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On the Horizon: Cochlear implant technology

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Introduction

The majority of patients with hearing loss significant enough to result in social dysfunction can be treated with non-surgical interventions. In many instances, environmental manipulations are sufficient to improve auditory communication, typically by way of improving the signal-to-noise ratio (SNR) or relative amplification. Examples include minimizing ambient noise such as avoiding crowded or noisy listening situations, selective seating such as sitting closer or with the better ear near important sound sources, or the use of frequency modulated (FM) or Infrared (IR) devices. When these manipulations are insufficient, amplification of the acoustic environment can be utilized. This may take many forms including personal listening devices or conventional hearing aids. In those with conductive hearing loss that is not amenable to conventional amplification that utilizes air conduction mechanisms, bone conductive solutions are available including osseointegrated and active middle ear implants.

Cochlear device implantation (CDI) remains the only reliable option for auditory communication rehabilitation in cases of severe and profound sensorineural hearing loss (SNHL) where the site of lesion is outside of the central auditory processing stream. Cochlear implants (CI) sample the acoustic environment, process the input signal into discrete frequency bands, compress the amplitude into an electrically useable range, and

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then stimulate the residual neural elements in a tonotopic manner to reproduce the frequency and amplitude analyzing capability of the cochlea. CIs represent the most successful neural prosthesis in clinical use and have a long and interesting history that has led to the modern devices currently available. Further refinements of the existing current iteration of these devices and the development of novel technology hold promise to continue to improve and benefit patient experience.

History of Cochlear Implant development

History of CDI spans over 60 years and has seen multiple iterations of the devices and speech processing strategies utilized although the initial use of electrical audition preceded CDI by almost 200 years. In addition to being the creator of the battery, Alessandro Volta performed the first documented electrical stimulation of the auditory system in 1790 when he applied a large voltage across his own ears and was able to generate auditory percepts he described as “crackling” or “bubbling”.[1-4] Later experiments applied alternating currents (Duchenne of Bouogne) as well as various charges, polarities and intensities (Brenner).[2, 4] Weaver and Bray (1930) described electrical signals from the feline cochlea that closely resembled the input stimulus waveform with the implication that it might be possible to replicate this result with electrical signals.[4, 5]

Djourno and Eyries (1957) implanted an electrode coupled with a receiver coil into a patient having undergone resection of the distal cochlear nerve due to extensive cholesteatoma and were able to stimulate the apparatus with an external coil for a period of several months. Amazingly, this patient was able to develop sound awareness and simple word recognition.[1, 2, 4, 6-8] William House began his pioneering work in the early 1960's, inspired by the work of Djourno and Eyries, starting with the implantation of either simple wires, wires with ball electrodes and even simple arrays into the scala tympani.[1, 2, 9] This early work in partnership with Jack Urban eventually resulted in the development of a commercially available implantable device in 1972 with clinical trials beginning the following year.[1, 9]

Though met with considerable skepticism and resistance from the basic science community including leading neurophysiologists and otologists,[1, 2, 4, 10] the validity of direct electrical stimulation of auditory nerve fibers as a rehabilitative strategy was confirmed in 1977 by a team commissioned by the National Institutes of Health that evaluated the outcome of patients implanted with single channel devices.[1, 4, 11] In a major advancement, Graeme Clark developed a multichannel CI, which was able to produce open-set word recognition.[12] Following the Food and Drug Administration (FDA) approval of the single channel CI, multichannel devices soon replaced the single channel device due to better frequency spectrum percepts and open-set word recognition. [1, 4] Based on these developments, multiple multichannel CI devices are available of varying numbers of electrode contacts, electrode lengths, electrode widths, and electrode-positioning technologies from 3 device manufactures (Advanced Bionics, Cochlear®, and MED-EL).

Environmental speech formant processing and electrode activation strategies developed in parallel to that of CI design over the past several decades.[1] The initial single channel CIs

utilized simple sinusoidal currents to drive neural responses while multichannel CIs used simultaneous stimulation of discrete locations of the modiolus in a tonotopic manner, this being termed Compressed Analog Strategy (CAS).[1, 2] While this latter stimulation paradigm allowed for limited open-set word recognition, the spread of the temporally synchronous current resulted in issues of channel interaction. Other early speech processing strategies included feature extraction (PEAK) and the use of multiple filter banks (SPEAK).[2] In 1991, Wilson and colleagues introduced the continuous interleaved sampling (CIS) strategy, which demonstrated significantly improved open-set word recognition when compared with previous analog strategies.[13] Today, all commercially available pulsatile strategies are based on CIS.[1]

Contemporary Cochlear Implants and Targets for Innovation

Successful auditory system stimulation resulting in meaningful perceptions requires several technological and biological components, all of which are targets for continued innovations. Acoustic stimuli must be detected and captured (microphone), processed (speech processing software and circuitry), turned into electrical signals (coil, receiver/stimulator) that are delivered to the spiral ganglion neurons (SGNs) (electrode array), transduced into action potentials, and delivered to the central auditory processing stream. Carlson *et al.* (2012) provides a review of the components of the modern CI.[1] Briefly, most CIs consist of an external device worn as a behind the ear device incorporating one or more microphones that convert acoustic energy into an analog signal. This signal is then typically digitized, compressed, filtered and encoded into a signal that will be used to drive SGN stimulation. This code is transmitted through the skin using radio frequency signals to a completely subcutaneous signal receiver that drives intracochlear electrode activation. A variable number of electrodes are encased within a carrier (commonly referred to as the “electrode” or “electrode array”), the length of which varies according to the specific device. SGNs are directly driven with electrical voltage delivered by the electrode array to generate action potentials, which are conducted to more central locations in the auditory system. Most CIs also have a return/inactive (ground) electrode that is either part of the body of the receiver/stimulator or a separate lead implanted in the soft tissues around the ear, typically deep to the temporalis muscle. The active electrodes (intracochlear) can be activated in 2 main configurations: monopolar and bipolar. In monopolar stimulation, each intracochlear active electrode uses the extracochlear inactive electrode as the current return. In the bipolar mode, two neighboring electrodes form an active/inactive pair. Each mode has its advantages and disadvantages, which are beyond the scope of this review.

