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# Advancing audiology practice and knowledge at the World Congress of Audiology a comprehensive collection

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# Advancing audiology practice and knowledge at the World Congress of Audiology 2024: a comprehensive collection

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# Optical method to preserve residual hearing in patients receiving a cochlear implant

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**Introduction:** Worldwide, thousands of patients with severe to profound hearing loss restore their hearing with cochlear implant (CI) devices. Newer developments in electrode design and manufacturing and a better understanding of cochlear mechanics allow for conserving critical structures, often translating into serviceable residual hearing and improving device performance. Monitoring insertion speed and intraluminal pressure helps mitigate some of these challenges. However, the information becomes available after irreparable damage has occurred.

**Methods:** We developed and tested a high-resolution optical system to navigate the intricate anatomy of the cochlea during electrode insertion. The miniaturized optical system was integrated in conventional cochlear implants electrode arrays and custom-made cochlear probes. Electrode insertion were conducted in eight cadaveric human temporal bones and video recordings were acquired. Micro-computed tomography (μCT) scans were performed to evaluate the position of the modified electrode arrays.

**Results:** Full insertions of the modified CI electrode were successfully conducted and verified by μCT scans. Video recordings of the cochlear structures visible in scala tympani were acquired, and no scala migration was detected.

**Discussion:** Surgeons can now follow the CI electrode's path during its insertion and reduce cochlear damage through early interventions and steering of the CI electrode. Our device will be compatible with robotic platforms that are already available to insert these electrodes.

KEYWORDS

**cochlear implants, hearing loss, cochlear implantation, hearing preservation, cochlear endoscopy**

## 1 Introduction

Hearing loss is a global health crisis. According to the World Health Organization (WHO), over 1.5 billion people globally suffer from hearing loss, disabling 466 million of them (Olusanya et al., 2019; World Health Organization, 2021). The same reports suggest that the numbers will almost double by 2050 (Olusanya et al., 2019; World Health Organization, 2021). Unaddressed hearing loss costs the global economy approximately US$980 billion annually (World Health Organization, 2021). Furthermore, a recent meta-analysis suggested that hearing is a modifiable risk factor for dementia (Loughrey, 2022; Lin et al., 2023; Cantuaria et al., 2024) and that treating hearing loss will decrease the

risk of long-term cognitive decline by 19% (Yeo et al., 2023). While mild and moderate hearing loss is treated with hearing aids, ∼30 million severely to profoundly deaf patients could benefit from a cochlear implant (CI) to restore some of their hearing (World Health Organization, 2021). Of those who could benefit from a CI, as of 2024, ∼1 million people have received a CI, with 60,000 additional individuals implanted annually (NIDCD, 2021).

While CIs are one of the most successful neural prosthetics, the surgery for electrode implantation is not without risks of further damaging the inner ear's delicate structures and worsening hearing loss (Miranda et al., 2014; De Seta et al., 2017; Starovoyt et al., 2023). The inner ear is exposed during the CI surgery by drilling a narrow passage to the middle ear. The CI electrode is then typically placed into the scala tympani, a fluid-filled compartment of the inner ear. The insertion occurs through either the natural opening in the cochlea, the round window (RW), or a cochleostomy, an artificial inner ear opening. The CI electrode insertion reaches a critical point after 8–10 mm. At this location, the scala tympani abruptly changes its radius of curvature (1.6–2.6 mm) and turns toward the apex. Significant contact between the CI electrode and the cochlear wall occurs and can result in an abrupt increase in insertion force, leading to electrode buckling, potential tissue damage, and basilar membrane penetration (Eshraghi, 2006). Damage and possible misalignment of the CI electrode trigger inflammation, leading to subsequent loss of residual hearing in up to 32% of implantations (Hoskison et al., 2017). This percentage might even be greater, as suggested by studies in cadaveric human temporal bones, which have shown damage in up to 40% of the electrode insertions (Eshraghi et al., 2003; Mirsalehi et al., 2017). Therefore, preserving residual hearing is crucial as it can enhance the CI user's performance and improve the recipient's speech comprehension, music appreciation, and overall quality of life.

That efforts for atraumatic electrode insertion have surged is not surprising, and the CI industry, surgeons, and researchers have explored changes in the device and CI implantation surgery to maximize hearing preservation. The first debate was about the correct location for the opening for the CI electrode. Over time, two methods for making a cochleostomy have been established: the RW and an antero-inferior cochleostomy in the basal cochlear turn (Sikka et al., 2017; Avasarala et al., 2022). Several studies on the outcomes of electrode insertion on cochlear damage and hearing preservation during CI surgery did not identify a definitive advantage of the electrode insertion through a cochleostomy or RW (Havenith et al., 2013; Rajput and Nilakantan, 2019). Different from previous studies, Santa Maria et al. (2014) reported a benefit in hearing preservation using the cochleostomy method, whereas better hearing preservation was reported after using the RW approach (Causon et al., 2015; Avasarala et al., 2022).

Critical to the success of CI surgeries is also the cochlear electrode array, which is surgically inserted into the cochlea to stimulate the auditory nerve electrically. The precise placement of the electrode is essential for activating the spiral ganglion neurons, which are responsible for transmitting sound signals to the brain. To enhance hearing restoration outcomes, maintaining the structural integrity of the inner ear components during this insertion procedure is necessary. These components include the basilar membrane, which is important for sound frequency discrimination; the modiolus, the central core of the cochlea that contains the spiral ganglion neurons; and the cochlear wall, which preserves the cochlea's internal environment.

Over the last two decades, efforts have been made to optimize the electrode array materials and their physical properties, including length, diameter, and compliance. The longest cochlear electrodes measure about 31 mm and are designed to be inserted as far as possible into a spiral structure with about 2.5 turns (Jagt et al., 2017).

Another approach to avoid cochlear damage during the surgery is monitoring the insertion process and taking preventative measures before the damage occurs. While various monitoring techniques exist to support the insertion process, such as impedance and insertion force measurements (Majdani et al., 2010; Miroir et al., 2012; Tan et al., 2013; Dong et al., 2021; Hafeez et al., 2021), cone-beam computed tomography (Bassiouni et al., 2014; Saeed et al., 2014), fluoroscopy (Perazzini et al., 2021), and electrocochleography recordings (O'Connell et al., 2017; Giardina et al., 2019), surgeons primarily rely on tactile feedback to establish the insertion trajectory and control the insertion process. This method can only detect increased resistance after the electrode contacts the cochlear wall, which potentially causes tissue trauma.

Innovative solutions have been explored, including robotic insertions, to achieve better control over the speed and force of electrode insertion into the cochlea (Kaufmann et al., 2020; Panara et al., 2021; De Seta et al., 2022), and optical techniques, such as optical coherence tomography (OCT) imaging, to determine the path and location of the advancing CI electrode (Starovoyt et al., 2022). Despite the potential benefits of OCT, the method faces certain constraints. Navigating the cochlear turns requires flexible waveguides with low propagation and bending losses. Without them, the effectiveness of OCT is limited to the initial few millimeters during the electrode insertion.

With the advent of nanocameras, new opportunities have arisen. Miniaturized cameras can provide real-time surgical field visualization, which is invaluable for surgeons when inserting CI electrodes. The further miniaturization of cameras and the progress in imaging technology seen in other fields (Kaur et al., 2020; Zhang et al., 2021; Kim et al., 2022; Duan et al., 2023; Lavenir et al., 2023) have enabled us to develop high-resolution endoscopic-like systems to navigate the intricate anatomy of the cochlea. Such a system not only assists in precise electrode insertion but also aids in identifying and avoiding potential obstacles, thereby reducing the risk of damage to delicate cochlear structures. These nanocamera systems could be further integrated with robotic platforms to enhance the procedure's accuracy and safety. Moreover, this optical method can be used to evaluate the health of the cochlea, particularly the basilar membrane, before and after implantation; determine the optimal insertion depth and trajectory; and potentially foresee and avert postoperative complications.

In the present study, we describe an optical system that can be integrated with a cochlear electrode array, providing visual real-time monitoring of the cochlea inner structures during the insertion procedure (Cury and Richter, 2023).

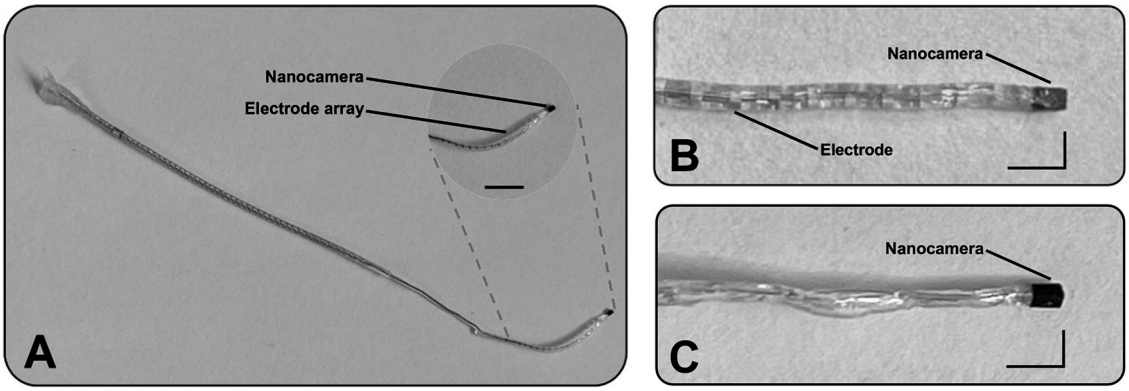


FIGURE 1
Illustration of two designs incorporating the optical system at their distal part. **(A)** The first prototype consists of a cochlear implant electrode array (J1–HiRes design from Advanced Bionics) with a nanocamera at its tip. The scale bar represents 5 mm. **(B)** Magnified view of the same prototype's tip. **(C)** Magnified view of the second design. Scale L-bars: vertical and horizontal segments represent 1 and 2 mm, respectively.

# 2 Materials and methods

## 2.1 Optical system

The optical system incorporates a nanocamera, an illumination source, and an image postprocessing module. The acquired images are then sent to a computer for display. The nanocamera used in our study is the OVM6948 (Omnivision, Santa Clara, California, United States). The OVM6948 is currently the smallest commercially available camera in the world, with an integrated image array, signal processing, timing, and control circuitry all housed on a single integrated circuit. Its current dimensions are remarkably compact, $0.65 \times 0.65\,mm^2$, with a z height of 1.16 mm, and it offers a resolution of $200 \times 200$ pixels. The camera can capture high-quality images and video up to 30 frames per second. Despite its miniature size, the image sensor incorporates advanced imaging technology, including microlenses. Furthermore, the camera chip is designed to be power-efficient, boasting a low power consumption of just 25 mW.

To deliver light into the cochlea, we explored two micro-LED models emitting yellow light ($\lambda = 591$ nm), each with a different size. The first is model 0402 from Evemodel (China), and measures $1.0 \times 0.5 \times 0.4\,mm^3$. The second model, the Nanopoint 0201 by SunLED, (California, USA), measures $0.65 \times 0.35 \times 0.20\,mm^3$ and is currently the smallest micro-LED available on the market.

The module for postprocessing the images captured by the nanocamera OVM6948 comprises two main components: a video bridge chip, specifically the OV426 (Omnivision, California, USA), and a digital signal processor (DSP). The OV426 is mainly chosen for its compatibility with the OVM6948, offering integrated analog-to-digital conversion and a digital video parallel output. This chip converts the camera's analog video signals into a digital format. After this initial processing, the DSP further processes the digital signals. The resulting video data, now fully processed, are transmitted to the computer via a USB connection. For the final step, the data are visualized using Amcap software, allowing for a detailed examination of the images captured by the nanocamera.

## 2.2 Integration of nanocameras in CI electrode arrays and development of cochlear probes

This study modified CI electrode arrays (J1–HiRes design, Advanced Bionics, California, United States) and developed custom-made cochlear probes. The CI arrays and the custom probes were equipped with the OVM6948 nanocamera at their tips (Figure 1). To attach the camera to the tip of the electrode, we removed the three most distal ring electrodes of the CI arrays, reducing their length by ~3 mm. The wires previously used for these electrodes and the ground wire were repurposed to connect the nanocamera using conductive epoxy and further secured with ultraviolet (UV)–curable polymer OrmoComp® (Kayaku Advanced Materials, Westborough, Massachussets, United States).

