee, B. Langguth, and S. Gallus, "Global Prevalence and Incidence of Tinnitus: A Systematic Review and Meta-analysis," *JAMA Neurology*, 08 2022. [Online]. Available: https://doi.org/10.1001/jamaneurol.2022.2189

[2] D. E. Tunkel, C. A. Bauer, G. H. Sun, R. M. Rosenfeld, S. S. Chandrasekhar, E. R. Cunningham Jr, S. M. Archer, B. W. Blakley, J. M. Carter, E. C. Granieri *et al.*, "Clinical practice guideline: tinnitus," *Otolaryngology–Head and Neck Surgery*, vol. 151, no. 2_suppl, pp. S1–S40, 2014.

[3] W. Schlee, T. Kleinjung, W. Hiller, G. Goebel, I.-T. Kolassa, and B. Langguth, "Does tinnitus distress depend on age of onset?" *PLOS ONE*, vol. 6, pp. 1–4, 11 2011. [Online]. Available: https://doi.org/10.1371/journal.pone.0027379

[4] J. Al-Swiahb and S. N. Park, "Characterization of tinnitus in different age groups: A retrospective review," 2016. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5187663/

[5] J. A. Kaltenbach, "Insights on the origins of tinnitus: An overview of recent research," 2009. [Online]. Available: https://doi.org/10.1097/01.HJ.0000345991.57291.9b

[6] J. Shargorodsky, S. G. Curhan, G. C. Curhan, and R. Eavey, "Change in Prevalence of Hearing Loss in US Adolescents," *JAMA*, vol. 304, no. 7, pp. 772–778, 08 2010. [Online]. Available: https://doi.org/10.1001/jama.2010.1124

[7] A. Galazyuk and T. J. Brozoski, "Animal models of tinnitus: A review," *Otolaryngologic Clinics of North America*, vol. 53, no. 4, pp. 469–480, 2020, tinnitus. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0030666520300372

[8] S. J. Sirh, S. W. Sirh, H. Y. Mun, and H. M. Sirh, "Integrative treatment for tinnitus combining repeated facial and auriculotemporal nerve blocks with stimulation of auditory and non-auditory nerves," *Frontiers in Neuroscience*, vol. 16, 2022. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fnins.2022.758575

[9] R. R. Figueiredo, A. A. d. Azevedo, and P. d. M. Oliveira, "Correlation analysis of the visual-analogue scale and the tinnitus handicap inventory in tinnitus patients," *Revista Brasileira de Otorrinolaringologia*, vol. 75, pp. 76–79, 2009.

[10] I. Adamchic, B. Langguth, C. Hauptmann, and P. A. Tass, "Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus," 2012.

[11] D. Raj-Koziak, E. Gos, W. Swierniak, J. J. Rajchel, L. Karpiesz, I. Niedzialek, E. Wlodarczyk, H. Skarzynski, and P. H. Skarzynski, "Visual analogue scales as a tool for initial assessment of tinnitus severity: psychometric evaluation in a clinical population," *Audiology and Neurotology*, vol. 23, no. 4, pp. 229–237, 2018.

[12] T. Kojima, N. Oishi, T. Nishiyama, and K. Ogawa, "Severity of tinnitus distress negatively impacts quality of life in patients with vestibular schwannoma and mimics primary tinnitus," *Frontiers in Neurology*, vol. 10, p. 389, 2019.

[13] C. W. Newman, G. P. Jacobson, and J. B. Spitzer, "Development of the Tinnitus Handicap Inventory," *Archives of Otolaryngology–Head Neck Surgery*, vol. 122, no. 2, pp. 143–148, 02 1996. [Online]. Available: https://doi.org/10.1001/archotol.1996.01890140029007

[14] F. K. Kuk, R. S. Tyler, D. Russell, and H. Jordan, "The psychometric properties of a tinnitus handicap questionnaire," *Ear and Hearing*, vol. 11, no. 6, 1990.

[15] C. Meric, E. Pham, and S. Chéry-Croze, "[translation and validation of the questionnaire "tinnitus handicap questionnaire, 1990]," *The Journal of otolaryngology*, vol. 26, no. 3, p. 167—170, June 1997. [Online]. Available: http://europepmc.org/abstract/MED/9244813

[16] J. G. Turner, T. J. Brozoski, C. A. Bauer, J. L. Parrish, K. Myers, L. F. Hughes, and D. M. Caspary, "Gap detection deficits in rats with tinnitus: a potential novel screening tool." *Behavioral neuroscience*, vol. 120, no. 1, p. 188, 2006.