The premise of CDI is simple: patterned electrical stimulation of cochlear afferent fibers. Thus both the properties of the processing of the acoustic signal, electrical stimulation code and the neural responses are critical. Unfavorable electrical stimulation or neural response characteristics will result in poor perceptual outcomes. The residual neural elements and their health as well as ability of the CI to deliver high fidelity electrical stimulation are the basic substrates of contemporary cochlear implantation. Neuronal health has received considerable attention in recent years with several works demonstrating that reduced intracochlear damage with device placement, presumably resulting in improved neuronal survival, is associated with improved speech perceptual abilities.[1, 14]

Remote CI programming, totally implanted devices, improved neural health and survival through targeted drug therapy and delivery, intraneural electrode placement, electroacoustical stimulation and hybrid CIs, and methods to enhance the neural: prosthesis interface are evolving areas of innovation reviewed in this article.

Totally Implantable Cochlear Implants

Totally implanted cochlear implants (TICI) may have some advantages when compared to the commercially available devices today[1, 15] which require an external device that couples to the implanted receiver/stimulator. External devices are exposed to the environment, which may render them more vulnerable to damage from extremes of temperature, moisture, and damage from dislodgement. Additionally, implantees typically remove the devices when water exposure is likely (e.g., bathing, swimming) or when perspiration will be great (vigorous exercise) and thus are “off-line” during these activities.[15, 16] While the size and profile of current external devices are smaller and less conspicuous than earlier generations, they are visible (more so than modern digital behind-the-ear hearing aids), which may not be desirable to many potential candidates for social reasons (Figure 1).[1] There are several technical barriers to implantation of a TICI including power source management, environmental sound detection, and management of component breakdown.[1, 15] Contemporary CI are powered via electromagnetic induction using radiofrequency signals via the coil of the external device and antenna of the receiver/stimulator. Any TICI would need to be powered internally, likely with the use of a rechargeable battery. Batteries will need to be able to recharge quickly, hold enough charge to power the CI for about a day, not generate significant heat and have a very low chance of leaking potentially dangerous battery chemicals even in the event of battery failure.[1, 15, 16] At this time, all rechargeable batteries eventually fail to hold significant charge and will need to be replaced (a strategy used with pacemakers). Additionally, current CIs utilize an external device worn behind the ear that houses 1 or more microphones and provides a largely unfettered access to the acoustic environment and takes advantage of the filtering properties of the head. A TICI will need to overcome the more limited direct access to sound sources. Options include microphone placement subcutaneously in the external auditory canal or behind the ear or using the tympanic membrane and/or ossicular chain as a microphone directly.[1, 15, 17-19] The speech processor and related electrical components will also need to be implanted. It is likely that with the increased number of components implanted, an explantation strategy will need to be devised as component failure becomes more likely. It is also probable that TICI will need some type of external hardware for battery recharging, programming, and switching between programs. It may also be desirable to allow the TICI to be powered and stimulated using a conventional external device.[15, 16] Briggs and colleagues (2008) published the first report using a TICI system in 3 subjects. The authors termed use of the TICI alone as “invisible hearing.” The devices utilized a subcutaneous microphone near the radiofrequency coil, lithium ion battery, and the ESPri 3G external sound processor for use in a conventional mode. Results indicated that the devices can be safely implanted and all 3 subjects reported benefit when using the devices in the invisible hearing mode. However, the subjects scored higher in measures of Consonant Nucleus Consonant (CNC) word score in quiet and City University of New York (CUNY) sentence scores in noise when using the

devices in conventional mode with the external speech processor. With continued improvement, it is likely that TICI will become a routine device option for patients.

Telemedicine and remote programming of Cochlear Implants

After CDI, the brain slowly learns to use the encoded electrical stimulation to extract information about the acoustic environment. This is a dynamic process with continued improvements being seen years after the initial device activation. Each electrode in the array must be tuned to the response properties of the region that it stimulates. This typically involves determining the psychophysical threshold as well as the maximum comfortable level of stimulation (also known as T and C levels, respectively). Over time, changes in T and/or C levels, individual electrode failures or extrusions, and non-auditory stimulations (e.g., facial nerve stimulation as a result of sound) require reprogramming the speech processor. CI programming has traditionally been performed in the clinic by an implant audiologist using proprietary equipment and software. This has required healthcare encounters at dedicated CI program centers, often necessitating a travel requirement for the patient and their family. Modern telecommunication technologies may offer an approach to programming where the patient and their CI team can work together to maximize each user's performance without a physical visit to the center. This can offer specific benefit to patients with limited access to transportation or who live in remote areas. Several recent reports document the safety and efficacy of remote programming.[20-22] Ramos and colleagues (2009) describe a fairly simple set up for remote programming based on software for video conferencing, computer operating systems, and standard CI programmer software and hardware.[20] In their experimental setup, a remote unit equipped with all required programmer equipment and attended by a local representative interacted with a remote location equipped with similar computing equipment and programs. The remote computer was able to control the local computer and thus run the programming software. In their study of 5 subjects who were programmed both with standard and remote programming sessions, they found that remote programming was safe and was not statistically different from standard programming. McElveen *et al.* (2010) also demonstrated the safety and non-inferiority of remote programming in 7 patients compared to 7 matched controls using a setup similar to Ramos *et al.* (2009).[21] Wesarg *et al.* (2010) evaluated 70 subjects over several different implant centers using a variety of technology and found no significant difference in map characteristics between remote and local programming sessions.[22] One common finding in these three studies is the presence of monitoring personnel to ensure the safety of the subject being programmed by watching for signs of painful stimulation and ensuring that there are no communication issues between the remote programming audiologist and the subject.[20-22] Patient and healthcare professional satisfaction with remote CI programming in these and other studies has been quite high, with one recent study reporting that >96% of respondents were satisfied with the remote programming sessions and 100% reporting that that they would use remote programming in the future.[20-23] These studies demonstrate that remote programming is likely safe and feasible and may offer an opportunity for better access and possibly improved outcomes for patients undergoing CDI who live at a considerable distance from their implant center.