For the custom-made cochlear probes, specifically designed to capture video within the cochlea, we employed four silver-coated wires with an inner diameter of approximately 76 µm and a total diameter of approximately 140 µm (A–M Systems, USA) to establish the nanocamera connection. These wires were secured for consistency using the same conductive epoxy and UV-curable polymer. Once connected, the assembly was encapsulated in silicone to replicate the external structure of a conventional CI electrode, although without the ring electrodes (Figure 1C).

The light source for the nanocamera was strategically attached laterally to the optical system. To ensure the design's compactness, the placement was such that the smaller dimension of the micro-LED contributed to a minimal increase in the overall width of the nanocamera's assembly. To secure the micro-LEDs firmly and maintain the assembly's integrity, we used UV-curable polymer OrmoComp®. Each prototype (modified CI electrode array and cochlear probe) utilized one version of micro-LED at a time rather than both versions simultaneously due to the limited space in the cochlea.

## 2.3 Testing of the nanocamera

To evaluate the performance of the optical system, we determined three parameters: spatial resolution, spatial frequency response, and optical distortion. To assess the spatial resolution, we captured an image on paper featuring a transition from black to white. We analyzed the intensity profile along a black-to-white transition using the ImageJ software. The camera system's resolution was determined by a single value: the distance of the 10%−90% pixel value along a line along the black–white transition (Smith, 1997). The results, given in image pixel counts, were converted into micrometers using the nanocamera's pixel size (1.75 μm; Omnivision, USA).

Using the edge response, we calculated the modulation transfer function (MTF; Smith, 1997) and quantified the system's ability to preserve detail across various spatial frequencies. This process involved deriving the line spread function (LSF) from the edge response, followed by a Fourier transform on the LSF.

To analyze spherical distortions, we captured an image of a piece of 1-mm graph paper and compared it with the same image distortion-free as a reference. The distortion was quantified as the relative change of the distance from the image center to the distorted and corrected cross section of the graph paper lines close to the edge of the image taken (McReynolds and Blythe, 2005).

## 2.4 Cochlear samples and video recordings

In this study, we randomly selected eight cadaveric human temporal bones to evaluate the insertion of our modified CI electrodes and custom cochlear probes. We used human cadaveric temporal bones without known congenital or acquired malformations or a history of chronic otologic disease. The preparation of the temporal bone consisted of a cortical mastoidectomy with posterior tympanotomy, the exposure of the RW, and the removal of the RW overhang. After the RW niche was exposed, the RW membrane was removed with a right-angle pick. The electrode was inserted through the RW. The nanocamera confirmed visual placement as well as depth of insertion. Critical structures were identified and preserved through video feedback. The insertions were conducted by a neurotologist at the University of Missouri.

## 2.5 Micro-computed tomography imaging

Micro-computed tomography (μCT) scans were conducted to evaluate the position of the CI array, with the nanocamera attached, within the human cadaveric temporal bone. Each temporal bone was fixed, and the modified CI array was carefully inserted into the cochlea following a standard surgical procedure (Section 2.4). After the insertion, μCT scans were captured on a Siemens Inveon micro-positron emission tomography/computed tomography (PET/CT) system (Malvern, USA). The section of the temporal bone analyzed had dimensions of 66 × 66 × 52 $mm^3$. From this section, 755 image slices were obtained, each with a separation of approximately 70 μm. The acquired data were reconstructed using the ImageJ software to generate two- and three-dimensional visualizations of the electrode's placement with the nanocamera within the cochlea. The scans were analyzed to assess the positioning, depth, and potential damage caused by the electrode insertion.

## 2.6 Statement of ethics

The study protocol was in accordance with the ethical standards established in the 1964/2013 (7th revision) Declaration of Helsinki for research involving human subjects. Human cadavers were donated for teaching and research purposes. Human temporal bones were collected at the end of an anatomy class for medical students. Before their use in research, the temporal bones were irreversibly stripped of all identifiers, thus making it impossible to link the biospecimens to their sources. After the completion of the study, the specimens were moved back to the gross anatomical laboratory to be cremated. Human biospecimens were collected, stored, used, shared, and disposed of according to the informed consent signed by the subject or under a waiver of informed consent granted by the independent ethical review body, the institutional review board, or the ethics committee in accordance with 45 CFR 46–Protection of Human Subjects.

# 3 Results

## 3.1 Prototyping

We designed two prototypes incorporating the world's smallest commercially available camera. The first design involved CI electrode arrays (J1–HiRes design) from Advanced Bionic. The optical system was integrated into the electrodes' tips (Figures 1A, B). The extended portion of the array is embedded with biocompatible silicone material to ensure compatibility and integration, and it matches the nanocamera packaging. The second design is a slim probe with the nanocamera at its tip (Figure 1C). This prototype mimics a CI array without its contacts. It is designed to "probe" the cochlea before CI implantation by acquiring real-time video footage of the human cochlea during its insertion.

## 3.2 Performance of the nanocamera

The spatial resolution, determined with the edge response method from a color step of black to white, was ∼5.25 μm, corresponding to ∼3 pixels (Figures 2A, B). From this transition, we determined the MTF, illustrated in Figure 2D. The MTF evaluates how effectively an optical system can transfer detail and contrast from the scene to the image across different spatial frequencies. An MTF value close to 1 indicates that the system almost perfectly preserves the contrast and detail for the specific spatial frequency, reflecting an ideal or nearly ideal performance in transferring the original scene's detail and contrast to the image. As can be seen in the graph, lines per pixel (lp/pp) quantifies the spatial frequency in terms of the number of distinguishable line pairs (one black and one white line) per pixel. For example, a value of 0.15

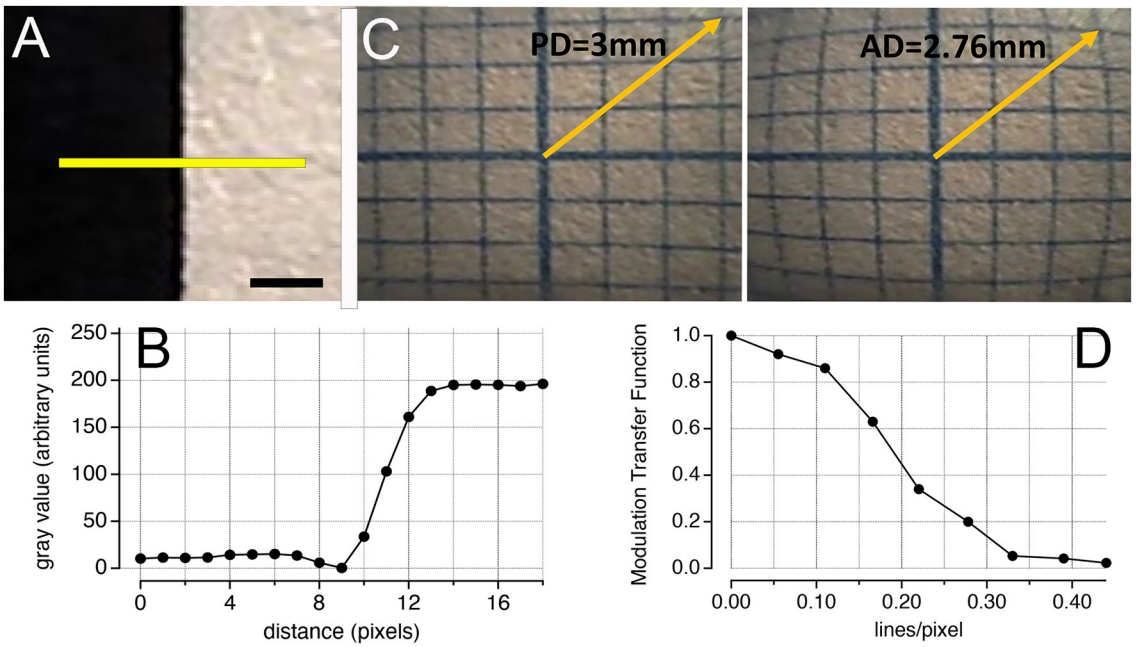


FIGURE 2
Performance of the nanocamera. **(A)** Image of a black–white transition. The yellow line was used to analyze the pixel profile using the software ImageJ. Scale bar: 0.5 mm. **(B)** Shows the pixel values along the transition in **(A)**. Using the edge response method, the spatial resolution was approximately 3 pixels. **(C)** Modulation transfer function obtained from **(B)**. **(D)** Barrel distortion of an image acquired at a 2-mm distance from the 1-mm graph paper. Comparing the distortion with the same image distortion-free (corrected by software), the effect was quantified at ~8.5%. PD, predictive distance; AD, actual distance.

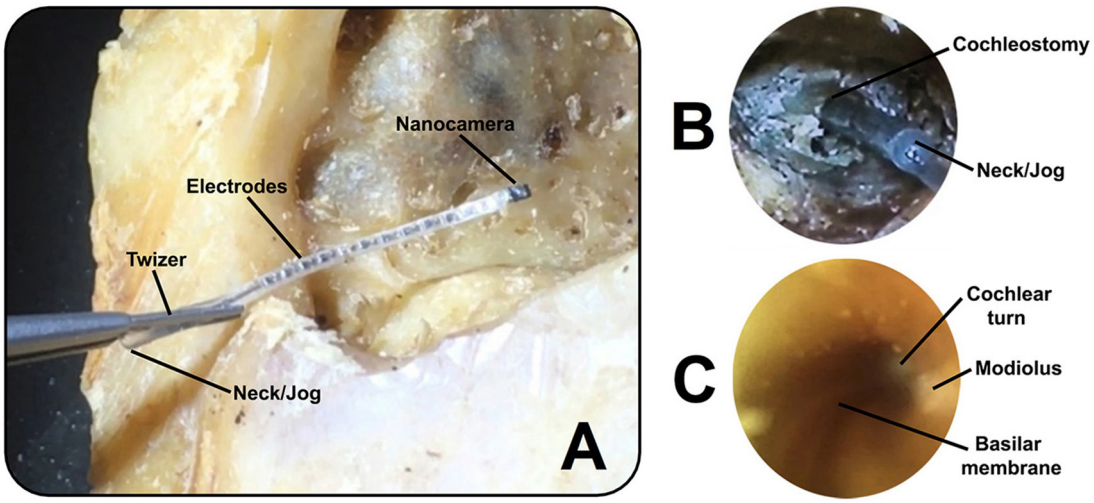


FIGURE 3
**(A)** Cochlear implant electrode array (first prototype) with the nanocamera before insertion into the human cochlea. **(B)** Full insertion of the modified cochlear implant electrode shown in **(A)** into the scala tympani, achieving an insertion depth of approximately 22 mm. **(C)** Image captured within the cochlea with the cochlear probe (second prototype) during insertion. The basilar membrane can be seen as a snail line along the conduit, with views of the modiolus and cochlear turn.

lp/pp implies that each line pair spans ~6.67 pixels, offering insight into the system's resolution capabilities. At this spatial frequency, the MTF value is 0.7, indicating that the system preserves 70% of the contrast and detail from the original scene.

When analyzing the image of the 1-mm graph paper, we identified barrel distortion (Figure 2D). By quantifying the displacement of points from their expected positions in the distortion-free image, we determined that the effect of the distortion is ~8.5%.

