



Review Article

Clinical and scientific innovations in auditory brainstem implants

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Abstract The auditory brainstem implant (ABI) was originally developed to provide rehabilitation of retrocochlear deafness caused by neurofibromatosis type 2 (NF2). Recent studies of the ABI have investigated outcomes in non-NF2 cohorts, such as patients with cochlear nerve aplasia or cochlear ossification and more recently, intractable tinnitus. New technologies that improve the ABI-neural tissue interface are being explored as means to improve performance and decrease side effects. Innovative discoveries in optogenetics and bioengineering present opportunities to continually evolve this technology into the future, enhancing spatial selectivity of neuronal activation in the cochlear nucleus and preventing side effects through reduction in activation of non-target neuronal circuitry. These advances will improve surgical planning and ultimately improve patients' audiological capabilities. ABI research has rapidly increased in the 21st century and applications of this technology are likely to continually evolve. Herein, we aim to characterize ongoing clinical, basic science, and bioengineering advances in ABIs and discuss future directions of this technology.

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Introduction

The first auditory brainstem implant (ABI) was developed at the House Ear Institute in 1979 as a single-channel implant for patients with neurofibromatosis type 2 (NF2).¹ Since that time, it has become an FDA-approved multichannel device, and the most commonly implanted surface stimulator of the central nervous system, with well over 1000 placed worldwide.

Analogous to the widely successful and popularly used cochlear implant (CI), the ABI is a neuroprosthetic device that can provide hearing perception to deaf patients. Unlike the CI, which electrically simulates first order auditory neurons in the cochlea (spiral ganglion neurons), the ABI bypasses the inner ear and directly stimulates second order neurons of the cochlear nucleus (Fig. 1).² This type of stimulation can provide auditory rehabilitation to patients who are not CI candidates, or those who have retrocochlear deafness such as patients with NF2. The majority of NF2 ABI users derive meaningful sound perception that aids in lip reading, and a small portion enjoy open set word intelligibility.^{3–6} These outcomes for ABI users remain modest as compared to CI users, who often achieve open set speech perception.

While the ABI is historically used in the NF2 population, several recent studies have explored the efficacy of the ABI in cases of retrocochlear deafness caused by non-tumor etiologies (e.g. cochlear or cochlear nerve aplasia, cochlear ossification), with encouraging preliminary results.^{7,8} The ABI is also being investigated as a treatment option for other conditions such as intractable tinnitus.^{9,10} After decades of stagnation in the basic implant design, the ABI is poised to advance through the integration of surgical navigation for optimizing array position, studies of conformable electrode arrays, and the use of optogenetics. The aim of this review is to highlight recent research advances in ABIs and to discuss future directions.

Methods

A literature review was conducted on PubMed, EMBASE, and [Clinicaltrials.gov](https://www.clinicaltrials.gov) of all relevant literature pertaining to

auditory brainstem implants from database inception through November 2020. A systematic title and abstract review was conducted by the authors for relevant literature pertaining to clinical and scientific advancements in auditory brainstem implant technology. Emphasis was directed towards the few systematic reviews and meta-analyses that were available, although various types of published studies were included. In addition, recent published work and ongoing basic science projects being conducted by the Massachusetts Eye and Ear Infirmary and the École Polytechnique Fédérale de Lausanne in Switzerland were included in the discussion.

Results and discussion

ABI clinical outcomes – NF2

Currently, the primary use of the ABI is to provide hearing perception to patients with NF2. These patients have multiple central nervous system tumors, including bilateral vestibular schwannomas, and can be deafened during tumor growth or management with radiation or surgery. In this population, the ABI is the most reasonable hearing rehabilitation option rather than the cochlear implant (unless the cochlear nerve is anatomically preserved). At this time, speech comprehension in ABI-implanted patients has not reached the level of improvement seen in CI users, and ABI patients tend to have a higher incidence of side effects. Additionally, rates of achieving open set speech awareness are relatively low overall for ABI patients, with most only achieving environmental sound awareness.¹¹ Nonetheless, ABIs have recently demonstrated improved efficacy for certain speech parameters in adult NF2 patients and has been instrumental in improving communication for some. A systematic review examining longitudinal hearing outcomes in adult ABI-implanted patients with NF2 determined that ABI use improves hearing more than lip reading alone and demonstrated improvement in parameters such as consonant comprehension and sentence comprehension. There were larger improvements in vowel comprehension over consonant comprehension and word comprehension over sentence comprehension.⁵