Optical neural stimulation and optical cochlear implants

Contemporary hearing rehabilitation currently relies on two main modalities: acoustic stimulation to the cochlea and/or electric stimulation of remaining cochlear nerve afferents.[24] Both strategies have advantages and limitations. Acoustic stimulation relies on the presence of mechanoacoustic stimulation of the cochlea, typically with amplified and filtered signals (e.g. conventional hearing aids) and necessarily relies on cochlear functions including the biomechanics of the basilar membrane and organ of Corti as well as the physiology of the inner and outer hair cells. In the case of conventional hearing aids, this requires a patent external auditory canal that can tolerate the placement of the hearing aid. In severe cases of SNHL, these biomechanical and physiological properties are deranged to the point where mechanoacoustical stimulation does not provide the subject with a hearing benefit. In many of these patients, a reduced but viable population of SGNs remain that can be driven with nearby electrical voltage changes and this provides the neural basis for electrical hearing via CDI. With modern CI electrode arrays and stimulation paradigms, CI users are commonly performing at perfect or near perfect levels on word recognition tests including hearing in noise situations.[25] However, despite these results, many patients continue to report difficulty hearing in noisy environments and with music perception.[24, 26, 27] As reviewed in Richter *et al.* (2013), while there are at most 22 electrodes, only 4-7 channels are truly independent versus the estimated 30-50 channels in normal hearing subjects. The main problem is thought to be the spread of current (spread of excitation) away from active electrodes.[28, 29] This spread of excitation may degrade the specificity of the neural elements being stimulated through channel interaction or cross talk.[30, 31] Channel interaction is an example of how the spread of the excitatory currents degrade the neural percepts with CIs. It is likely that increasing the number of independent channels will improve listening in noise or music appreciation.[28, 29] Virtual channels, created by steering current between two electrodes, and bipolar electrode stimulation[32] have been used to decrease channel interaction but have yet to result in significant improvement over more traditional stimulation methods.[28]

The use of photons as the energy source for neural stimulation has been proposed as one mechanism to more specifically stimulate neural elements (reviewed in Richter *et al.* 2013, Eshraghi *et al.* 2012, Jeschke & Moser 2015, and Moser 2015).[4, 24, 27, 28] The precision that light stimulation may offer could allow for the creation of more focal stimulation and thus more independent channels of information flow.[27] Light energy has been found to excite many different types of tissues including peripheral nerve, cortical cells, cardiomyocytes, and isolated neurons.[27, 28] Additionally, the light energy could be delivered via local light sources such as miniature light emitting diodes (μLEDs) or could be transported via special wave guides.[27] There are several proposed mechanisms for how light can stimulate neural tissues: 1) photoactivation of light gated ion channels (optogenetics), 2) thermal stimulation of heat-gated ion channels (thermogenetics), 3) direct activation through alterations in local plasma membrane electrical properties, 4) uncaging of neurostimulatory compounds, and 5) modulation of intracellular calcium metabolism.[4, 24, 27, 28] Of these, optical stimulation mechanisms, optogenetic and infrared light stimulation have received the most attention.

Optogenetics and thermogenetics require the expression of ion channels in the tissue to be excited, which in the case of hearing loss and CIs in particular, are the SGNs.[27, 28] Since the discovery of channelrhodopsin 1 & 2 (ChR1 & ChR2), the expression of these channels has become a popular method for neural stimulation throughout the neurosciences.[24, 27, 33, 34] The molecules function as transmembrane light gated ionotropic channels. A number of channelrhodpsins have been developed with a variety of kinetic properties,[27] which with creative expression including specific subcellular compartmental localization, could allow for a variety of light wavelengths and channels to precisely tune neural responses. Though cation channels and anion pumps have been expressed and used to drive neuronal activity in rodent auditory brainstem neurons and auditory neocortex, the expression of these channels requires either the post-fertilization transfer of the genetic material, typically utilizing a viral vector, or transgenic techniques, neither of which are used in humans at this time.[24, 27, 28, 35, 36] Additionally, the channel kinetics of the available channels limit the rate of stimulation to around 50-60 Hertz (Hz), much lower than the several hundred Hz spiking that can been seen in SGNs as they follow the envelope of a sound stimulus.[24, 37]

In similar fashion to optogenetics, thermogenetics utilizes a thermosensative ion channel that has recently been described, which has been shown to allow for depolarization of neurons with the focal application of heat, such as infrared (IR) light.[28, 38] Similar limitations to the expression of these channels as for optogenetic stimulation exist.

In addition to excitation of exogenously expressed thermosensitive channels, IR light has been shown to directly stimulate neurons.[28, 39] The mechanism underlying this is thought to be focal thermal changes in the plasma membrane capacitance, which results in depolarization. Shapiro *et al.* (2012) demonstrated that this excitation is due to a focal, reversible increase in temperature due to IR energy absorption by water. This increase in temperature results in a change in the local capacitance of the plasma membrane and leads to membrane depolarization.[35] When compared with optogenetic and thermogenetic techniques, IR stimulation has the advantage of not requiring the expression of special ion channels or the infusion of special compounds. In a series of reports, Richter and colleagues demonstrated neural excitation with IR energy and defined the amount of energy required for this excitation, the temporal fidelity, and spread of excitation from focal IR pulse, which was better than that of electrical stimulation.[40, 414239, 43] Littlefield and colleagues (2010) demonstrated that IR light could activate auditory nerve fibers by using IR light directed through the round window.[39] However, several recent studies have challenged the underlying assumptions of how IR energy stimulates the auditory system. The rapid rise in temperature could result in pressure wave formation (up to about 60dB SPL equivalent), which could then stimulate remaining hair cells and drive an auditory response (optoacoustic effect).[37, 44] Additionally, Verma *et al.* (2014) demonstrated that in a completely deafened cochlea, IR stimulation was unable to drive cochlear nucleus responses.[37] There are numerous challenges to implementing these strategies. However, as water is the main molecule that absorbs IR energy, the light source needs to be very near to the target neuron as the surrounding fluids will cause a significant decrement in the amount of energy available to drive neural responses.[28] When compared to existing CI technology, the energy

requirement for IR stimulation was far in excess.[24, 40] Further work needs to be performed to clarify the mechanisms of how IR directly stimulates central auditory pathways.

IR light can also be used to free "caged" compounds that can drive neural excition.[4] One example of this would be the use of light to break a photosensitive bond between glutamate and an inactivating caging compound.