We fully inserted the CI electrode arrays with the nanocamera (first prototype; Figure 3A) in eight cadaveric human temporal bones (Figure 3B). Utilizing the second design, we captured

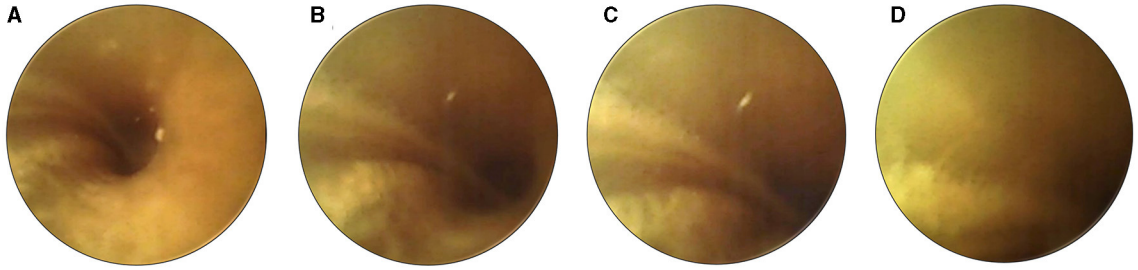


FIGURE 4
Sequential images illustrate the careful maneuvering of the cochlear probe (second prototype) during insertion. As the device approaches proximity with the cochlear wall **(A–D)**, the surgeon halts the insertion (as seen in image **D**). This pause allows necessary adjustments to the probe's position to prevent or minimize potential damage.

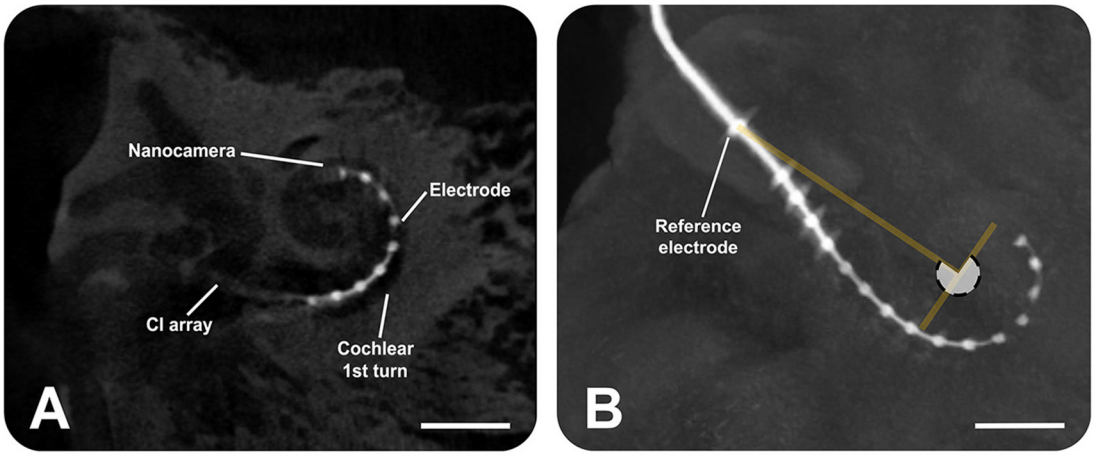


FIGURE 5
Micro-computed tomography scans show the insertion of the cochlear implant electrode array (Advanced Bionics) equipped with the nanocamera into the human cochlea. **(A)** Sagittal slice, providing a cross-sectional view. **(B)** Sagittal view from the three-dimensional volume rendering of the human temporal bone, highlighting the electrode. The angular insertion depth is ~270° as the white transparent circle shows. The scale bars represent 4 mm.

real-time video footage during the probe's insertion into the scala tympani of human cadaveric ears. Critical structures that can be seen include the basilar membrane, the modiolus, and the cochlear wall (Figure 3C). Results showed no malformations of the cochlea in the specimens analyzed.

The real-time video footage enabled the surgeon to navigate the slim probe in the cochlear turn, reducing its interaction with the delicate inner ear structures (Figures 4A–D). The surgeon could immediately stop inserting the probe when its tip approached the cochlear wall, modiolus, or any other sensitive structure (Figure 4D).

### 3.3 μCT imaging

After the CI electrode array, equipped with the nanocamera, was inserted in the cochlea, μCT scans confirmed its positioning after insertion (Figure 5). The angular insertion depth is approximately 270° (Figure 5B).

## 4 Discussion

This article introduces a novel optical system that can be integrated into a CI electrode array to monitor its insertion process. The aim is to minimize surgical damage to the ear and prevent further hearing loss, which could adversely affect the performance of CI users. Benchtop evaluations confirm that integrating a nanocamera into conventional CI electrodes and cochlear probes does not compromise their compliance during insertion. This outcome is attributed to the selection of wire diameters used to connect the nanocamera, which falls within the range of those found in conventional CI array electrodes. Video recordings of the cochlear structures visible in scala tympani were acquired, and no scala migration was detected. Full insertions of the CI electrode with the nanocamera into cadaveric human temporal bones were successfully conducted and verified by high-resolution μCT scans.

The nanocamera implemented in our study does not have as many pixels as other miniaturized cameras on the market with a higher pixel count; however, that this optical system is

the only one that fits into the cochlea and beyond the first turn is important to highlight. Given the cochlea's limited size, the 200 × 200 pixels employed on a small field of view enable detailed visualization of the inner ear's structures, as shown in Figures 3C, 4. Considering the performance of the nanocamera, the spatial resolution, determined using the edge response method, was ∼5 μm, which translates to ∼3 pixels. The minimum distance between two objects, at which the nanocamera can distinguish them as separate entities, is ∼5 μm. When we translate this spatial resolution into the context of the MTF plot (Figure 2C), at a spatial frequency of 0.32 lines per pixel (lp/pp), we are looking at a scenario in which a white-and-black line pattern spans a 3-pixel distance. At this spatial frequency, the MTF significantly decreases to approximately 0.05. This reduction in MTF at 0.32 lp/pp—a frequency corresponding to the maximum spatial resolution—highlights a critical aspect of optical system performance: as we approach the limit of what the system can resolve, the contrast between closely spaced details is substantially compromised.

Regarding the optical effect from Figure 2C, we found a barrel distortion, characterized by image magnification decreasing with distance from the optical axis, causing objects to appear bowed outward toward the edges of the image. This phenomenon typically occurs when the magnifying power of the lens decreases too quickly with distance from its center. In the context of our nanocamera, this distortion is a consequence of the miniaturized lens design. Although this optical effect can introduce alterations, postprocessing the image further can improve its visualization.

With the imaging system, surgeons can now follow the CI electrode's path during its insertion and reduce cochlear damage through early interventions and steering of the CI electrode. This technology not only aids in precise placement during surgery but also improves presurgical planning by offering a detailed view of the cochlea's internal structure. Furthermore, it allows the electrode's final depth and positioning to be carefully evaluated. It is critical to assess the potential for electrode migration over the implant's lifespan and ensure optimal orientation toward the spiral ganglion neurons. At the recent Conference on Implantable Auditory Prostheses in California, the benefits of robotic CI electrode insertion over manual insertion have been discussed. Robotic insertion holds the promise of inflicting significantly less damage to the cochlea. However, a salient challenge for these robotic systems centers on guiding the insertion speed and providing feedback on the insertion process. Historically, anchored in force measurements, feedback could experience a paradigm shift with visual feedback through advanced camera systems, providing surgeons or the robot with a more intuitive and responsive insertion process.

Integrating micro-LEDs with the nanocamera at the device's tip presents specific challenges regarding illumination. Initially, that the nanocamera alone, without any micro-LED attached, measures 0.65 × 0.65 mm is important to note. When the micro-LED from Evemodel is incorporated alongside the CI array and cochlear probe, the resultant thickness at the device's tip increases to ∼1.1 mm. In contrast, the smaller nano-point micro-LED reduces the thickness to ∼0.85 mm compared to the larger light source model. This reduction is crucial, considering the cochlea's confined space and the fact that any increase in size at the nanocamera's location can significantly impact the ease of insertion, particularly around the cochlea's first turn, where space is most restricted. A clear distinction emerges when examining the tip sizes of our modified CI arrays and cochlear probes against those of standard CI electrodes. Standard CI arrays have a smaller thickness at their tip (Shin et al., 2021). For example, Med-El (Austria) features a tip size of 0.4 × 0.5 $mm^2$, Cochlear (Australia) at 0.3 mm, Todoc (South Korea) at 0.35 × 0.45 $mm^2$, and Advanced Bionics (same electrode used) at 0.4 mm. Compared to these, our prototypes present a larger tip profile due to the nanocamera size and micro-LED, even after successful full insertions (Figure 3B), confirmed with μCT scans (Figure 5), and no scala migration observed in video acquisitions. This highlights the need for further progress in our designs.

Addressing the challenges presented by integrating micro-LEDs with the nanocamera, waveguides offer a valuable alternative for illumination in the cochlea. These waveguides can reduce the size-related issues associated with micro-LEDs, providing a more compact light delivery system. The success of these waveguides depends on their mechanical and optical properties, such as propagation and bending losses, which are crucial for effective performance in the cochlea's confined space (Kampasi et al., 2021). Developing waveguides that meet these requirements is vital to enhance the design for easier insertion and improved functionality within the cochlea. The polymer OrmoComp (Kayaku Advanced Materials, Westborough, USA) emerged as a promising solution. This polymer is an ormocer, a material that merges the qualities of organic polymers with inorganic ceramics. Upon UV curing, it exhibits properties similar to glass, reflecting the durability and stability of ceramics yet maintaining the flexibility of organic materials. This combination results in a medium that is both thermally and chemically stable and optically highly transparent and is suitable for light transmission across visible and near-infrared wavelengths (Heinrich, 2021). Furthermore, its biocompatibility makes it a promising material for medical applications (Schizas and Karalekas, 2011).

Given these promising attributes, we are currently developing and characterizing waveguides with OrmoComp as the core, featuring a 100-μm inner diameter and a 16-μm thickness polyimide cladding. Alternative cladding materials, such as the fluoropolymer CYTOP (AGC Inc. Chemicals Company, Tokyo, Japan) and UV-curable resins, are also being explored (Evertz et al., 2021). As our research progresses, we are focusing on critical aspects, such as the waveguides' resistance to photobleaching and their stability in electrolytic environments resembling cochlear perilymph, and evaluating their long-term performance and biocompatibility through studies in animal models. These investigations are crucial in comprehensively determining the suitability of waveguides for clinical applications in which a miniaturized means of light delivery is required, as in our study.

While the current design of our optical system has enabled successful full insertions into human temporal bones, there is still potential for further improvements. A recent advancement comes from Omnivision, which released a new nanocamera design called OCHT10. This model maintains the same package size as the OVM6948 but doubles the pixel count, increasing the resolution to 400 × 400. This enhancement in resolution is attributed to a smaller manufacturing process that allows for a pixel size reduction to

approximately 1 μm. Furthermore, the new design achieves a 20% reduction in power consumption, lowering it to approximately 20 mW, which marks a considerable improvement over the previous model. This progress in quality image by increasing the spatial resolution (smaller pixel size) can help capture finer details. Such an enhancement has the potential to improve the MTF of the optical system, allowing for a more precise depiction of details at higher spatial frequencies. Nonetheless, that MTF performance is not solely determined by pixel resolution is important to highlight. The overall quality of the optical system plays a crucial role, including factors such as the lens design, diffraction limit, and inherent sensor noise (Simon, 2019).

Another potential enhancement under exploration is the reduction of the nanocamera's dimensions, targeting a form factor smaller than a CI electrode's ring contact. This strategy for miniaturization could be feasible by adopting the 1-μm pixel size utilized in the OCHT10 while maintaining a resolution of 200 × 200 pixels, similar to that of the OVM6948. Reaching such a compact design could significantly benefit surgical procedures by reducing contact with the basilar membrane at critical turns and enhancing the ease of maneuvering the device during surgery.

Continuing this trend of miniaturization, achieving an even smaller packaging nanocamera size combined with increased resolution might involve further reducing the pixel dimension. Recent advancements in micro-manufacturing processes have made ultra-small pixel sizes possible, as seen in Samsung's development of the world's smallest pixel (0.56 μm). However, pixel size reduction is not without its set of challenges. Smaller pixel sizes can lead to several constraints, each impacting image quality. First, increased shot noise, resulting from the quantum nature of photons, is more pronounced in smaller pixels, causing grainier images (Chen et al., 2000). Second, the smaller surface area of each pixel leads to diminished light sensitivity, affecting the image sensor's dynamic range. This reduction in dynamic range limits the sensor's ability to capture a broad spectrum of light intensities, which is crucial for detailing the brightest and darkest areas of visual information (Chen et al., 2000). Third, optical crosstalk becomes a significant concern as pixel proximity increases. This inconvenience arises when light intended for one pixel inadvertently influences adjacent ones, especially at steep angles, and reduces image contrast (Hirakawa, 2008). Fourth, the quantum efficiency, or the ability of the sensor to convert light into an electronic signal, decreases as light hits the sensor at steeper angles. This effect is more pronounced in smaller pixels, leading to inconsistent image quality across different sensor areas (Bianconi et al., 2022). In addition to these pixel-related concerns, making the optical system smaller requires carefully designing lenses to avoid optical aberrations, such as distortion, that can compromise the image quality. Addressing these complex challenges is essential in image sensor design to ensure that the benefits of miniaturization do not come at the cost of reduced imaging capabilities in medical applications.