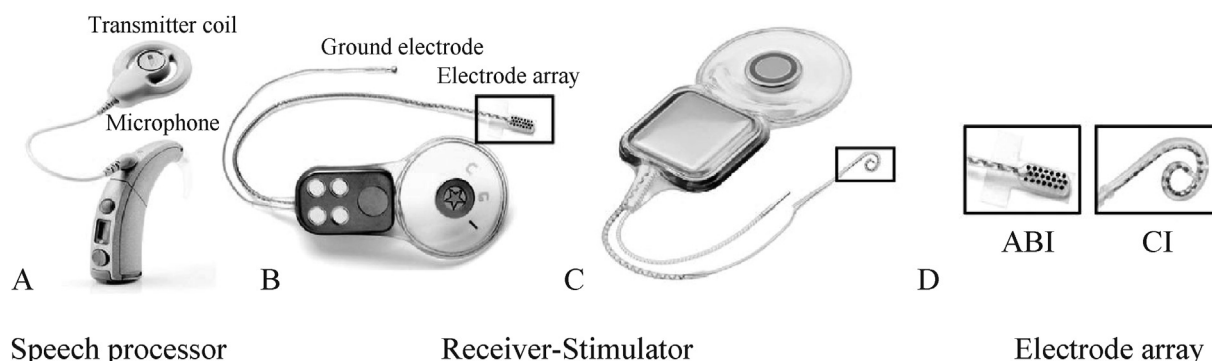


Fig. 1 Auditory brainstem implant (ABI) is a modified cochlear implant A: External device consists of microphone and sound processor; B–C: Receiver-stimulator connected to electrode array which is placed on cochlear nucleus through a posterior fossa craniotomy approach; D: ABI surface array, with 21 electrode contacts (0.7 mm diameter, left), Modiolar-hugging CI array with 22 half-banded contacts is shown for comparison (Courtesy of Cochlear Ltd, Macquarie University, Sydney, Australia, with permission).

ABI clinical outcomes – non-NF2, pediatric indications

There has been a recent burgeoning interest in the applications of ABI technology in non-NF2 patients. Initial studies have demonstrated improved outcomes in non-NF2 patients over those with NF2, with a significant percentage achieving open set perception and outcomes comparable to CI users.¹² There has been an increase in ongoing clinical trials in this area, especially in pediatric patients with cochlear ossification, bilateral cochlear nerve deficiency and aplasia. Several centers in the US (Massachusetts Eye and Ear Infirmary, University of North Carolina—Chapel Hill, New York University, and the Los Angeles Pediatric ABI Research team) have conducted pediatric ABI studies.¹³

Hearing outcomes in pediatric ABI patients are variable, with some pediatric user demonstrating some discrimination of speech sounds.¹⁴ Other studies have shown development of environmental sound awareness in a closed environment in ABI-implanted prelingually deaf children, but showed no development of open-set speech perception three years post-implantation.¹⁵ These outcomes remain modest compared to the typical improvement seen following CI implantation. The reasons for this difference are multifactorial and not completely understood. Recently, a long term follow-up study of 30 pediatric ABI patients found that children who received an ABI before age 3 performed better on auditory perception testing and had higher speech intelligibility scores as compared to children implanted over 3 years of age.¹⁶ The largest study to date examining bimodal stimulation was done in 12 pediatric patients with CI and contralateral ABI for pontocerebellar hypoplasia, and found that auditory perception scores, MAIS scores, pattern perception, and word recognition scores were all significantly higher than CI-only or ABI-only conditions in these patients.¹⁷

In the past, there had been few studies examining the growth and subsequent language development of pediatric ABI patients. Excitingly, recent literature has shown improvements in both nonverbal communication and oral language development following ABI implantation. In a study by Faes and Gillis, two pediatric patients with ABI and congenital hearing loss demonstrated improvements in lexical development with increasing implant usage. The authors concluded that there was an overall positive effect of ABI on spoken language development in these patients.¹⁸ In another small study, 7 out of 10 ABI-implanted children with prelingual deafness secondary to bilateral cochlear malformations or cochlear nerve aplasia developed receptive language outcomes and expressive language skills comparable to congenitally deaf children implanted with a CI at similar ages with additional comparable disabilities.¹⁹

Hearing loss has a significant impact on quality of life. As such, the ABI has the potential to improve a patient's self-reliance, social interactions, and education. Even with varying levels of hearing benefit provided by ABI, parents overall reported improvements in their child's health-related quality of life.²⁰ Poor outcomes were often associated with cases with a background of additional comorbidities, including neurodevelopment delay.