With continued refinement, focused optical stimulation of the SGNs holds promise to overcome many of the technical and perceptual challenges currently presented in modern CIs. This may take several forms but is mainly geared toward the creation of more functionally independent channels of information flow. It is also highly likely that novel coding and stimulation strategies will be needed for optical CIs that will take advantage of the hopefully increased number of information channels and channel independence.[24]

Intraneural Cochlear implantation

Contemporary intrascalar CI electrode arrays are arguably the most successful neurosensory rehabilitation prosthesis, though as reviewed above, significant perceptual challenges remain including listening in noise, music perception, impaired pitch perception, and poor sound localization even with bilateral CIs.[45] These deficits may be a result of the spread of excitation (review above) from the levels of current required to overcome the distance between the electrodes in the implant array and the excitable neural elements, the shunting of current away from these neural elements by the electroconductive perilymph, and the shielding effects of the modiolar bone covering the neural elements.[8, 45] Optical stimulation, as outlined above, is one mechanism that holds promise to refine the ability to precisely stimulate neural elements and thus reduce the spread of excitation and channel interaction. Another strategy is direct stimulation of the neural elements in the modiolus with intraneural electrodes. Intraneural implantation may offer several advantages over intrascalar electrode arrays including lower threshold currents due to direct interaction of the electrode and the neural elements (possible allowing for an increased number of independent channels), the ability to access more apical fibers resulting in better stimulation of lower characteristic frequency neural elements, the electrode is farther from the facial nerve resulting in lower risk of facial nerve stimulation, and less anatomic limitations to implantation for dysplastic or ossified cochleas.[8] Increased potential for neural injury due to insertional trauma represents a significant hurdle for stimulation with intraneural electrodes.

Djourno and Eyries (1957) were the first to chronically implant an electrical auditory prosthesis as described above. From 1964 through the middle of the 1980's, Simmons and colleague published a series of reports investigating the direct intraoperative stimulation of the auditory nerve, implantation of an intraneural device into the auditory nerve, subsequent work in animal models and a return to human direct nerve implantation.[8, 46-54] Amazingly, the initial human experiments resulted in auditory perceptions.[46, 48] Subsequent work in cats and then humans demonstrated that chronically implanted intraneural electrodes yield stable long-term thresholds and were well tolerated though evidence of partial SGN loss and insertional neural trauma was found.[49-51, 53, 54] As reviewed and cited in Arts *et al.* (2003), the next development was that of the "Michigan" array, a series of electrodes on 1 or more

thin shanks.[8] In a series of experiments, these arrays were found to be well tolerated in both stimulating and non-stimulating conditions of the cochlear nerve and cochlear nuclei in animal models. When implanted in the modiolus, there was comparatively less cochlear and neural damage when compared to the published work of Simmons (1979).[8, 54] Both modiolar and intracanalicular auditory nerve implantations have been used. Investigators at the University of Utah have developed a multielectrode implant, termed the Utah electrode array (UEA) that utilizes a series of needle electrodes arranged in a square configuration that could be implanted into the modiolar nerve after a facial recess surgical approach.[55] Badi and colleagues demonstrated that in cats implantation with variations of the UEA into the auditory nerve is feasible, appears to result in minimal histological trauma to implanted nerves, and can elicit auditory responses.[55-57] Lastly, Middlebrooks & Snyder (2007) implanted straight electrode arrays into the modiolar nerve and found that these electrodes could produce low current threshold, frequency specific responses in the inferior colliculus central nucleus with less electrode interaction and spread of excitation when compared to intrascalar electrodes.[45] The studies by Simmons, those with the Michigan array, those with the UEA and the work by Middlebrooks & Snyder (2007) each demonstrate that intraneural electrodes evoke auditory neural responses with less current levels than intrascalar electrodes.[8, 45, 54, 56] These studies demonstrate the feasibility of chronic intraneural implantation and stimulation and the possibility of increased numbers of independent channels with reduced channel interaction compared to current electrode arrays. Further, intraneural implants, if proven safe and at least not inferior to conventional intrascalar CIs, may offer a more reliable option for patients with malformed, brittle or ossified cochleae.

Hearing Preservation and Electroacoustical stimulation

The benefits of CDI and electric hearing are well established and CDI can now be considered the standard of care for patients with severe to profound SNHL and no meaningful benefit from conventional amplification. However, many patients with severe to profound high frequency hearing loss and limited word discrimination retain substantial residual hearing in the low frequencies. This residual hearing often provides significant benefit; however, the profound SNHL in the high frequencies results in poor speech and language abilities.[58] These patients are able to gain information about the low frequency components of speech (vocal fold vibratory patterns) but are not able to process high frequency components of speech such as fricative phonemes.[59] Conventional amplification is of limited benefit in these situations.[60] Such patients are left in a therapeutic bind: they do not benefit significantly from amplification but conventional cochlear implantation with standard electrode arrays and carriers typically results in complete loss of the residual hearing.

Considerable recent work has focused on preserving the residual low frequency hearing after CDI, such that the implanted ear is simultaneously stimulated with electrical signals with higher frequency information (where many formants of English language speech are found) and acoustic signals, which will convey low frequency information. Two main hearing preservation strategies have been employed: incomplete insertion of standard electrodes and design of shorter electrode carriers. Preservation of low frequency hearing with standard length electrode arrays is typically accomplished by terminating electrode advancement at

the level of the basal turn[58, 61-65], thereby reducing the risk of the electrode traversing the basilar membrane and damaging the organ of Corti and neural elements. Shorter electrode carrier designs include the Hybrid S, Hybrid S10, and L24 by Cochlear® and the M or Flex-EAS electrodes by MED-EL. As reviewed in Mowry *et al.* (2012), results from studies looking at the speech and language outcomes and preservation of hearing have been favorable with shorter electrode carriers (from both companies) and standard electrode carriers with shorter insertion angles.[58] Controversy exists as to whether a standard or short electrode carrier is the best. Standard electrode carriers have higher rates of loss of residual hearing including anacusis. However, if residual hearing is lost, longer electrodes have the potential to offer more independent channels of information, depending on insertion depth, due to the higher number of electrodes in the array and wider spacing, which can reduce channel interaction.