Further enhancements to the optical system are on the horizon, expanding its potential beyond insertion monitoring. One promising path of exploration is the evaluation of cochlear health through the phenomenon known as birefringence. *Birefringence* refers to the differential refraction of light as it passes through anisotropic materials, resulting in a change in the polarization state of the incident light. In the context of the cochlea, the basilar membrane exhibits birefringence due to the organized orientation of its collagen fibrils (Kalwani et al., 2013). The unique patterns of light interference, as they interact with this biological structure, can provide critical insights into the health and integrity of the cochlea. Remarkably, no diagnostic optical probe is specifically tailored for this purpose within the cochlea. The development and integration of such an optical system would not only be groundbreaking, but it could also serve as a tool for clinicians to evaluate cochlear health. This assessment would provide vital information about the basilar membrane's condition before and after implantation, allowing for the anticipation and prevention of postoperative complications in CI users.

In conclusion, integrating optical systems into CI electrodes significantly advances auditory prosthetics. This novel approach, offering real-time visual feedback during the implantation process, can enhance surgical precision and potentially reduce damage to the cochlea. While it is anticipated to contribute to preserving residual hearing, clinical studies are essential to understand its impact fully. Beyond the immediate surgical applications, these optical systems also promise to advance cochlear health assessment by providing valuable insights for postoperative care. Moreover, preserving the integrity of the inner ear structures benefits CI users and opens doors to future therapeutic strategies, such as gene delivery into the inner ear (Kanzaki, 2018; Lahlou et al., 2023). This development, at the forefront of CI technology, could improve surgical techniques and outcomes for CI users' experience, marking an important step toward optimizing auditory prosthetics.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

Ethical approval was not required for the studies involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

## Author contributions

JC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. AR: Investigation, Methodology, Writing – original draft, Writing – review & editing, Supervision. RS: Investigation, Writing – original draft, Writing – review & editing. XT: Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Methodology. RT: Writing – original draft, Writing – review & editing, Conceptualization.

C-PR: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization.

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## Conflict of interest

C-PR and JC filed patents on the fabrication of waveguides and the visualization system for real-time monitoring of the electrode insertion into the cochlea. JC, XT, RT, and C-PR are co-founders of Cochlear Vision, LLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

C-PR and XT declared that they were editorial board members of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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# Waveguides for neurostimulation in the cochlea

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**Introduction:** Optical stimulation has been suggested for neural stimulation to improve cochlear implants. Light allows for more spatially selective activation of neuron populations than electrical current, offering more independent frequency bands along the spiral ganglion. These bands are available to encode acoustic information with anticipated better frequency resolution, improving cochlear implant user performance in noisy listening environments, tonal languages, and music perception.

**Methods:** Optical cochlear implants (oCIs) can deliver light either directly via small emitters within the cochlea or via waveguides from external optical sources. We investigated three waveguide designs made from OrmoComp®, a polymer that cures through ultraviolet (UV) radiation. Waveguides were fabricated via injection molding and coated using dip-coating or thermal reflow, or through aspiration of OrmoComp® into polyimide tubing that served as the cladding of the waveguide. The choice of fabrication technique directly determined the waveguides' total diameter: thermal reflow yielded ≈940 μm, dip-coating produced ≈306 μm, and aspiration resulted in ≈132 μm core diameter waveguides. Given the human cochlea's small size, we focused on analyzing the 306-μm and 132-μm waveguides, evaluating their optical performance (propagation and bending losses) and mechanical properties (bending stiffness and insertion forces). Furthermore, we evaluated some of these designs in *in-vivo* guinea pigs experiments.

**Results:** For the 100-μm core diameter waveguides, the propagation losses were 12.34 ± 1.26, 1.18 ± 0.88, 1.49 ± 0.58, and 3.43 ± 0.68 dB/cm at 534, 1,375, 1,460, and 1,550 nm, respectively. The respective bending losses at a 2 mm radius of curvature were 5.50 ± 1.32, 0.56 ± 0.26, 0.79 ± 0.18, and 0.64 ± 0.23 dB, and at 1 mm 8.54 ± 1.30, 2.05 ± 0.84, 2.11 ± 0.50, and 1.44 ± 0.37 dB. The bending stiffness of a 1 mm segment of the 100-μm-diameter waveguides was 18.9 ± 2.2 N/m. Insertion forces for the 100-μm-diameter waveguides into an acrylic human-size scala tympani model were < 25 mN. For the waveguides with 306 and 940 μm total diameter, the propagation losses ranged between 0.43 and 2.40 dB/cm at 534, 680, 1,375, and 1,550 nm, between 2.19 and 3.78 dB/cm at 450 and 1,460 nm. Bending losses for 360 degrees at 1,375 nm were 5.0, 2.4, and 0.46 for a bending radius of 2.5-, 3-, and 4-mm.

**Discussion:** Our study demonstrated that the polymer OrmoComp® is suitable for fabricating waveguides to transmit near-infrared radiation. *In-vivo* experiments showed optically evoked auditory responses originating from optical stimulation in the guinea pigs' first cochlear turn while

radiation was delivered. Incoming experiments will focus on evaluating long-term performance of these waveguides in guinea pigs and cats. This study will be designed to provide insights into the waveguides' performance and biocompatibility over extended periods, essential for their potential clinical application in future oCIs.

KEYWORDS

**laser, neural stimulation with light, infrared, waveguides, cochlear implants**

# 1 Introduction

In the mammalian inner ear, outer hair cell action increases acoustically induced basilar membrane vibrations, and inner hair cells convert the mechanical vibrations into a series of action potentials (APs). The timing and rate of the APs encode the acoustic information, which is then sent to the brain. The cochlea also works as a frequency analyzer by separating the spectrum of a complex acoustic signal into small frequency bands with the help of the basilar membrane, encoding each frequency band at a different site along the spiral ganglion. High frequencies cause the largest vibrations toward the cochlear base and low frequencies toward the cochlear apex.

In severely-to-profoundly deaf individuals, outer hair cells are lost, and the mechano-electrical transduction no longer works. Cochlear implants (CIs) restore some hearing by stimulating the remaining auditory neurons in the spiral ganglion directly with electrical current pulses. Despite the CIs' overall success, individual user performance varies largely (Helms et al., 1997; Dunn et al., 2008; Noble et al., 2008; Tyler et al., 2008; Wilson, 2015). Some patients master challenging hearing tasks, such as communicating over the phone in different languages, while others receive little benefit from CIs. Challenges for all users are noisy listening environments, tonal languages, and music perception (Wilson and Dorman, 2008; Webb et al., 2015).

Psychophysical studies have shown that normal-hearing listeners have 50 to 100 independent channels to process complex acoustic signals (Shannon et al., 2004; Mehta et al., 2020). In contrast to normal hearing listeners, in CI users, the interaction between neighboring CI electrode contacts reduced the number of independent stimulation sites to about 7–10 (Brill et al., 1997; Fishman et al., 1997; Friesen et al., 2001; Liu et al., 2004). The low number of channels for cochlear implant users to process information originates in the current spreading from the electrodes to the surrounding tissue. It limits the spatial precision of stimulation, compromising CI performance in pitch perception. It has been argued that the increase in the number of independent stimulation sites will improve CI user experience in noisy listening environments, tonal languages, and music (Fu and Nogaki, 2005; Smith et al., 2013; Feng and Oxenham, 2018). To increase the number of independent channels for stimulation, CI electrodes were placed closer to the neurons (Doshi et al., 2015; Stieghorst and Doll, 2016; Dhanasingh, 2018; Yilmaz-Bayraktar et al., 2022); multipolar stimulation was applied "to steer" the electrical current toward the spiral ganglion neurons (Firszt et al., 2007; Koch et al., 2007; Berenstein et al., 2008; Bonham and Litvak, 2008; Buechner et al., 2008; Brendel et al., 2009; Luo et al., 2010, 2021; Srinivasan et al., 2012; Luo and Garrett, 2020). Efforts are still on the way to achieve the desired increase in independent channels.

Reducing the interaction between adjacent channels during electrical stimulation in CIs remains a significant challenge. In this context, optical stimulation emerges as a promising alternative. The method uses transient light pulses for neural modulation or stimulation and has been particularly noted for its ability to target small, specific neuron populations (Izzo et al., 2006; Hernandez et al., 2014; Richter and Tan, 2014; Jeschke and Moser, 2015). Building on these findings, Matic et al. (2011) and Dieter et al. (2020) showed that optical radiation could be delivered more selectively than electrical current to groups of auditory neurons in the cochlea. Increased spatial selectivity in stimulation could offer a significant leap in the performance of CIs, promising neural prosthesis with enhanced spatial precision and reduced interference between channels. Optogenetics (OG) and infrared neural stimulation (INS) are two optical techniques currently under consideration (Richter and Tan, 2014; Littlefield and Richter, 2021). The light delivery to the cochlea is a critical step in each optical stimulation method. It can be delivered by an array of optical sources inserted into scala tympani along the cochlear spiral ganglion or by bundles of optical waveguides similarly inserted. In a similar approach to conventional cochlear electrodes, in which a single electrode targets an area of the cochlea, each light source in the array or waveguide in the bundle will optically aim at a specific section along the cochlea.

Recent research on optical waveguides has seen significant developments. For instance, studies on polymer-based waveguides have been conducted (Helke et al., 2022; Triplett et al., 2022). Additionally, there have been advancements in high-density micro-LEDs cochlear probes (Klein et al., 2018), incorporating up to 144 light sources. The light delivery system's (LDS) size and stiffness are critical for both methods. It must be stiff enough to sustain the insertion forces without curling. Still, it must also be compliant enough to follow scala tympani during insertion without damaging or penetrating the basilar membrane. The LDS size is also determined by the optical power to be delivered. The size is typically larger for the optical sources with the higher radiant power.

While the LDSs can be used for optogenetic or stimulation with infrared light, we focus on INS because it does not require the expression of light-sensitive channels (opsins) in the auditory

neurons. INS works through spatiotemporal heating of a target volume (Shapiro et al., 2012). We have shown that arrays of optical sources are feasible with similar dimensions, bending stiffness, and insertion force values of commercially available CI electrodes (Xu et al., 2018). However, the challenge for active sources in the cochlea is their poor electrical-to-optical energy conversion efficiency, with most of the energy not converted into emissions converted into heat. Consequently, a limiting factor for the insertion of active optical sources into the cochlea is the self-heating of the dies. For example, the conversion efficiency of the bare laser diode die, CHP-176 (SemiNex, Peabody, PA, United States), is 14%. Its emission wavelength is 1,315 nm, and its cavity length is 1,250 μm. The conversion efficiency of a similar die with twice the cavity length of 2,500 μm is 28%. While larger optical sources have a better electrical-to-optical energy conversion efficiency, the size of the scala tympani poses a constraint, particularly for larger dies. On the other hand, larger, more efficient light sources can be placed outside the cochlea, with waveguides delivering the radiation to the cochlea. Placing the active source outside the cochlea has the advantage that no active optical sources are in the cochlea, reducing unnecessary heat delivery and potential cochlear damage. Furthermore, a different risk of active optical sources inserted into the cochlea is the current delivered to the light sources. An accidental "current leak" into the tissue from a defective wire or insulation can cause tissue damage. It should be noted that the literature currently lacks data evaluating the long-term performance of optical sources within implantable devices. With the possible progression toward optical CIs, the precise positioning of the light sources—whether inside the cochlea or externally (using bundles of waveguides for effective light transmission)—will become a critical consideration.