The applications of ABIs in the deaf pediatric population is theoretically enhanced by the increased brain plasticity in this population and the absence of audiologic memory in prelingually deaf patients, allowing them to be prime candidates for central auditory development in concert with implanted ABIs.²¹ Additionally, implantation at an earlier age has been associated with enhanced auditory benefits also theorized to be secondary to increased neural plasticity at younger ages.⁸ Longer time with implantation and ABI rehabilitation has also been associated with increased audiological benefits, although this effect appears to level off after a few years post-implantation. Overall, auditory development is still delayed as compared to children with CI and normal hearing. There are still relatively few children who are able to achieve open-set speech perception and there is a need for further studies on longitudinal auditory and communicative development in children post-ABI implantation.

ABI clinical outcomes – tinnitus

ABIs are continually being revolutionized and the applications of this technology are likely to evolve in the future. Inherently, the goal of an ABI is to utilize differential activation of neuronal clusters to produce the perception of a desired auditory stimulus, the characteristics of which are still being elucidated. This principle has applications beyond purely sensorineural hearing loss. Tinnitus is a condition characterized by phantom noise or "ringing" perceived in one or both ears (or centrally) in the absence of external sound. Tinnitus is felt to be associated with underlying dysregulation between excitatory and inhibitory central neurons. Early studies have suggested the role of the dorsal cochlear nucleus (DCN) in tinnitus pathogenesis with improvements in tinnitus handicap questionnaires following ABI implantation.¹⁰ Additionally, a case study utilizing H₂¹⁵O-PET in an ABI-implanted patient may suggest that this improvement is secondary to partial peripheral auditory reafferentation that deactivates brain areas that act as tinnitus generators.²² Currently, a clinical trial is underway in Europe to determine the safety and efficacy of the ABI in the treatment of intractable unilateral tinnitus with ipsilateral severe hearing loss in a cohort of ten adults.⁹

ABI complications and management

Another important consideration in ABI placement is the non-insignificant rate of complications and the need for close adherence to follow-up appointments after implantation. Perioperative complications can include electrode migration, CSF leakage, wound infection, cranial nerve injuries, meningitis, hydrocephalus, headaches, balance difficulties, and hemorrhage.^{16,23} Rates of major and minor complications range are around 6% and 17%, which are comparable to complication rates with CIs. To date, there have been no reports of mortality associated with ABIs in the published literature. Non-auditory minor side effects thought to be secondary to aberrant stimulation are far more common and can include dizziness, somatic tingling, and cranial nerve stimulation. These side effects tend to

lessen over time and require close follow up with audiologists and adjustments in calibration and number of active electrodes. For this reason, adherence to post-operative care is a necessity in ABI patients to ensure continual audiological benefit while attempting to minimize deleterious side effects.

Recent advances in ABI technology

The main components of the ABI system, such as the external speech processor and receiver stimulator are similar to those of the CI and have seen improvements that mirror CI technology. The basic concept of the ABI and its multichannel surface array, however, have remained largely unchanged for several decades. The forefront of ABI technology research includes the integration of optogenetics, development of conformable electrode arrays, and correlation of ABI array position with clinical outcomes.²⁴

Optogenetics

Optogenetics utilizes genetically modified cells that express light sensitive channels (referred to as opsins) that allow modulation of neural activity with millisecond precision.²⁵ Optical stimulation can theoretically improve spatial selectivity to enhance specificity of neuronal activation, thus overcoming the traditional challenges of channel cross talk and current spread present with electrical stimulation (Fig. 2). In 2014, Klapoetke et al.²⁶