The initial short electrode device, the Hybrid-S (Cochlear®) had 6 electrodes in the array in a carrier that was 6 mm in length.[58] Results from the first 6 patients, 3 implanted with a 6 mm carrier and 3 with a 10 mm carrier, demonstrated that all 6 subjects preserved their hearing and all demonstrated benefit; the 3 subjects implanted with the 10 mm carrier performed considerably better than those implanted with the 6 mm carrier.[66] Based on these successful results, a phase I FDA trial using the Hybrid S 10 mm carrier enrolled 87 patients with severe-to-profound high frequency SNHL and the preliminary results again demonstrated favorable results.[67] The vast majority of subjects demonstrated initial and long-term hearing preservation after surgery (98 and 91%, respectively). About a 30% of subjects suffered a ≥30 dB loss in the low frequencies. The majority of patients performed better than pre-operative measures; 18% did not improve or performed worse.[67] The L24 carrier (Cochlear®) is 16 mm in length but with 22 electrodes in the array. Results from a multicenter trial in Europe demonstrated that subjects maintained low frequency hearing at 30 dB (96%) and 15 dB (68%) that was stable over time.[68] Both the Hybrid S and L24 trials found that habituation periods were significant with continued improvement occurring after 12 months of use.[58] In a study of 18 patients undergoing implantation with the M electrode (MED-EL), 12 patients had residual hearing that could be amplified though only 6 consistently used their CI in hybrid mode on a routine basis.[69] Numerous studies have reported preservation of hearing after sub-total insertion of various full-length standard carriers.[58] Patients implanted with short electrode carriers (Hybrid S/L [Cochlear®] or M/Flex-EAS [MED-EL]) achieve significant improvements in speech discrimination in quiet as well as in noisy listening conditions.[58, 67, 68] Similar results have been found in subjects implanted with standard electrode arrays with sub-total insertion.[58] Electric and acoustic stimulation with residual hearing preservation appears to be a viable option for patients with significant levels of pre-operative low frequency hearing.

Neuroprotection

Most patients with severe-to-profound hearing loss have a reduced population of SGNs presumably as a result of gradual neural degeneration following injury to the cochlear epithelium and hair cell loss. While the residual neurons in these patients suffice to perform well on standard speech perception testing using previous versions of electrode arrays and stimulation strategies,[70, 71] it is likely that emerging devices and stimulation strategies will

be more dependent on a healthy complement of neurons to achieve optimal results.[72] Further, insertion of the electrode array itself into the scala tympani can result in trauma to the neurosensory elements through violation of the basilar membrane, entry into the scala media, disruption of the organ of Corti, injury to the stria vascularis and/or fracture of the modiolus.[1, 9] As reviewed in Carlson *et al.* (2012), damage to the residual neural elements is thought to underlie some of the variability in CI outcomes. These findings have led to the development and refinement of less traumatic surgical techniques (so called "soft surgery").[4, 9, 73-76] As reviewed in Eshraghi *et al.* (2013), even in situations where no identifiable macroscopic trauma can be found in animal cochleae undergoing implantation, molecular and cellular evidence for damage can be found[9, 73] and may explain the losses of residual hearing seen in several hearing preservation trials using specialized electrodes and techniques.[58, 67, 68] Molecular events that could contribute to cell death include the generation of reactive oxygen species (ROS) and pro-inflammatory cytokines that lead to the activation of pro-apoptotic signals such as c-Jun-N-terminal kinase (JNK), a member of the mitogen-activated protein kinase (MAPK) family.[9, 73] Various drugs that target the aforementioned molecular signals and various delivery systems to deliver these drugs are currently being investigated. The glucocorticoid, dexamethasone, and JNK pathway inhibitors are the most well studied pharmaceutical therapeutics. Targeted delivery systems have included transtympanic injections (such as transtympanic corticosteroids for sudden hearing loss or aminoglycoside for Meniere's Disease), mini-osmotic pumps and biodegradable gels that elute the compound of interest over time. Targeted delivery is preferable to systemic administration as this can reduce the side effects and other non-desirable effects of the medications[9, 73], which in turn may allow for higher local doses and longer treatment durations. For example, in the setting of sudden hearing loss, intratympanic corticosteroids can be used instead of systemic therapy in cases where the biochemical side effects are difficult to tolerate (e.g., diabetes).

Dexamethasone has been used by numerous authors to reduce inflammation induced by cochlear device implantation and has demonstrated a protective effect in animal models. Eshraghi *et al.* (2007) and Vivero *et al.* (2008) found that infusion of the dexamethasone via a miniosmotic pumps protected the operated ears in guinea pigs from trauma induced hearing loss with electrode insertion.[77, 78] Likewise, Ye *et al.* (2007) found that triamcinolone, another glucocorticoid compound, reduced hearing loss caused from surgical trauma (cochleostomy).[79] James *et al.* (2008) used dexamethasone in a hyaluronic acid/ carboxymethylcellulose bead placed near the round window and this was found to protect against hearing loss from electrode trauma.[80]

The JNK pathway mediates apoptosis signaling and inhibitors have been used in various organ systems as neuroprotectants (e.g., retinal ganglion cells and cortical neurons).[73] Ex-vivo studies of murine cochleae found that treatment with D-JNKI-1, a peptide JNK inhibitor, prevented hair cell apoptosis induced with acoustic or aminoglycoside trauma.[81] Eshraghi and colleagues performed a series of experiments in guinea pigs that demonstrated the protective effects of D-JNK-1 from electrode insertion trauma induced hearing loss both acute and delayed components.[82, 83] Both of these previous studies used mini-pumps to infuse the JNK inhibitor. Eshraghi *et al.* (2013) used D-JNK-1 mixed with a hyaluronate gel

applied to the RWM a half an hour before electrode insertion and again demonstrated physiologic and histological protection from the damaging effects of electrode insertion.[73] Further, inhibition of JNK using genetic and molecular approaches and pharmacological compounds rescues cultured SGN from apoptosis.[84] However, general JNK inhibitors, such as D-JNK-1, inhibit SGN neurite regeneration. To the extent that neural regeneration (see below) becomes a therapeutic goal in addition to prevention of neuron apoptosis, it will be important to consider the effects of specific molecular targets on neurite growth in addition to neuronal survival. Other examples of stimuli and signaling molecules that promote SGN survival yet inhibit neurite regeneration include membrane depolarization, protein kinase A, calcium-calmodulin dependent kinase II, and members of the Bcl-2 family of proteins.[85-89] Meanwhile, other factors, in particular the neurotrophins, neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BNDF), promote both SGN survival and neurite regeneration (see below).[90]