[17] A. Galazyuk and S. Hébert, "Gap-prepulse inhibition of the acoustic startle reflex (gpias) for tinnitus assessment: current status and future directions," *Frontiers in neurology*, vol. 6, p. 88, 2015.

[18] C. A. Grimsley, R. J. Longenecker, M. J. Rosen, J. W. Young, J. M. Grimsley, and A. V. Galazyuk, "An improved approach to separating startle data from noise," *Journal of neuroscience methods*, vol. 253, pp. 206–217, 2015.

[19] Y. Choe and I. Park, "Proposal of conditional random inter-stimulus interval method for unconstrained enclosure based gpias measurement systems," *Biomedical Engineering Letters*, vol. 9, pp. 367–374, 2019.

[20] L. M. Luxon, F. Luxon, J. M. Furman, A. Martini, J. M. Furman, A. Martini, and S. D. Stephens, *Textbook of audiological medicine*. Taylor & Francis Group, 2003.

[21] V. M. Gilani, M. Ruzbahani, P. Mahdi, A. Amali, M. H. N. Khoshk, J. Sameni, A. K. Yazdi, and H. Emami, "Temporal processing evaluation in tinnitus patients: results on analysis of gap in noise and duration pattern test," *Iranian journal of otorhinolaryngology*, vol. 25, no. 73, p. 221, 2013.

[22] P. Fournier and S. Hébert, "Gap detection deficits in humans with tinnitus as assessed with the acoustic startle paradigm: does tinnitus fill in the gap?" *Hearing research*, vol. 295, pp. 16–23, 2013.

[23] K. Boyen, D. Başkent, and P. van Dijk, "The gap detection test: Can it be used to diagnose tinnitus?" *Ear amp; Hearing*, vol. 36, no. 4, p. e138–e145, Jul. 2015. [Online]. Available: http://dx.doi.org/10.1097/AUD.0000000000000156

[24] S. E. Shore and C. Wu, "Mechanisms of noise-induced tinnitus: Insights from cellular studies," *Neuron*, vol. 103, no. 1, pp. 8–20, 2019. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0896627319304337

[25] B. Langguth, P. M. Kreuzer, T. Kleinjung, and D. De Ridder, "Tinnitus: causes and clinical management," *The Lancet Neurology*, vol. 12, no. 9, pp. 920–930, 2013. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1474442213701601

[26] Y. Agrawal, E. A. Platz, and J. K. Niparko, "Prevalence of hearing loss and differences by demographic characteristics among us adults: data from the national health and nutrition examination survey, 1999-2004," *Archives of internal medicine*, vol. 168, no. 14, pp. 1522–1530, 2008.

[27] ——, "Risk factors for hearing loss in us adults: data from the national health and nutrition examination survey, 1999 to 2002," *Otology & neurotology*, vol. 30, no. 2, pp. 139–145, 2009.

[28] B. Langguth, T. Kleinjung, W. Schlee, S. Vanneste, and D. De Ridder, "Tinnitus guidelines and their evidence base," *Journal of Clinical Medicine*, vol. 12, no. 9, p. 3087, 2023.

[29] J. A. Kaltenbach and C. E. Afman, "Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus," *Hearing research*, vol. 140, no. 1-2, pp. 165–172, 2000.

[30] T. Brozoski, C. Bauer, and D. Caspary, "Elevated fusiform cell activity in the dorsal cochlear nucleus of chinchillas with psychophysical evidence of tinnitus," *Journal of Neuroscience*, vol. 22, no. 6, pp. 2383–2390, 2002.

[31] J. E. Peelle, "Human auditory pathway," Nov 2018. [Online]. Available: osf.io/u2gxc

[32] P. J. Jastreboff *et al.*, "Salicylate-induced abnormal activity in the inferior colliculus of rats," *Hearing research*, vol. 82, no. 2, pp. 158–178, 1995.

[33] S. Seki and J. J. Eggermont, "Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss," *Hearing research*, vol. 180, no. 1-2, pp. 28–38, 2003.

[34] A. T. Beck, *Cognitive therapy of depression*. Guilford press, 1979.

[35] H. J. Jun and M. K. Park, "Cognitive behavioral therapy for tinnitus: evidence and efficacy," *Korean journal of audiology*, vol. 17, no. 3, p. 101, 2013.

[36] H. Hesser, C. Weise, V. Z. Westin, and G. Andersson, "A systematic review and meta-analysis of randomized controlled trials of cognitive–behavioral therapy for tinnitus distress," *Clinical psychology review*, vol. 31, no. 4, pp. 545–553, 2011.

[37] P. Martinez-Devesa, R. Perera, M. Theodoulou, and A. Waddell, "Cognitive behavioural therapy for tinnitus," *Archivos de Prevencion de Riesgos Laborales*, vol. 16, no. 2, pp. 96–97, 2013.