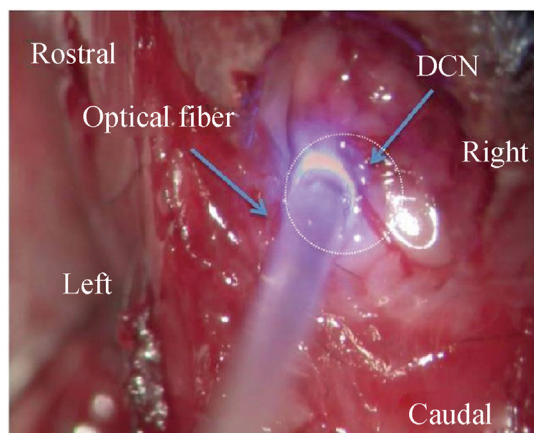


Fig. 2 Optogenetic stimulation of the dorsal cochlear nucleus (DCN) in mouse. Studies from our group have tested the feasibility of using light to elicit physiologic responses in the central auditory pathways. Following genetic modification of second order auditory neurons in DCN (using viral transduction) that express light sensitive proteins called opsins, an optical fiber was used to deliver radiant energy of a specific wavelength to elicit DCN neuronal activation as measured by downstream responses in inferior colliculus neurons. Image taken after left-sided suboccipital craniotomy, partial cerebellar aspiration, and exposure of DCN (Adapted from Hight AE, Kozin ED, Darrow K, et al. Superior temporal resolution of Chronos versus channelrhodopsin-2 in an optogenetic model of the auditory brainstem implant. *Hear Res.* 2015; 322:235–241. with permission).

described *Chronos*, a blue light channelrhodopsin derived from *Stigeoclonium helveticum* with faster kinetics than previously known channelrhodopsins. After viral mediated gene transfer was performed on the DCN, *Chronos* was shown to have higher synchrony of light evoked responses along the tonotopic axis in the inferior colliculus than channelrhodopsin 2, the prior most commonly used opsin.^{27,28} Recently, Chronos-ES/TS, which has improved plasma membrane trafficking, has allowed ultrafast optogenetic control of neurons.²⁹ Light delivery system technology has also been an area of development with direct applications to the ABI. The ability to utilize photonic stimulation using multichannel optrodes in neuronal activation has been demonstrated in animal models.¹⁸ Ultimately, further advances in light-based neural stimulation provide the opportunity for increased spatial resolution of ABIs and enhanced perceptual ability from auditory signaling.

Conformable ABI surface array

The clinical ABI has a stiff Silastic carrier with 21 electrode contacts. Although the array does bend, it does not conform and retains a flat and rigid configuration in the milieu of the lateral recess of the IVth ventricle, brainstem surface and cerebellum. The development of a conformable ABI electrode array has the potential to mitigate side effects such as pain, twitching, vagal responses, and dizziness seen in some ABI users. These effects are thought to be secondary to non-specific activation of neighboring neurons through aberrant electrical current and physical characteristics of the ABI paddle that are non-complementary to the 3-dimensional intricacy of the array–brain interface. Therefore, ABI array design more suited to selective neuronal activation and with better conformation to the curvilinear dorsal cochlear nucleus has been an important research focus by our research team. ABI prototypes using penetrating electrodes were unsuccessful in improving speech recognition compared to the standard surface electrodes and were eventually withdrawn from use.³⁰ Collaborative studies between Massachusetts Eye and Ear Infirmary and Professor Stephanie Lacour team at the École Polytechnique Fédérale de Lausanne in Switzerland have utilized the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT): polystyrene sulfonate (PSS) on electrode sites which demonstrated higher electrochemical stability and biocompatibility. This prototype was shown to improve ABI functionality and optimize stimulation.³¹ Recent work on surface stimulation of the DCN using microfabricated flexible electrode arrays with smaller diameter and increased density of electrodes has elucidated the neurophysiological properties of auditory processing. Guex et al.³² tested an improved array in animal models of ABI and showed that these conformable microarrays can provide more targeted and more evenly dispersed electrically evoked responses that may reduce side effects from aberrant electrical activity into surrounding regions. Recently, Vachicouras et al.³³ developed a novel soft ABI that improves the existing properties of current ABI design and has shown promise in a mouse model and human cadavers (Fig. 3). Advancements include (1) microstructured stretchable interconnects that allow improved elasticity and functionality with strain, (2)