Typically, pharmacologic compounds must diffuse through the round window to gain access to the scalar contents. As reviewed in Salt and Plontke (2009), a variety of substances (local anesthetics, ototoxic medications, neurotransmitters and monoclonal antibodies) have been placed into the middle ear with the goal of intralabyrinthine distribution.[91] Recently, measurements from the scala tympani have demonstrated that drug distribution is accomplished mainly with passive diffusion movement and concentration gradient is found between the basal and apical ends of the scala; thus to achieve high apical drug concentrations, prolonged exposure to the round window is required.[9, 91] The drug of interest must be able to liberate from the carrier substance, be absorbed into the perilymph (typically through the round window membrane), and distribute throughout the inner ear tissue via diffusion.[91] Carrier compounds which allow for the sustained release of drug over time include liposomes, drug-loaded biodegradable microspheres and drug polymer congregates.[91] Alternatively, microcatheters and pumps can be used to infuse the drug to the round window membrane.[73, 82, 91] With specific regard to the CI, several authors have discussed strategies for drug delivery utilizing the cochlear implant device including bathing the implant in a drug or gel prior to implantation, drug liberation from the electrode array carrier, drug release from a reservoir within the carrier, infusion through a separate channel in the carrier and coating the carrier with a sustained release formulation (Figure 2).[91-94] Richardson *et al.* (2009) demonstrated that polymer electrodes that elute neurotrophins with electrical stimulation resulted in lower brainstem response thresholds and higher SGN counts when compared to controls (non-electrically stimulated).[93]

In summary, targeted drug therapy to help improve hair cell and neuronal survival, as well as innovative drug delivery mechanisms hold significant promise for improving performance with current devices and preserve the normal structures future innovations.

Improving the electrode and cochlear nerve interactions

As reviewed above, CDI allows for the perception of the acoustic environment by selective stimulation of the remaining modiolar neural elements in a frequency specific manner. However the distance between the stimulating electrodes and the neural elements that they activate fails to recapitulate the intimate, precise innervation pattern of the cochlea.

Improvements in how the electrode and neural elements interact may allow for enhanced specificity in the coupling of specific electrodes and nerve fibers resulting in lower stimulation current requirements and thus potentially less channel interaction.[1] Direct nerve implantation (reviewed above) is one mechanism being studied that results in physical contact of the electrode in the array with cochlear nerve afferent fibers. Two other strategies are currently being studied: electrode carrier positioning techniques that result in a periomodiolar position of the electrode array and neural stimulation to induce neural growth to the electrode. It is possible that a combination of all three strategies will be utilized in some combination in the future to take selective advantage of benefits that each strategy may offer.

Perimodiolar position strategies have been utilized clinically in the past decade. Early designs used ridged positioning elements that resulted in significant intracochlear trauma and were associated with a significantly elevated risk of meningitis and were subsequently withdrawn from the market.[1, 95, 96] Animal models have corroborated the clinical findings that cochlear trauma increases the risk of otogenic meningitis.[97] Recently, precurved electrode carriers (Cochlear® Contour Advance™ electrode array) have been used with great success. Roland *et al.* (2005) demonstrated that with the advance of stylet (AOS) technique resulted in low levels of cochlear trauma through a reduction in the forces imparted to the lateral cochlear wall.[98] This device uses a rigid stylet that is contained within the electrode carrier that holds the carrier in a nearly straight alignment for the initial insertion. Once the electrode carrier in at the 1st turn of the basal cochlea, the stylet is grasped and the electrode is advanced further allowing the carrier to return to its nascent, curved shaped in a tight spiral around the modular wall. This device is now routinely used in many institutions. Midscalar positioning (electrode carrier array located in the middle of the scala tympani without contact to either the modiolus or lateral wall) can also be utilized. Advantages of this intrascalar position is that it may avoid some of the trauma that is seen with electrode carrier interactions with either the lateral or modular walls while bringing the electrodes closer to the remaining neural elements than traditional lateral wall configurations.[99, 100] Histologic studies have demonstrated that the Advanced Bionics midscalar electrode carrier (HiFocus™ Mid-scala) does allow for a low insertional trauma when inserted off of a stylet.

CIs require the presence of type I afferent fibers to work as evidenced by the profound lack of benefit seen in children with cochlear nerve aplasia who have undergone CDI. Progressive loss of these auditory fibers or other neuropathologic changes has been postulated to result in reduced performance with CIs.[101] One explanation for the loss of SGNs with hearing loss is the resulting loss of neurotrophic factors produced in the cochlear epithelium.[101] Neurotrophins are implicated in the development of SGNs and their long-term survival in both ex-vivo and in-vivo animal models when exogenously administered.[101, 102] In addition to their neuroprotective effects, neurotrophins have also been demonstrated to enhance resprouting of auditory nerve peripheral processes.[102] Wise *et al.* (2005) demonstrated that the application of BDNF and NT3 enhanced sprouting from neural elements near the site of drug application.[103] Viral vectors have been used to force expression of BDNF in a murine model and found enhanced neural regrowth.[104] Thus it

appears possible that exogenously administered or endogenously expressed neurotrophic factors may have a role in preserving the neural substrate for CIs and possibly inducing neural sprouting to further enhance the prosthesis-nerve interface. However for such axon regeneration to be useful, it must be precisely guided to faithfully recapitulate the precise tonotopic arrangement of the afferent auditory innervation. Thus, additional work has been performed to look at neurite guidance cues in an effort to understand and potentially modulate and control neurite growth patterns with the idea that it might be possible to guide neurite growth in an advantageous way. Patterning of biochemical guidance clues have been shown to direct SGN growth cone pathfinding and neurite growth. For example, stripes of EphA4, a chemorepulsive peptide, guide neurite growth since the neurites avoid the EphA-coated stripes.[105] In addition to biochemical factors, physical surface features have recently been shown to precisely direct SGN neurite growth.[106, 107] The ability of these surface features to guide SGN neurite growth depends on channel amplitude and periodicity, mechanical and surface properties (e.g. polarity), and pattern complexity.[108-110] Advantages of such surface features compared with patterning of bioactive molecules include ease and cost of production, reproducibility, and shelf-life stability.[108, 110] Taken together, neurotrophic enhanced neural sprouting and the use of directional neurite growth strategies including physical surface and biochemical cues may allow for a more intimate interface of the CI electrode array and the neural elements it stimulates.