Waveguides can be optical fibers fabricated from low $H_2O$-containing glass. These glasses, often silica-based, are engineered to minimize attenuation losses. In terms of mechanical properties, pure silica fibers typically possess a tensile strength ranging between 2.4 to 4.8 GPa. Depending on the fabrication process, their modulus of elasticity is around 72 GPa. These glass fibers exhibit rigidity when bundled, making them prone to breakage (Balster et al., 2014).

Polymeric waveguides emerge as promising alternatives due to their mechanical properties (Helke et al., 2022; Triplett et al., 2022). However, alongside their benefits, waveguides also face challenges. They experience optical losses influenced by two main factors: material properties, which determine propagation losses, and the precision in fiber surface preparation and connections, which contribute to coupling losses. Moreover, when forming bundles of waveguides, the increased stiffness could pose a challenge during their insertion into the cochlea, requiring careful navigation of delicate inner ear structures. Today, exploring polymeric waveguides for CIs is an active area of research, focusing on identifying the most suitable materials that can balance mechanical flexibility with optimal optical properties. To further explore the opportunities of waveguides in the design of neural modulation devices, in this study, we introduced and tested waveguides made of OrmoComp®, a polymer. We characterized these waveguides mechanically and optically to determine their performance, focusing on their application in future optical CIs.

# 2 Methods

## 2.1 Ethics statement

Care and use of animals followed the National Institutes of Health's Guide for Care and Use of Laboratory Animals. Northwestern University's Animal Care and Use Committee approved the use of guinea pigs and all animal procedures (#IS00012338). The guinea pigs were housed in groups of up to four animals; food and water were provided *ad libitum*; enrichments, nesting materials, and shelters were given. All methods are reported and are in accordance with ARRIVE guidelines.

## 2.2 Waveguide fabrication

Injection molding is one method for fabricating waveguides. The viscous (2 ± 0.5 Pa*s) polymer OrmoComp® (Kayaku Advanced Materials, Westborough, MA, United States) was injected into a mold made of silicone tubing (AlliedSil, PAT-01, Implantech, United States) and cured with ultraviolet (UV) light within 5 min. The cure time depended on the diameter of the waveguide, the mold's thickness, and the UV light's extinction. After removing the waveguides from the mold, some were coated using thermal reflow with Carbothane PC-3575A, which is a clear polycarbonate-based aliphatic thermoplastic polyurethane with a refractive index $n_{\text{Carbothane}} = 1.49$. On the other hand, some waveguides were dip-coated with the amorphous fluoropolymer CYTOP (AGC Inc. Chemicals Company, Tokyo, Japan), with a refractive index of $n_{\text{Cytop}} = 1.34$ (Leosson and Agnarsson, 2012).

The thermal reflow technique (Marinins et al., 2018) involves a controlled heating process in which layers of material, such as Carbothane PC-3575A, becomes malleable and begin to flow. Driven by surface tension effects, this polycarbonate material reshapes to form a smooth, circular cladding around the previously cured OrmoComp® core. The reflowed material solidifies as it cools, ensuring a high-quality, rounded cladding that optimizes light confinement within the core (Figure 1A).

The dip-coating technique (Evertz et al., 2021) involves immersing the core material of the waveguide into a liquid solution containing the cladding material, in our case, the CYTOP, and then withdrawing it at a controlled speed to achieve uniform coating layers. As the core is lifted from the solution, a thin layer of the cladding material adheres to its surface. Figure 1B shows some of the waveguides coated with CYTOP. In our study, a specialized version of CYTOP (CTX109AE), designed for dip-coating, was used in a concentration of 9%.

The mold from the silicone tubing determined the waveguide's core diameter, about 300 μm. The cladding thickness, which was approximately 320 μm for the thermal reflow and ~3 μm for the dip coating, determined the total diameter of the waveguide. For our examples, dip-coated waveguides were about 306 μm; waveguides coated by thermal reflow had diameters of about 940 μm.

The total internal reflection angle ($\theta$) for our waveguides was calculated based on the refractive index of cured OrmoComp® ($n_{OrmoComp}$) at 589 nm, which is 1.52 (Micro Resist Technology

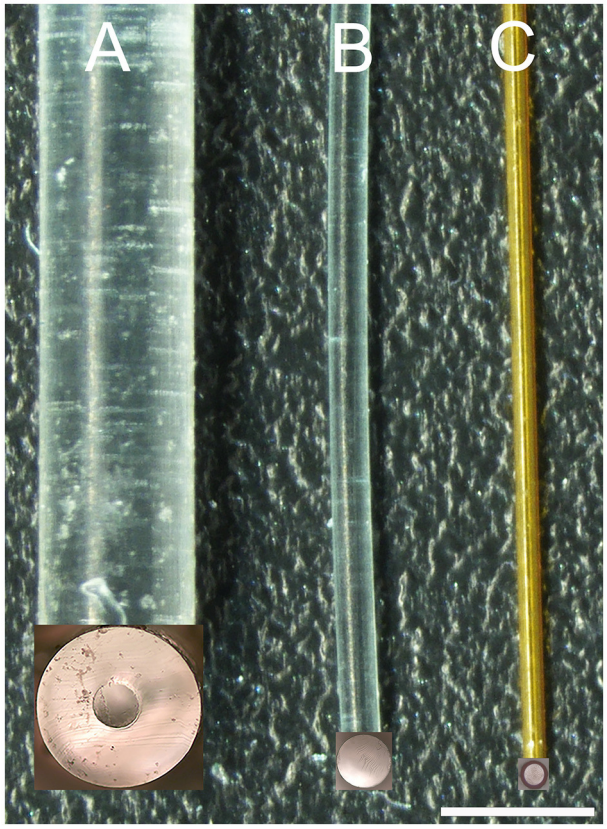


FIGURE 1
Image of three waveguides. **(A, B)** are 300 μm core diameter waveguides created by injection molding. The cladding in **(A)** was formed by thermal reflow with Carbothane and in **(B)** by dip-coating with CYTOP. **(C)** is the image of a 100-μm core diameter waveguide created by aspirating OrmoComp into polyimide tubing. The inserts at the bottom end of each waveguide show the uniform surface of the corresponding cross-sections of the waveguides after cutting with a sharp blade. The scale bar is 960 μm.

GmbH, Berlin, Germany), and the refractive indices of the different cladding types. Applying Equations 1, 2, we found that $\theta$ is 61.8° for the dip-coated waveguides and 78.6° for the thermal reflow waveguides.

$$\theta = \arcsin \frac{n_{Cytop}}{n_{OrmoComp}} \quad (1)$$

$$\theta = \arcsin \frac{n_{Carbothane}}{n_{OrmoComp}} \quad (2)$$

To reduce the core diameter of the waveguides, we used polyimide tubing (MicroLumen, Oldsmar, FL, United States) with an outer diameter of 132 μm and an inner diameter of 100 μm (Figure 1C). The polyimide tubing was the cladding for the waveguide. OrmoComp®, which formed the waveguide's core, was aspirated into the tubing and cured with ultraviolet light ($\lambda$ = 450 nm). The aspiration technique involves attaching one end of the polyimide tubing to a small syringe while immersing the other end in OrmoComp®. The polymer is drawn into the tube when suction is applied using the syringe. This process can be monitored under a microscope. Once the required length of the waveguide is achieved, the polymer is cured using UV light. These waveguides were about 20 cm long and were shortened to 2–2.5 cm with a sharp razor blade before their mechanical and optical characterization. Given the refractive index of polyimide ($n_{\text{polyimide}}$) spans from 1.39 to 1.45, as indicated by Linshang Technology Co., Ltd. (Shenzhen, China), the total internal reflection angle for our waveguide was between 66.1° and 72.5° (Equation 3).

$$\theta = \arcsin \frac{n_{polyimide}}{n_{OrmoComp}} \quad (3)$$

## 2.3 Light sources, and coupling, propagation, and bending losses

To measure the 300-μm and 100-μm core diameter waveguide's optical properties, we directly placed, under visual control through a surgical microscope, a 200-μm or 100-μm optical fiber (P200-5-VIS NIR and P100-5-VIS NIR, Ocean Optics, Dunedin, FL) on the waveguide, respectively (Figure 2A). For the 100-μm core diameter waveguide, the optical fiber and the waveguide were aligned with a tightly fitting custom-made sleeve. The waveguide was inserted into one side, and the optical fiber into the other side of the sleeve. Before the optical fiber and waveguide insertion into the sleeve, both tips were dipped into OrmoComp®. After the optical glass fiber and the waveguide made contact, ultraviolet (UV) light at a wavelength $\lambda$ = 365 nm cured the polymer. All optical measurements were conducted in air. To minimize light scattering at the optical fiber-waveguide interface from reaching the sensor, black silicone, and black tape were employed.

### 2.3.1 Optical sources

All light sources in our setup were diode lasers spanning a range of wavelengths. For visible light, we used lasers emitting at 450 nm (blue, 5.5 W, 12V CNC Laser Module, 3D Zaiku, Indonesia), 534 nm (green, LSR532H-FC-1.5, CivilLaser, China), and 680 nm (red, 05-LHP-121, Melles Griot, Carlsbad, CA). For the near-infrared (NIR) spectrum, we employed 4-pin fiber-coupled laser diodes from SemiNex, Peabody, MA, United States, which included wavelengths of 1,375 nm (model 4PN-117), 1,460 nm (model 4PN-101), and 1,550 nm (model 4PN-108). The pulse duration was 100 μs. Pulses were delivered at a rate of 5 pulses/second. While faster pulse repetition rates are possible, the slow pulse rate was selected to avoid interactions between subsequent pulses when measuring the neural responses. The NIR lasers were powered using the ILX Lightwave LDC-3724C Laser Diode Controller from IXL Lightwave (Newport Corporation, Bozeman, MT, United States), ensuring precise control over the laser operation.

### 2.3.2 Propagation losses

To determine the optical properties of the waveguides, we measured the radiant energy ($Q$) at the tip of the optical fiber

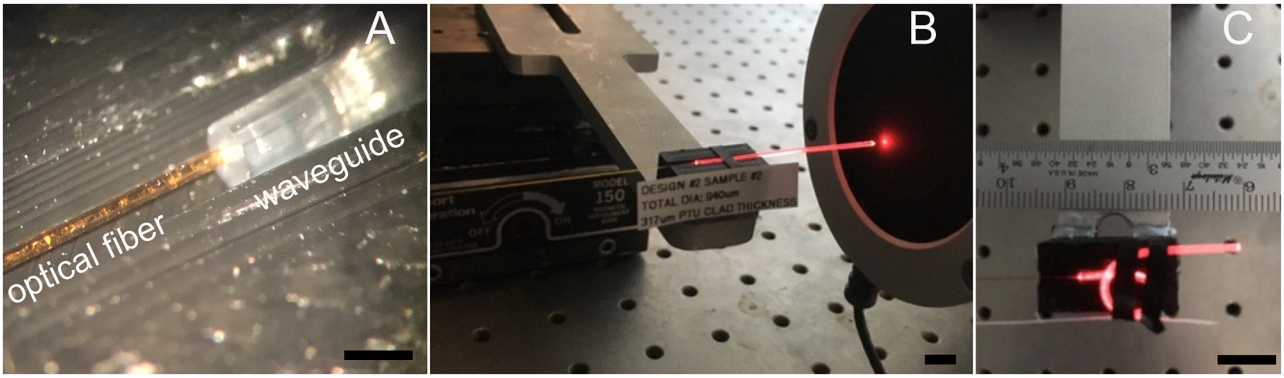


FIGURE 2
Optical transmission measurements. **(A)** Shows the 200-μm optical fiber after placing it on the 300 μm-core waveguide. **(B)** Shows the red pilot light of the infrared laser transmitted by the waveguide, which guides the energy sensor placement before conducting the measurements at the infrared radiation wavelengths. **(C)** Shows the configuration for determining the bending losses. Light emitting from the bent section will not produce a broader stimulated section because INS requires a focalized light beam in tissue. Light coming out in the bending part of the waveguide will be scattered everywhere. The scale bar in **(A)** is 1 mm. Scale bars in **(B, C)** equal 10 mm.

and the tip of the waveguide after coupling the optical fiber to the opposite end of the waveguide. The radiant energy of the infrared light was measured using a thermopile J50LP-1A energy sensor connected to a 3 sigma power meter (Coherent, Portland, United States) (Figure 2B). For the visible light, we used a power meter PM100D in combination with the sensor S130VC (Thorlabs, Newton, NJ, United States). From the two measures, the total losses ($L_{total}$, Equation 4) were calculated and divided by the length of the waveguide ($l_{\text{waveguide}}$) in centimeters (cm).

$$\triangle L_{total} = \frac{10^{*}\log\left(\frac{Q_{fiber\ tip}}{Q_{waveguide\ tip}}\right)}{l_{waveguide}}\left[\frac{dB}{cm}\right] \quad (4)$$

After quantifying the total transmission loss, we shortened the waveguide by about one millimeter using a dual-edge sharp razor blade and measured the transmission loss of the "new waveguide" (Ding et al., 2019; Ferreira et al., 2023). It is important to note that careful measures were employed to minimize scattering and reflections at the waveguide's tip, such as positioning the blade perpendicularly to the waveguide to ensure a smooth interface and maintaining close contact between the waveguide and the power meter. To verify the quality of the cut interface, microscopic images of the waveguide cross-section were taken post-cut (Figure 1).