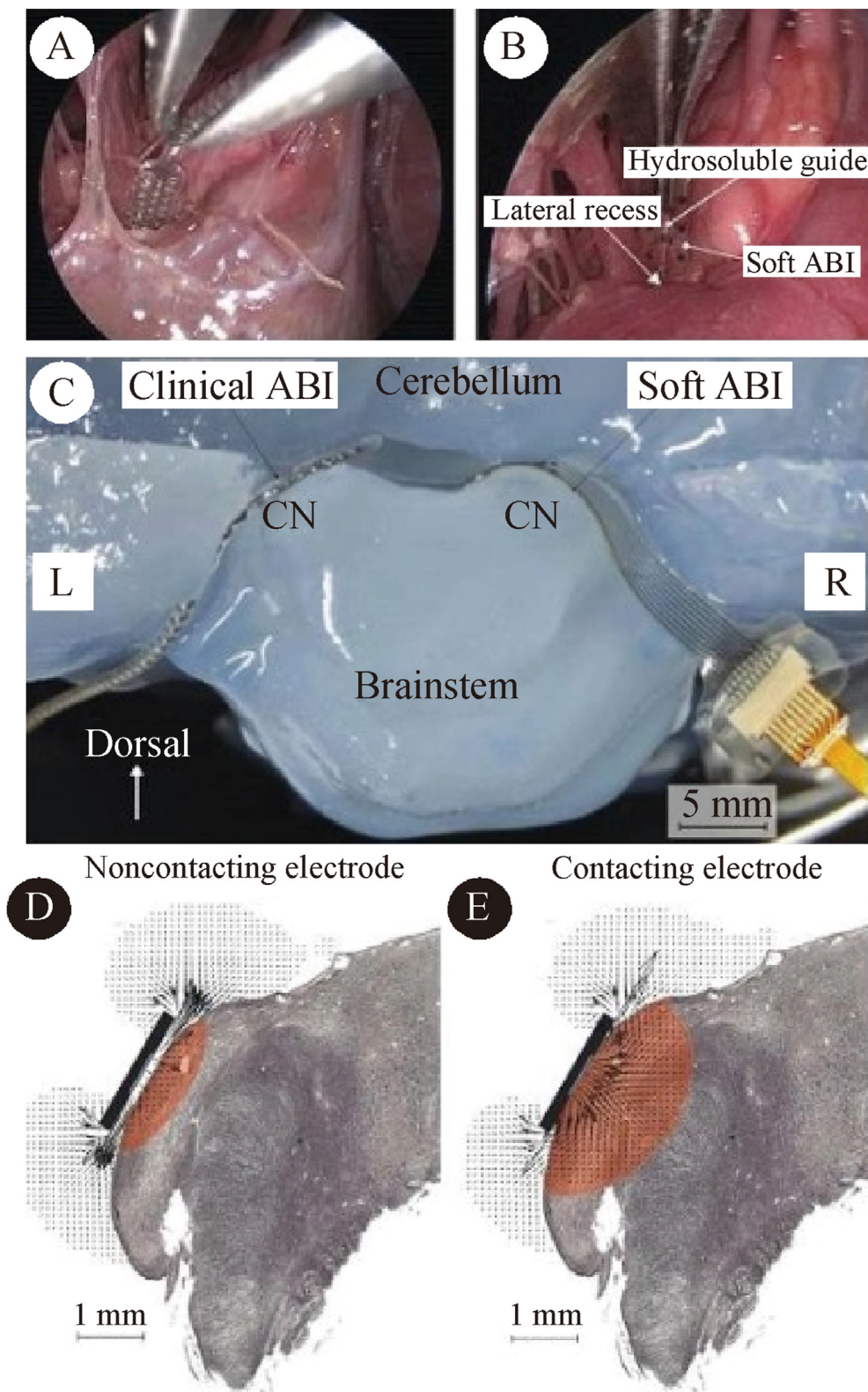


Fig. 3 A–B: Comparison of clinical ABI array (A) and novel soft ABI array (B) being inserted into the left lateral recess in a cadaveric model; C: Agarose model of human brainstem demonstrating conformability of our soft ABI array on the curvilinear surface of the right DCN; D–E: Schematic showing current density (black arrows) and estimated neural tissue activation (orange) showing a stiff ABI array (D) with poor contact on DCN and a soft ABI array (E) with good contact on DCN, activating a deeper portion of the cochlear nucleus (Adapted from Vachicouras N, Tarabichi O, Kanumuri V et al. Microstructured thin-film electrode technology enables proof of concept of scalable, soft auditory brainstem implants. *Sci Transl Med* 2019; 11. with permission).