Conclusions

Cochlear implantation and CIs have a long history filled with innovations that have resulted in the high performing devices currently available. There are several promising technologies reviewed above which hold the promise to drive performance even higher.

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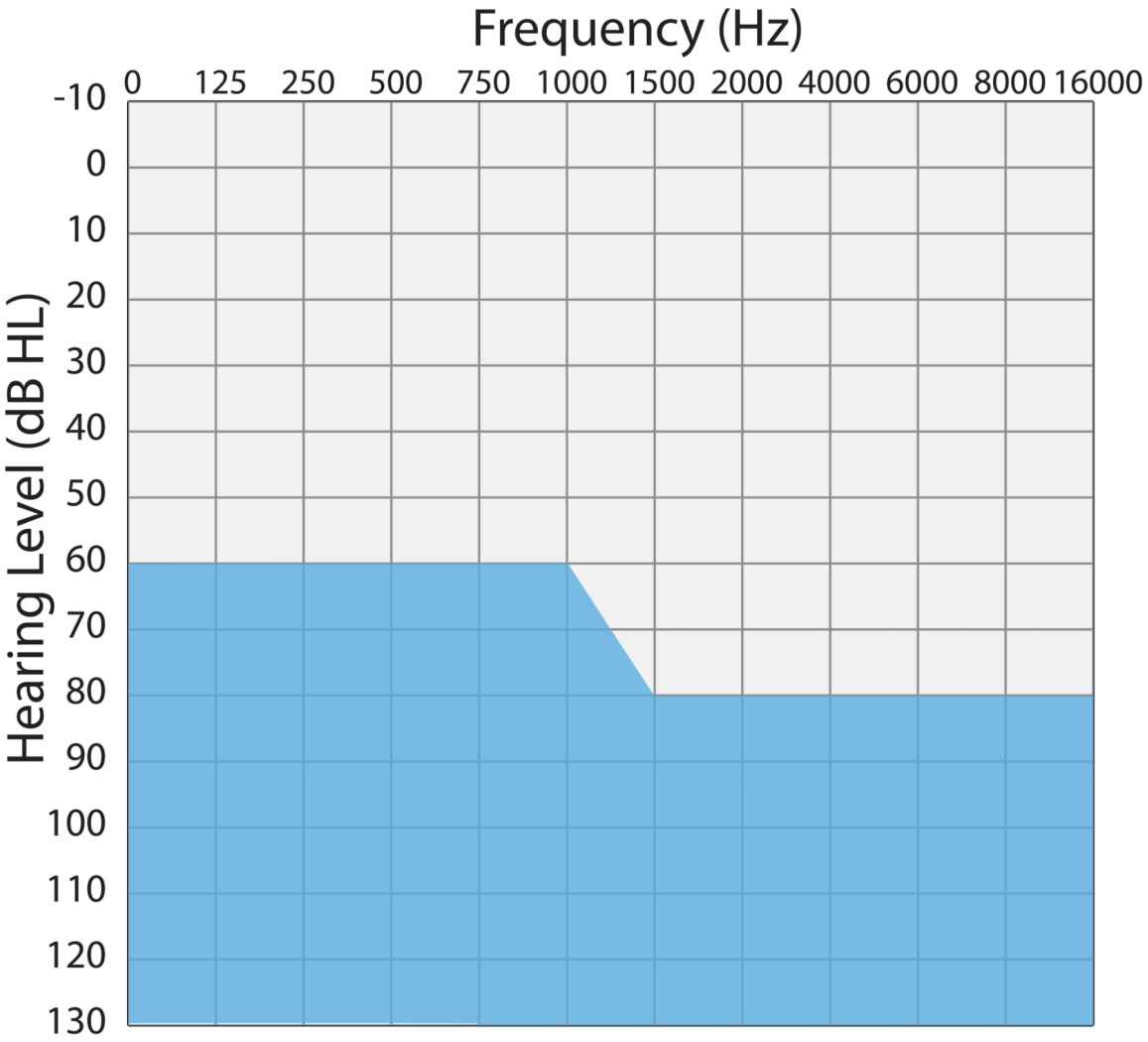
Key Points

- Cochlear device implantation (CDI) remains the only reliable option for auditory communication rehabilitation in cases of severe and profound sensorineural hearing loss (SNHL) where the site of lesion is outside of the central auditory processing stream.
- Cochlear implants (CI) sample the acoustic environment, process the input signal into discrete frequency bands, compress the amplitude into an electrically useable range, and then stimulate the residual neural elements in a tonotopic manner to reproduce the frequency and amplitude analyzing capability of the cochlea.
- CIs represent the most successful neural prosthesis in clinical use and have a long and interesting history that has led to the modern devices currently available. Further refinements of the existing current iteration of these devices and the development of novel technology hold promise to continue to improve and benefit patient experience.