Plotting the lengths of the waveguides (abscissa) vs. the total loss (ordinate) allows data fitting with a linear function. The results provide the intercept as the coupling loss, $L_{coupling}$, and the fit slope as the propagation loss, $L_{prop}$.

### 2.3.3 Bending losses

To determine the waveguide's bending losses, we measured the radiant energy ($Q$) at the tip of the waveguide while straight (Figure 2B) and compared the value with the radiant energy measured for the same waveguide while bent (Figure 2C). The procedure was performed at different curvature radii. With the two values, we calculated the bending losses ($L_{bending}$) using Equation 5.

$$L_{bending} = 10{*}\log\left(\frac{Q_{waveguide\ tip\_straight}}{Q_{waveguide\ tip\_bend}}\right)[dB] \quad (5)$$

## 2.4 Measuring mechanical properties and cochlear insertion forces for the waveguides

The bending stiffness of our OrmoComp® waveguides and the HiFocus 1J Advanced Bionics CI electrode arrays was evaluated to ensure that the waveguides are sufficiently flexible for safe insertion into the cochlea yet stiff enough to avoid folding and buckling. From these measurements, we calculated Young's moduli for the waveguides. A key aspect of our waveguide design is the circular shape, which offers a significant advantage in maintaining consistent stiffness regardless of the bending axis. It is essential to recognize that for conventional CI electrodes, stiffness is significantly influenced by the internal wires' configuration. Different manufacturing approaches profoundly impact the electrode's bending stiffness, such as using "braided" wire arrangements vs. aligning wires in a single plane. We used the HiFocus 1J Advanced Bionics CI electrode array to establish a benchmark. We measured its bending stiffness in two orientations: parallel and perpendicular to the electrode contact surface. These measurements provided a comparative framework against which we assessed the performance of our waveguides.

Figure 3A shows the setup for the bending stiffness measurements. The force meter (Serie 5, Mark-10, NY, United States), mounted to a motorized translational stage (LTS150, Thorlabs, Newton, NJ, United States), moved at a 90-degree angle relative to the long axis of the waveguide (Figure 3A). The edge of the razor blade, glued to the tip of the force meter, advanced until it contacted the waveguide, 1 mm away from the waveguide's fixation point. After the force meter contacted the waveguide, the Mark 10 continuously measured the force and stored the values every 100 ms while advancing for 300 μm. The

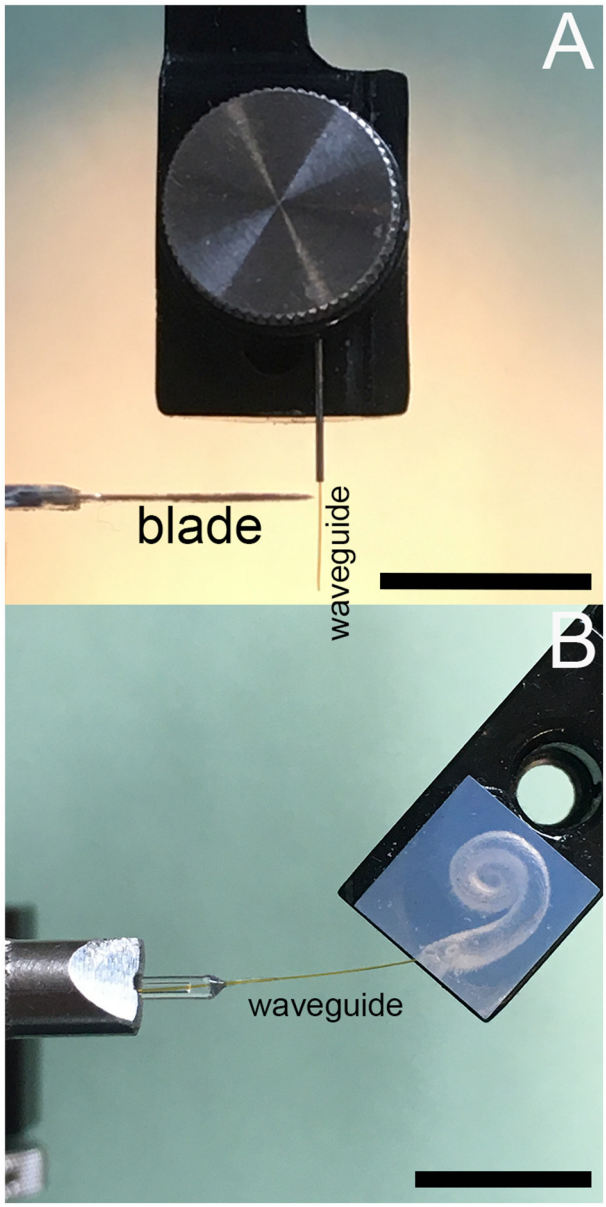


FIGURE 3
**(A)** Shows the waveguide bending stiffness measurements setup, and **(B)** for insertion force measurements. Scale bars equal 10 mm.

velocity was 0.1 mm/s. The values increased linearly over that distance, with the slope of the linear section providing the stiffness measure for the waveguide.

The results of the bending stiffness measurements reported as N/m were used to calculate Young's modulus ($E$) using Equation 6.

$$E = \frac{F * l^3}{3 * I * y} \tag{6}$$

where $E$ denotes Young's modulus, $F$ the loading force, $l$ the distance between the clamped end of the waveguide and the point where the force is applied, $y$ the displacement of the waveguide at the loading site; and the corresponding moment of inertia $I$ for a circular rod $I_{\text{rod}}$ (Equation 7) and a circular tube $I_{\text{tube}}$ (Equation 8), where $d$ is the diameter of the rod, $d_o$ and $d_i$ are the outer and inner diameter of the tube.

$$I_{rod} = \frac{\pi * d^4}{64} \tag{7}$$

$$I_{tube} = \frac{\pi * (d_o{}^4 - d_i{}^4)}{64} \tag{8}$$

Figure 3B shows the setup for the insertion force measurement of a single waveguide into an acrylic model of the human scala tympani. The waveguide was mounted to the tip of the force meter. While the instrument advanced, it measured the force to insert the waveguide into the acrylic model of the human scala tympani. The advancement speed was 0.1, 0.3, and 0.5 mm/s, respectively.

## 2.5 Animals and surgery

Procedures are the same as published previously (e.g., Richter et al., 2011; Agarwal et al., 2021; Xu et al., 2021). Nine male adult albino guinea pigs (age 6–12 months; weight 454–1,290 g) were used for the experiments. The animals were purchased from Kuiper Rabbit Ranch (Gary, IN, United States). After arrival at Northwestern University, the animals were housed for at least 2 weeks for acclimatization before any procedure was performed.

### 2.5.1 Anesthesia

During the terminal experiment, each guinea pig was anesthetized with an initial intraperitoneal injection of 1.3 mg/kg of urethane in 0.1 M sterile saline solution. Urethane injections were supplemented with ketamine (44 mg/kg) and xylazine (5 mg/kg) at the beginning of the surgical procedure. Atropine sulfate (0.05 mg/kg) was also administered at the start of the experiment to reduce bronchial secretions. Anesthesia was maintained by supplements of ketamine (44 mg/kg) and xylazine (5 mg/kg) along with a saline solution (0.5 ml). The paw withdrawal reflex was used to monitor the level of anesthesia. After the animal was anesthetized, it was transferred to a double-walled acoustic chamber (Serial No. 3579, Model No. 1202A; Industrial Acoustics Company, INC. Bronx, NY, United States). It was placed supine on a thermostatically controlled heating pad (T/pump, Model TP700; Stryker Medical, Portage, MI, United States), maintaining the core body temperature at 38°C. Vitals, including heart rate, respiratory rate, blood oxygenation, and rectal temperature, were monitored and logged every 15 min. A tracheotomy was performed, and a plastic tube (1.9 mm outer diameter, 1.1 mm inner diameter, Zeus Inc., Orangeburg, SC, United States) was secured in the trachea. The breathing was supported by mechanical ventilation with oxygen throughout the experiment using an anesthesia workstation (Hallowell EMC, Pittsfield, MA, United States).

#### 2.5.2 Deafening of the animals

The guinea pig cochleae were damaged by a single transtympanic injection of 200 μL saline solution containing 50 mM of neomycin. The use of this ototoxic drug aimed to generate various levels of residual hearing in the animals, simulating the auditory conditions commonly observed in most cochlear implants' candidates. Injecting neomycin into the middle ear has not been able to completely deafen the animals. It is not a reliable procedure for completely deafening the animals. Following the neomycin injection, the animals were kept for more than 4 weeks for neural degeneration to occur. The damage was variable, as seen by the compound action potential (CAP) thresholds. For the transtympanic injection, the guinea pigs were sedated by gas inhalation of isoflurane 3% in oxygen 97%. The procedure took about 5 min. During the recovery from anesthesia, the animals were monitored until fully recovered.

#### 2.5.3 Surgical access to the cochlea

After the guinea pigs were anesthetized, their head was fixed with dental acrylic (Methyl Methacrylate, CO-ORAL-ITE DENTAL MFG CO, Diamond Springs, CA, United States) to a custom-made head holder, using three 1.5 mm stainless steel self-tapping cortex screws (Veterinary Orthopedic Implants, St. Augustine, FL, United States) as anchors. The guinea pig was then placed in the prone position. A c-shaped retroauricular incision was made, and the cervicoauricular muscles were removed. The cartilaginous outer ear canal was exposed and sectioned. After opening the bulla approximately 2 × 3 mm (Figures 4A, B) with a motorized drill (World Precision Instruments, Sarasota, FL, United States), the basal turn of the cochlea was identified (Figure 4C), and a cochleostomy was created (Figure 4D) with a 0.5 mm Buckingham footplate hand drill (Richards Manufacturing Co., Memphis, TN, United States) or with the motorized drill.

### 2.6 Placement of the optical fiber and the waveguide and hearing assessment

Figure 4D shows an image with the polished optical fiber (P200-5-VIS NIR, Ocean Optics, Dunedin, FL, United States) inserted through the openings in the cochlear wall. The polished optical fibers were 230 μm in diameter, with a core of 200 μm. Their numerical aperture was 0.22 ± 0.02, and the acceptance angle was 24.8° (numbers were provided by the vendor, Ocean Optics, Dunedin, FL, United States). The optical fibers or waveguides were mounted on a micromanipulator (MHW103, Narishige, Tokyo, Japan) and placed through the cochleostomy into the scala tympani. Each of the opposite ends of the 3 m long optical fibers was attached to a diode laser output. The insertion depth of the waveguide with a "flat" surface was between 200 and 300 μm, and the fiber was directly placed in front of the spiral ganglion. For the angled surface (45 degrees toward the optical axis), the insertion was about 1 mm. CAPs were measured with a 125-μm diameter silver wire electrode placed on the round window. After completion of the experiments, the deeply anesthetized animals were euthanized by injecting 0.2 mL Euthasol and decapitation.