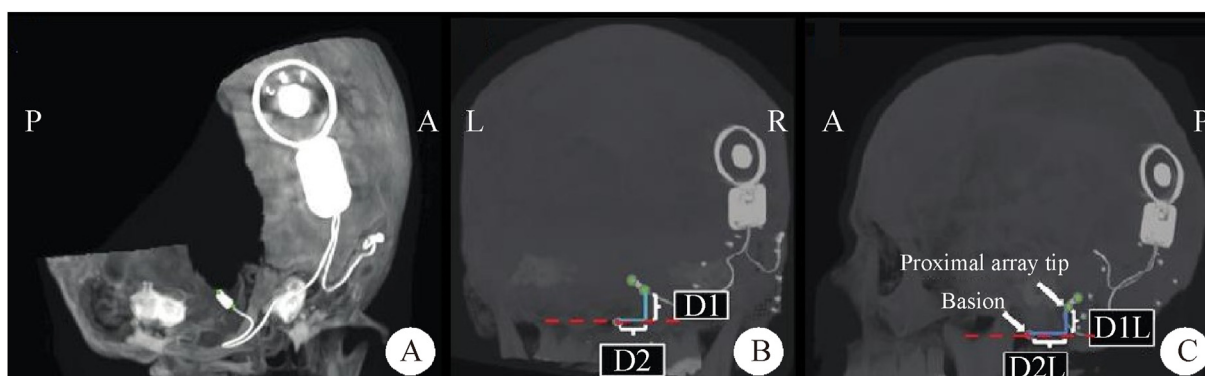


Fig. 4 Three-dimensional (3D) computed tomographic (CT) studies of ABI array position A: Volume rendering of 3D CT imaging from postoperative ABI patient using maximal intensity projection; B–C: Fixed bony skull base landmarks were used as reference points for quantitative measurements of ABI position from the posterior view (B) and lateral or sagittal views (C). A: anterior; P: posterior; L: left; R: right.

hydrosoluble mechanical guides that improve surgical placement of the array by allowing improved transitory stiffness, (3) flexible coatings with high electrochemical area that permit use of higher currents, and (4) decreased use of metal in electrodes which permit enhanced visualization of device position through the reduction of artifact on high resolution imaging modalities. Continued bioengineering of improved conformable arrays will continue to improve the pre-existing ABI design with subsequent improvement in stimulus localization.

Improving ABI implant placement

ABI placement is challenging due to a lack of distinguishing physical characteristics of the target nucleus and anatomical constraints that impede its visualization. The surgical approach for ABI placement is directed through the foramen of Luschka and into the lateral recess of the fourth ventricle, using the roots of cranial nerves VII and IX as surgical landmarks.³⁴ These challenges lead to variance in the placement of the electrode pad with respect to the cochlear nucleus. Far field electrically evoked auditory brainstem responses (eABR) are necessary to characterize auditory stimulatory patterns intraoperatively and adjust array positioning in real time.³⁵ Additionally, endoscopic visualization techniques can be employed to improve exposure and guide electrode placement.³⁶ There is an increasing interest in image-guided placement of arrays intra-operatively and exploring patient specific architecture of the cochlear nucleus to aid in surgical planning. A study by Barber et al³⁷ using three-dimensional multiplanar reconstruction of patient CT scans demonstrated that angle and location of array placement on the cochlear nucleus is often variable, which relates to differences in electrical thresholds and active electrodes (Fig. 4). This is thought to partially contribute to differences in clinical outcomes, although further characterization of the tonotopic organization of the cochlear nucleus is needed to further delineate relationships between array position and audiological outcomes. Recently, Diffusion Tensor Imaging (DTI) has been shown to have potential in more accurate localization of the cochlear nucleus and may assist in higher precision placement of the ABI array by mapping out white matter tracts.³⁸ There is a need for further research that combines

advanced MR and CT imaging to better tailor placement of ABI arrays and enhances tactical use of imaging at the time of ABI placement.

Conclusions

The clinical ABI has been instrumental in improving audiological rehabilitation in NF2 patients for many years. A new wave of research aims to improve ABI technology and expand its indications to non-NF2 groups, such as pediatric patients and adults with intractable tinnitus. Advances in bioengineering, imaging modalities, and basic science are continuing to transform ABI research and improve outcomes for ABI-implanted patients.

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Declaration of competing interest

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