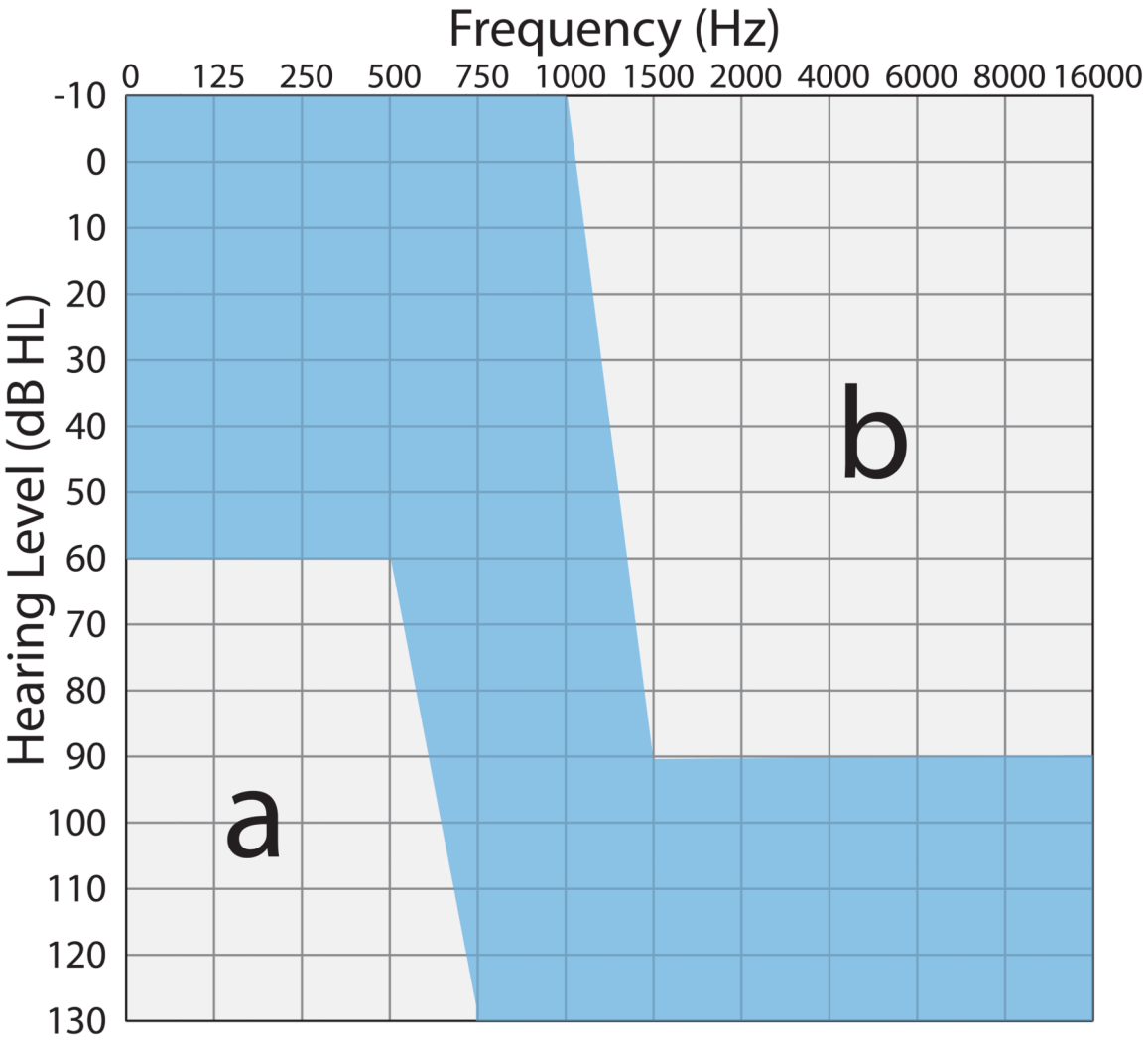


Figure 1.

Audiometric profiles of candidates for implantation with conventional (A) and hybrid (B) devices. The blue shaded area represents where pure-tone thresholds should lie. Candidates for hybrid cochlear implant devices must not have pure-tone thresholds in the grey regions representing thresholds that are either too poor (a) to utilize acoustic stimulation or good (b) to benefit from electrical stimulation of high frequency regions.

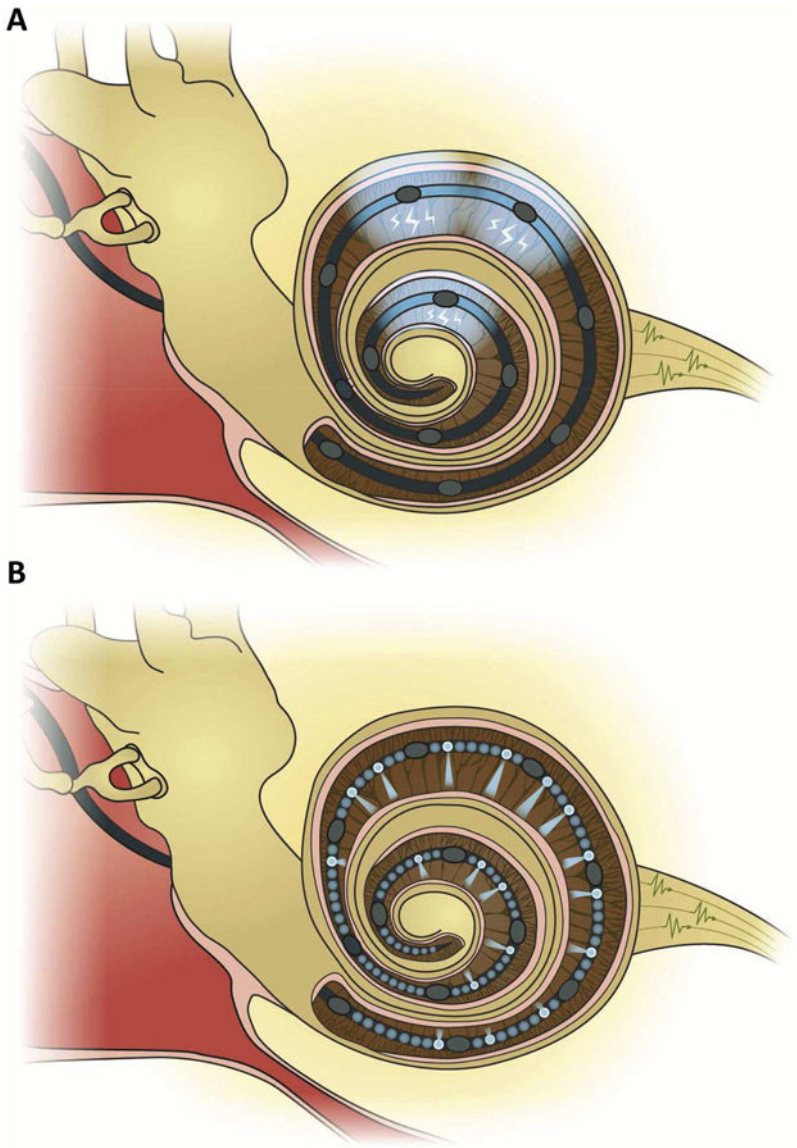


Figure 2.

Schematic representation of cochlear implant devices utilizing either electrical (A) or optical (B) stimulation. Devices in current clinical use employ electrical stimulation and contain variable numbers of electrode channels depending on the specifics design of the electrode array; electrical currents spread outward from the electrodes to depolarize the remaining spiral ganglion cells. Overlapping electric fields result in channel interactions and degradation of the spectral and temporal resolution that is possible from the stimulating signal pattern. Optical stimulation, such as focused light delivered through microscale light emitting diodes (mLEDs), may allow for more focused stimulation of spiral ganglion cells. Thus, it should be possible to generate more independent channels of information, which could result in better spectral and temporal percepts of the acoustic environment.

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