### 2.7 Data analysis and presentation

Section 2.3 described the method to determine the total losses, propagation losses, and bending losses. Results were plotted vs. the length of the waveguides. Fitting the data to a linear function provided the coupling and the propagation losses for each radiation wavelength. The y-intercepts provide the coupling losses, and the slopes of the line function the propagation losses. A correlation analysis for each plot provided the correlation coefficient, the confidence intervals, and the radiant power for the measurements. Bending losses were calculated by comparing the total losses at the end of the straight fiber and after a 360-degree bend. For waveguides with a 300 μm core, bending tests were conducted at radii of curvature of 2.5, 3, and 4 mm. In contrast, for the 100 μm core waveguides, smaller radii of curvature of 1 and 2 mm were used. The choice of larger curvature radii for the thicker waveguides was due to their greater stiffness, which made achieving smaller radii more challenging and risked damaging the waveguide structure during testing. All results were tabulated, and the corresponding averages ± one standard deviation (σ) were calculated. Averages ± (σ) for the bending stiffnesses of the waveguides were calculated. The insertion forces for the waveguides were measured, and their values were plotted and compared to the insertion forces of conventional CI electrodes. A qualitative analysis of the data was made. Auditory brainstem response (ABR) thresholds for each animal were plotted with the averages and the corresponding standard deviations.

### 2.8 Statistical analysis

Differences of the average propagation and bending losses at different wavelengths were tested for statistical significance using Igor Pro 8 (WaveMetrics Inc., Lake Oswego, OR). The Shapiro-Wilk test was applied to test for normal distribution of the data. An Analysis of Variance (ANOVA) was performed, followed by the Tukey's Honest Significant Difference (HSD) *post-hoc* test. Significance was tested at a 0.05 level.

## 3 Results

### 3.1 Coupling and propagation losses

#### 3.1.1 Propagation losses for the 100-μm core diameter waveguide

Table 1 and Figure 5 show the coupling and propagation losses for the waveguides. Losses are expressed in dB and are plotted vs. the length of each corresponding waveguide. The propagation losses at 534, 1,375, 1,460, and 1,550 nm radiation wavelengths were 12.34 ± 1.26, 1.18 ± 0.88, 1.49 ± 0.58, and 3.43 ± 0.68 dB/cm, respectively (Table 1, Figure 5). The number of waveguides examined is indicated by "N" in the plots. In Figure 5, the coupling losses were removed after fitting the data for each waveguide and subtracting the y-intercept from each data point of this particular waveguide. The slope of the plotted data provides the propagation loss. Remember, when referring to the change in radiant energy with the length of the waveguide, the propagation

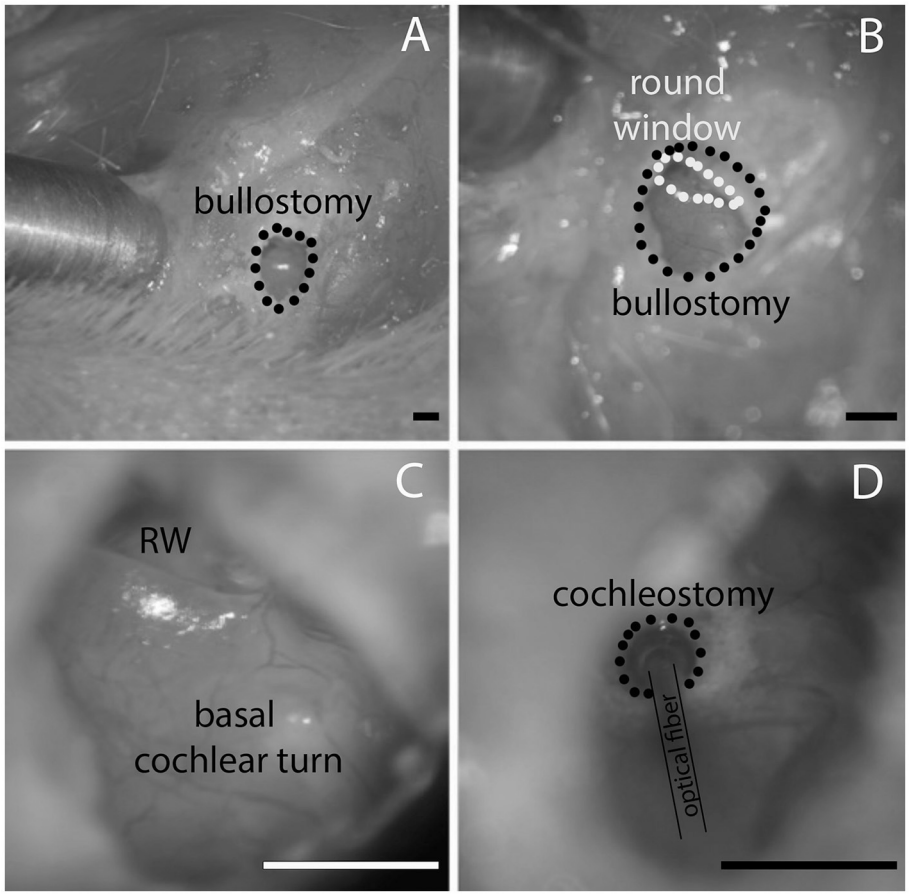


FIGURE 4
**(A)** Shows the opening of the opening in the bulla, **(B)** is the magnified view from **(A)** at a different angle that the round window comes into view. **(C)** Shows the round window (RW) and the basal cochlear turn. **(D)** Shows the location of the cochleostomy in the basal cochlear turn and the placement of the optical fiber. Likewise, the waveguide is inserted through the same cochleostomy. The scale bars equal 1.6 mm.

loss is given in decibels (dB), a logarithmic measure that denotes the ratio of input to output power. In this logarithmic scale, a linear increment in dB corresponds to an exponential change in radiant energy when expressed in Joules. Differences in propagation losses were statistically significant when compared to 534 nm (Supplementary Table 1). For the infrared wavelengths, differences in propagation losses were significant when compared to 1,550 nm (Supplementary Table 1).

### 3.1.2 Propagation losses for the 300-μm core diameter waveguide

For the 306-μm diameter waveguides, denoted as design #1 (300 μm core plus the 3-μm thick CYTOP cladding), the propagation losses at 450, 534, 680, 1,375, 1,460, and 1,550 nm radiation wavelengths were 3.78 ± 0.85, 0.43 ± 1.61, 0.77 ± 1.62, 0.98 ± 0.92, 3.55 ± 1.80, and 0.97 ± 1.04 dB/cm, respectively (Table 2). The coupling losses varied for the 306-μm diameter waveguide because of the limited reproducibility in placing the optical fiber onto the waveguide (Table 2). Differences in propagation losses were statistically significant when compared to 450 nm (Supplementary Table 1).

For the 960-μm diameter waveguides, denoted as design #2 (300 μm core plus the 330 μm thick Carbothane cladding), the propagation losses at 450, 534, 680, 1,375, 1,460, and 1,550 nm radiation wavelengths were 2.19 ± 0.46, 0.58 ± 0.32, 0.87 ± 0.18, 1.46 ± 0.14, 3.71 ± 0.61, and 2.40 ± 0.54 dB/cm, respectively (Table 2). Differences in propagation losses were statistically significant between 450 nm and 534 nm or 680 nm, between 1,460 nm and 534 nm or 450 nm, and between 1,550 nm and 534 nm or 680 nm (Supplementary Table 1).

## 3.2 Bending losses

### 3.2.1 Bending losses for the 100-μm core diameter waveguide

Bending losses for the 100-μm waveguides ($N = 5$) were larger for 1 mm than the 2 mm curvature radius (Table 3). At 2 mm, the average bending losses were 5.50 ± 1.32, 0.56 ± 0.26, 0.79 ± 0.18, and 0.64 ± 0.23 dB at wavelengths 534, 1,375, 1,460, and 1,550 nm, respectively. At 1 mm, the average losses were 8.54 ± 1.30, 2.05 ± 0.84, 2.11 ± 0.50, and 1.44 ± 0.37 dB at wavelengths 534, 1,375, 1,460, and 1,550 nm,

TABLE 1 Propagation and coupling losses for the 100-μm core diameter waveguides (wg) at 534, 1,375, 1,460, and 1,550 nm wavelengths.

| 100-μm core; polymer waveguide; losses | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Wavelength | 534 nm | | 1,375 nm | | 1,460 nm | | 1,550 nm | |
| Waveguide | Coupling [dB] | Propagation [dB/cm] | Coupling [dB] | Propagation [dB/cm] | Coupling [dB] | Propagation [dB/cm] | Coupling [dB] | Propagation [dB/cm] |
| wg1 | 57.20 | 10.37 | 8.81 | 1.43 | 7.82 | 1.04 | 5.82 | 3.91 |
| wg2 | 24.28 | 13.60 | 7.36 | 0.53 | 6.40 | 1.66 | 5.76 | 3.95 |
| wg3 | 29.33 | 11.98 | 6.22 | 0.89 | 4.87 | 2.42 | 8.90 | 3.88 |
| wg4 | 41.51 | 13.19 | 10.35 | 2.66 | 8.63 | 1.29 | 3.56 | 2.90 |
| wg5 | 42.37 | 12.55 | 9.66 | 1.40 | 9.52 | 1.02 | 9.92 | 2.49 |
| wg6 | | | 18.10 | 0.16 | | | | |
| avg | 38.94 | 12.34 | 10.08 | 1.18 | 7.45 | 1.49 | 6.79 | 3.43 |
| std | 12.84 | 1.26 | 4.21 | 0.88 | 1.84 | 0.58 | 2.58 | 0.68 |

The data is plotted in Figure 5.

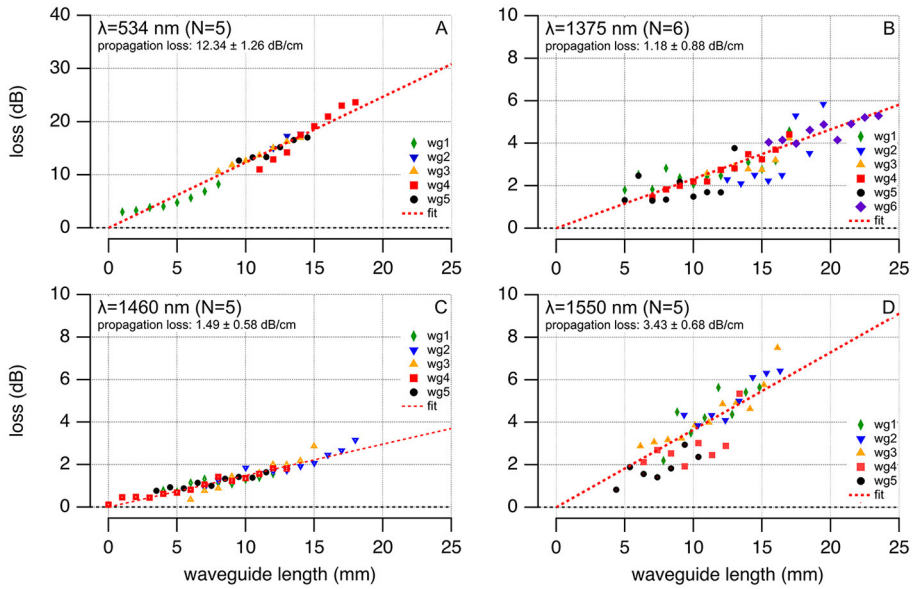


FIGURE 5
Propagation losses for 100-μm core diameter polymer waveguides at varying wavelengths are shown for 534 nm ($N = 5$, average loss 12.34 ± 1.26 dB/cm), 1,375 nm ($N = 6$, average loss 1.18 ± 0.88 dB/cm), 1,460 nm ($N = 5$, average loss 1.49 ± 0.58 dB/cm), and 1,550 nm ($N = 5$, average loss 3.43 ± 0.68 dB/cm). Each wavelength's data, denoted by differently colored waveguides (wgx), are plotted with waveguide lengths on the abscissa and total losses on the ordinate, fitting a red dash linear function to determine propagation loss.

correspondingly. Supplementary Table 1 shows the outcomes of the statistical evaluation of the differences in bending losses. Differences were statistically significant when compared to 534 nm Bending losses at different radii were statistically significant only at 534 nm.