[38] G. Andersson and L. Lyttkens, "A meta-analytic review of psychological treatments for tinnitus," *British journal of audiology*, vol. 33, no. 4, pp. 201–210, 1999.

[39] P. J. Jastreboff and M. M. Jastreboff, "Tinnitus Retraining Therapy: A Different View on Tinnitus," *ORL*, vol. 68, no. 1, pp. 23–30, 03 2006. [Online]. Available: https://doi.org/10.1159/000090487

[40] M. Parazzini, L. Del Bo, M. Jastreboff, G. Tognola, and P. Ravazzani, "Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators," *International journal of audiology*, vol. 50, no. 8, pp. 548–553, 2011.

[41] B. J. Gantz and C. W. Turner, "Combining acoustic and electrical hearing," *The Laryngoscope*, vol. 113, no. 10, pp. 1726–1730,

2003. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1097/00005537-200310000-00012

[42] S. Y. Bessen, J. E. Saunders, E. A. Eisen, and I. L. Magro, "Perceptions of sound quality and enjoyment after cochlear implantation," *OTO Open*, vol. 5, no. 3, Jul. 2021. [Online]. Available: http://dx.doi.org/10.1177/2473974X211031471

[43] A. L. Sampaio, M. F. Araújo, and C. A. Oliveira, "New criteria of indication and selection of patients to cochlear implant," *International journal of otolaryngology*, vol. 2011, 2011.

[44] B. S. Kou, D. B. Shipp, and J. M. Nedzelski, "Subjective benefits reported by adult nucleus 22-channel cochlear implant users." *The Journal of otolaryngology*, vol. 23, no. 1, pp. 8–14, 1994.

[45] F. J. Kloostra, R. Arnold, R. Hofman, and P. Van Dijk, "Changes in Tinnitus after Cochlear Implantation and Its Relation with Psychological Functioning," *Audiology and Neurotology*, vol. 20, no. 2, pp. 81–89, 12 2014. [Online]. Available: https://doi.org/10.1159/000365959

[46] R. Arts, T. Netz, M. Janssen, E. George, and R. Stokroos, "The occurrence of tinnitus after ci surgery in patients with severe hearing loss: A retrospective study," *International journal of audiology*, pp. 1–8, 09 2015. [Online]. Available: https://doi.org/10.3109/14992027.2015.1079930

[47] R. Arts, E. George, R. Stokroos, and K. Vermeire, "Review: Cochlear implants as a treatment of tinnitus in single-sided deafness," *Current opinion in otolaryngology head and neck surgery*, vol. 20, pp. 398–403, 08 2012.

[48] A. L. de Freitas Borges, P. L. e Silva Duarte, R. B. S. de Almeida, A. L. L. Ledesma, Y. J. de Azevedo, L. V. Pereira, and F. Bahmad, "Cochlear implant and tinnitus–a meta-analysis," *Brazilian Journal of Otorhinolaryngology*, vol. 87, no. 3, pp. 353–365, 2021. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1808869420302159

[49] Y. Liu, H. Wang, D. X. Han, M. H. Li, Y. Wang, and Y. L. Xiao, "Suppression of tinnitus in chinese patients receiving regular cochlear implant programming," *Annals of Otology, Rhinology & Laryngology*, vol. 125, no. 4, pp. 303–310, 2016.

[50] N. Quaranta, S. Fernandez-Vega, C. D'elia, R. Filipo, and A. Quaranta, "The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus," *Acta oto-laryngologica*, vol. 128, no. 2, pp. 159–163, 2008.

[51] P. V. de Heyning, K. Vermeire, M. Diebl, P. Nopp, I. Anderson, and D. D. Ridder, "Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation," *Annals of Otology, Rhinology & Laryngology*, vol. 117, no. 9, pp. 645–652, 2008, pMID: 18834065. [Online]. Available: https://doi.org/10.1177/000348940811700903

[52] G. G. Ramakers, A. van Zon, I. Stegeman, and W. Grolman, "The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: a systematic review," *The Laryngoscope*, vol. 125, no. 11, pp. 2584–2592, 2015.

[53] G. G. Ramakers, V. J. Kraaijenga, Y. E. Smulders, A. van Zon, I. Stegeman, R. J. Stokroos, R. H. Free, J. H. Frijns, W. J. Huinck, G. A. Van Zanten *et al.*, "Tinnitus after simultaneous and sequential bilateral cochlear implantation," *Frontiers in surgery*, vol. 4, p. 65, 2017.

[54] R. Bovo, A. Ciorba, and A. Martini, "Tinnitus and cochlear implants," *Auris Nasus Larynx*, vol. 38, no. 1, pp. 14–20, 2011.

[55] Á. Ramos, R. Polo, E. Masgoret, O. Artiles, I. Lisner, M. L. Zaballos, C. Moreno, and Á. Osorio, "Cochlear implant in patients with sudden unilateral sensorineural hearing loss and associated tinnitus," *Acta Otorrinolaringologica (English Edition)*, vol. 63, no. 1, pp. 15–20, 2012.

[56] G. Mertens, M. De Bodt, and P. Van de Heyning, "Cochlear implantation as a long-term treatment for ipsilateral incapacitating tinnitus in subjects with unilateral hearing loss up to 10 years," *Hearing Research*, vol. 331, pp. 1–6, 2016.

[57] S. A. Idriss, P. Reynard, M. Marx, A. Mainguy, C.-A. Joly, E. C. Ionescu, K. K. Assouly, and H. Thai-Van, "Short-and long-term effect of cochlear implantation on disabling tinnitus in single-sided deafness patients: A systematic review," *Journal of Clinical Medicine*, vol. 11, no. 19, p. 5664, 2022.

[58] H. Olze, "Cochlear implants and tinnitus," *HNO*, vol. 63, pp. 291–297, 2015.

[59] Z. Song, Y. Wu, D. Tang, X. Lu, L. Qiao, J. Wang, and H. Li, "Tinnitus is associated with extended high-frequency hearing loss and hidden high-frequency damage in young patients," *Otology & Neurotology*, vol. 42, no. 3, p. 377, 2021.

[60] A. K. Punte, D. De Ridder, and P. Van de Heyning, "On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness," *Hearing research*, vol. 295, pp. 24–29, 2013.

[61] R. A. Arts, E. L. George, M. Janssen, A. Griessner, C. Zierhofer, and R. J. Stokroos, "Tinnitus suppression by intracochlear electrical stimulation in single sided deafness–a prospective clinical trial: follow-up," *PloS one*, vol. 11, no. 4, p. e0153131, 2016.

[62] R. R. Sarreal and P. Bhatti, "Characterization and miniaturization of silver-nanoparticle microcoil via aerosol jet printing techniques for micromagnetic cochlear stimulation," *Sensors*, vol. 20, no. 21, 2020. [Online]. Available: https://www.mdpi.com/1424-8220/20/21/6087

[63] T. Costa, C. Shi, K. Tien, J. Elloian, F. A. Cardoso, and K. L. Shepard, "An integrated 2d ultrasound phased array transmitter in cmos with pixel pitch-matched beamforming," *IEEE Transactions on Biomedical Circuits and Systems*, vol. 15, no. 4, pp. 731–742, 2021.

[64] B. M. Carlson, "Chapter 7 - special senses—vision and hearing," in *The Human Body*, B. M. Carlson, Ed. Academic Press, 2019, pp. 177–207. [Online]. Available: https://www.sciencedirect.com/science/article/pii/B9780128042540000077

[65] M. Sugawara, G. Corfas, and M. Liberman, "Influence of supporting cells on neuronal degeneration after hair cell loss," *Journal of the Association for Research in Otolaryngology : JARO*, vol. 6, pp. 136–47, 07 2005. [Online]. Available: https://doi.org/10.1007/s10162-004-5050-1

[66] O. Macherey, "Hearing restoration using focused ultrasound neurostimulation – hear-us," May 2022. [Online]. Available: https://anr.fr/Project-ANR-19-CE19-0015

[67] y. . . u. . h. W Alexander, title = Some harmful effects of noise.

[68] P. S. Sundar, C. Chowdhury, and S. Kamarthi, "Evaluation of human ear anatomy and functionality by axiomatic design," *Biomimetics*, vol. 6, no. 2, p. 31, 2021.

[69] J. Ashmore, "Biophysics of the cochlea – biomechanics and ion channelopathies," *British Medical Bulletin*, vol. 63, no. 1, pp. 59–72, 10 2002.

[70] A. R. Arulpragasam, M. van 't Wout-Frank, J. Barredo, C. R. Faucher, B. D. Greenberg, and N. S. Philip, "Low intensity focused ultrasound for non-invasive and reversible deep brain Neuromodulation-A paradigm shift in psychiatric research," *Front Psychiatry*, vol. 13, p. 825802, Feb. 2022.

[71] B. Conlon, B. Langguth, C. Hamilton, S. Hughes, E. Meade, C. O. Connor, M. Schecklmann, D. A. Hall, S. Vanneste, S. L. Leong, T. Subramaniam, S. D'Arcy, and H. H. Lim, "Bimodal neuromodulation combining sound and tongue stimulation reduces tinnitus symptoms in a large randomized clinical study," *Science Translational Medicine*, vol. 12, no. 564, p. eabb2830, 2020. [Online]. Available: https://www.science.org/doi/abs/10.1126/scitranslmed.abb2830

[72] K. L. Marks, D. T. Martel, C. Wu, G. J. Basura, L. E. Roberts, K. C. Schvartz-Leyzac, and S. E. Shore, "Auditory-somatosensory bimodal stimulation desynchronizes brain circuitry to reduce tinnitus in guinea pigs and humans," *Science Translational Medicine*, vol. 10, no. 422, 2018, cited By :73. [Online]. Available: https://www.doi.org/10.1126/scitranslmed.aal3175

[73] S. Shore and J. Moore, "Sources of input to the cochlear granule cell region in the guinea pig," *Hearing Research*, vol. 116, no. 1-2, p. 33 – 42, 1998, cited by: 46. [Online]. Available: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031885055&doi=10.1016%2fS0378-5955%2897%2900207-4&partnerID=40&md5=bf35968c98b99bae80232f2148194dfd

[74] S. E. Shore, Z. Vass, N. L. Wys, and R. A. Altschuler, "Trigeminal ganglion innervates the auditory brainstem," *Journal of Comparative Neurology*, vol. 419, no. 3, p. 271 – 285, 2000, cited by: 173; All Open Access, Bronze Open Access, Green Open Access. [Online]. Available: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0034088855&doi=10.1002%2f%28SICI%291096-9861%2820000410%29419%3a3%3c271%3a%3aAID-CNE1%3e3.0.CO%3b2-M&partnerID=40&md5=35c4d51c83f5a3880de0a2c1b0de9a06

[75] J. Zhou and S. Shore, "Projections from the trigeminal nuclear complex to the cochlear nuclei: A retrograde and anterograde tracing study in the guinea pig," *Journal of Neuroscience Research*, vol. 78, no. 6, p. 901 – 907, 2004, cited by: 122; All Open Access, Green Open Access. [Online]. Available: https://www.scopus.com/inward/

record.uri?eid=2-s2.0-10644273487&doi=10.1002%2fjnr.20343&partnerID=40&md5=57286799bf93471b4474d8dfe0705d16

[76] B. Conlon, C. Hamilton, S. Hughes, E. Meade, D. A. Hall, S. Vanneste, B. Langguth, and H. H. Lim, "Noninvasive bimodal neuromodulation for the treatment of tinnitus: Protocol for a second large-scale double-blind randomized clinical trial to optimize stimulation parameters," *JMIR Res Protoc*, vol. 8, no. 9, p. e13176, Sep 2019. [Online]. Available: https://doi.org/10.2196/13176

[77] Lenire, Jan 2024. [Online]. Available: https://www.lenire.com/

[78] Neosensory, Feb 2024. [Online]. Available: https://neosensory.com/product/neosensory-duo-for-tinnitus/

[79] M. V. Perrotta, I. Kohler, and D. M. Eagleman, "Bimodal stimulation for the reduction of tinnitus using vibration on the skin," *bioRxiv*, pp. 2022–11, 2022.

[80] H. L. Kochilas, A. T. Cacace, A. Arnold, M. D. Seidman, and W. B. Tarver, "Vagus nerve stimulation paired with tones for tinnitus suppression: Effects on voice and hearing," *Laryngoscope Investigative Otolaryngology*, vol. 5, no. 2, pp. 286–296, 2020. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1002/lio2.364

[81] H. J. Shim, M. Y. Kwak, Y.-H. An, D. H. Kim, Y. J. Kim, and H. J. Kim, "Feasibility and safety of transcutaneous vagus nerve stimulation paired with notched music therapy for the treatment of chronic tinnitus," *Journal of Audiology and Otology*, vol. 19, no. 3, p. 159–167, Dec. 2015. [Online]. Available: http://dx.doi.org/10.7874/jao.2015.19.3.159

[82] N. D. Engineer, J. R. Riley, J. D. Seale, W. A. Vrana, J. A. Shetake, S. P. Sudanagunta, M. S. Borland, and M. P. Kilgard, "Reversing pathological neural activity using targeted plasticity," *Nature*, vol. 470, no. 7332, pp. 101–104, 2011.

[83] D. De Ridder, S. Vanneste, N. D. Engineer, and M. P. Kilgard, "Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: A case series," *Neuromodulation: Technology at the Neural Interface*, vol. 17, no. 2, pp. 170–179, 2014. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1094715914600544