### 3.2.2 Bending losses for the 300-μm core diameter waveguide

Waveguides with a 300-μm core and 940-μm total diameter were too large and stiff to measure bending losses at a 4 mm or smaller bending radius. Bending losses for a full circle (Figure 2C) for the waveguides with 306 μm in total diameter were determined at 1,375 nm. The losses are 5.0, 2.40, and 0.46 dB for a bending radius of 2.5, 3, and 4 mm, respectively. It is important to emphasize that even though we could measure the bending losses, the 306 μm waveguides demonstrated considerable stiffness.

## 3.3 Mechanical properties of a single waveguide

The bending stiffness was measured as described in Methods (Section 2.4). The bending stiffness of a conventional CI electrode is

41.1 ± 21.6 N/m (Figure 6). The large variability in stiffness for the traditional CI electrodes originates in the different measurement sites along the electrode. These electrodes are more compliant at the tip than at the base. Although Young's modulus for the silicone rubber spans 2.7–4.3 MPa (Feng et al., 2017), the mechanical properties of the CIs electrode are also determined by the arrangement of the platinum wires encapsulated within the silicone. Therefore, it is not straightforward to use the results from our stiffness measurements and directly derive the corresponding Young's modulus.

For the 100-μm waveguides made from OrmoComp®, the cladding (empty tubing) contributed significantly to the bending stiffness; it was 15.40 ± 2.00 N/m (Figure 6). The corresponding Young's modulus estimation for the empty tubing, using 1 mm for the distance between the clamped end of the waveguide and the point where the force is applied, 100 μm for the inner diameter, and 132 μm for the outer diameter of the tubing, is about 0.51 GPa. The stiffness increased by filling the tubing with OrmoComp®; the bending stiffness was 18.9 ± 2.2 N/m (Figure 6). The bending stiffness of the waveguide with a 300-μm core diameter was 73.50 ± 6.70 N/m (Figure 6). The bending stiffness measurements indicate that the core's Young's modulus is approximately 0.062 GPa. This estimate aligns well with published data (Buchroithner et al., 2020), which report Young's modulus of OrmoComp® for structures of a similar size to be in the range of 0.047 to 0.102 GPa.

TABLE 2 Design #1 (cladding formed by dip-coating) reveals the propagation losses for the 300-μm core plus the 3-μm thick CYTOP cladding with a total diameter of 306 μm. Design #2 (cladding formed by thermal reflow) shows the propagation losses for the 300 μm core and cladding obtained by the reflow technique, adding 330 μm thickness, summating to a total of 960-μm diameter waveguide.

| 300-μm core; polymer waveguide; propagation losses | | |
|---|---|---|
| Wavelength | Design #1 | Design #2 |
| | Loss (avg ± σ) [dB/cm] | Loss (avg ± σ) [dB/cm] |
| 450 nm | 3.78 ± 0.85 | 2.19 ± 0.46 |
| 534 nm | 0.43 ± 1.61 | 0.58 ± 0.32 |
| 680 nm | 0.77 ± 1.62 | 0.87 ± 0.18 |
| 1,375 nm | 0.98 ± 0.92 | 1.46 ± 0.14 |
| 1,460 nm | 3.55 ± 1.80 | 3.71 ± 0.61 |
| 1,550 nm | 0.97 ± 1.04 | 2.40 ± 0.54 |

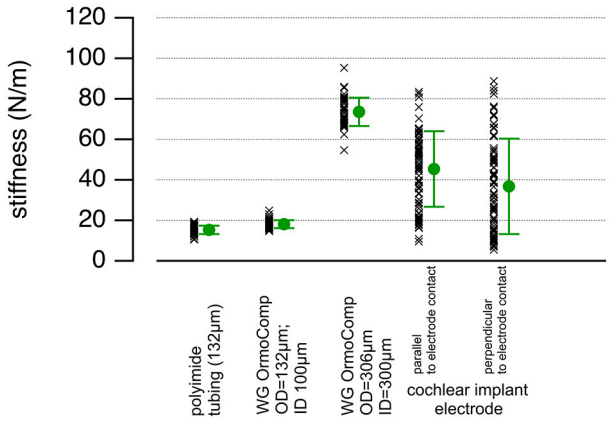


FIGURE 6
The plot shows the stiffness values, averages, and standard deviations for the 132 μm and 306 μm total diameter waveguides and the HiFocus 1J Advanced Bionics CI arrays. The data vary for the conventional HiFocus electrodes because the stiffness decreases toward the tip of the electrode, and the data were pooled.

TABLE 3 Bending losses for the 100-μm core polymer waveguides.

| 100-μm core; polymer waveguides; bending losses | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wavelength | | 534 nm | | | 1,375 nm | | | 1,460 nm | | | 1,550 nm | | |
| Waveguide | Radii of curvature [mm] | Loss [dB] | avg [dB] | σ [dB] | Loss [dB] | avg [dB] | σ [dB] | Loss [dB] | avg [dB] | σ [dB] | Loss [dB] | avg [dB] | σ [dB] |
| wg1 | 2 | 6.77 | 5.50 | 1.32 | 0.13 | 0.56 | 0.26 | 0.79 | 0.79 | 0.18 | 1.04 | 0.64 | 0.23 |
| wg2 | | 3.21 | | | 0.75 | | | 0.7 | | | 0.6 | | |
| wg3 | | 5.36 | | | 0.87 | | | 0.98 | | | 0.41 | | |
| wg4 | | 5.29 | | | 0.56 | | | 0.5 | | | 0.43 | | |
| wg5 | | 6.86 | | | 0.79 | | | 0.97 | | | 0.71 | | |
| wg1 | 1 | 9.53 | 8.54 | 1.30 | 3.59 | 2.05 | 0.84 | 1.73 | 2.11 | 0.50 | 1.98 | 1.44 | 0.37 |
| wg2 | | 7.68 | | | 1.48 | | | 3.09 | | | 1.61 | | |
| wg3 | | 7.12 | | | 1.69 | | | 2.07 | | | 0.87 | | |
| wg4 | | 7.79 | | | 1.25 | | | 1.79 | | | 1.25 | | |
| wg5 | | 10.58 | | | 2.22 | | | 1.87 | | | 1.47 | | |

Each waveguide (wg) was used to collect data at specific wavelengths at 534, 1,375, 1,460, and 1,550 nm. The curvature radii were 1 mm and 2 mm.

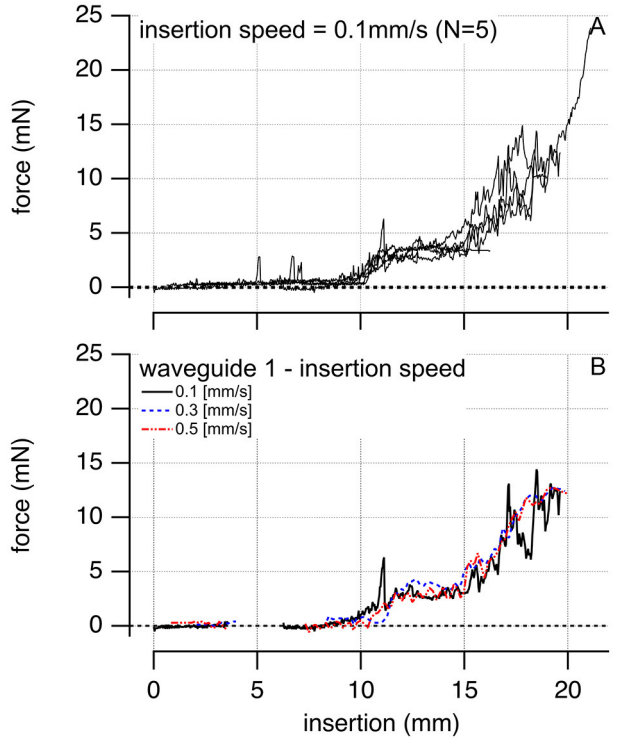


FIGURE 7
The plots show examples of inserting a single 100-μm core diameter waveguide into the scala tympani of a human-size acrylic cochlear model. **(A)** Is the insertion force for $N = 5$ different waveguides inserted at a velocity of 0.1 mm/s. Insertion forces for the waveguides are comparable. **(B)** Shows one of the waveguides inserted at different velocities, 0.1, 0.3, and 0.5 mm/s, respectively.

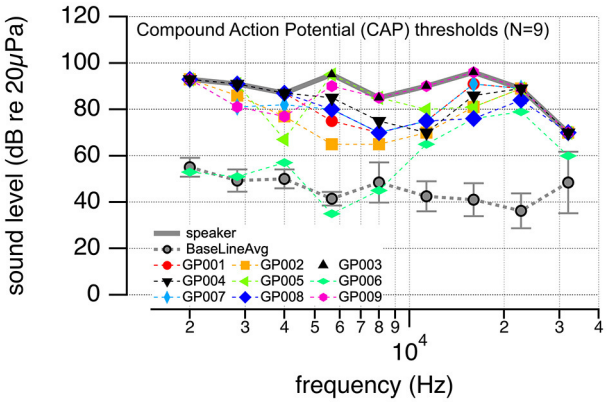


FIGURE 8
The plot shows the compound action potential (CAP) thresholds to pure tone stimulation at different frequencies. The solid gray line is the maximum sound level that could be achieved with the given settings. The dotted gray line shows the average (±one standard deviation) CAP thresholds for nine normal-hearing animals. The markers show the thresholds for the animals used in this study. All have drastic threshold elevations.

## 3.4 Insertion forces measurements

Insertion forces for the 306 μm total diameter waveguides into an acrylic human-size scala tympany model range from 10–200 mN and increase with the distance of the electrode insertion. During the process, we observed no buckling. Waveguide insertion forces into a selected acrylic model of the scala tympani of the human cochlea compared with the values obtained for electrode arrays used in contemporary CI systems. In our tests, 100-μm core waveguides required insertion forces not exceeding 25 mN, as depicted in Figure 7A. Various insertion speeds, ranging between 0.1 and 0.5 mm/s, did not influence the insertion forces, as shown in Figure 7B. In both panels, at a depth of 8–10 mm, the waveguides encounter the first curve in the cochlea model. This anatomical feature accounts for the observable surge in insertion forces.

## 3.5 Verification of the waveguides in guinea pigs

### 3.5.1 Compound action potential threshold curves of the guinea pigs in the study

CAP thresholds to pure tone stimuli served to assess baseline hearing for nine guinea pigs. One animal had no response at any frequencies tested. CAP-thresholds for the animals are shown in Figure 8. The gray line represents the maximum speaker sound level, and the dotted gray line is the average threshold of normal-hearing animals ± one standard deviation. The remaining markers show the thresholds determined for the animals in the study. Markers on the gray line indicate that no response could be recorded at the highest sound level delivered by the speaker.

### 3.5.2 Response growth function for the flat polished glass fiber and the waveguides

After placing the 200-μm core optical fiber through the cochleostomy in the basal turn of each guinea pig's cochlea, we assessed the responses to 100-μs optical pulses at 1,375 nm delivered at 10 Hz. Figure 9 shows the results. Figure 9A shows the input-output contours, which demonstrate the growth of the CAP amplitude with increasing radiant energy/pulse. Guinea pigs GP004, GP005, and GP007 did not respond to optical stimulation and were not included in further data analysis. Figure 9B shows the CAP amplitude optically evoked by 100 μs square pulses at 100 μJ/pulse radiant energy. It is plotted vs. the thresholds of the animals to acoustic stimulation at 500 Hz (blue hexagons), 1,000 Hz (green hexagons), and 8,000 Hz (orange hexagons). The correlation coefficients for the laser and acoustically evoked responses obtained with a linear correlation test (Igor Pro 8) are −0.62, −0.27, and −0.34 at 8,000, 1,000, and 500 Hz, respectively. No systematic correlation was found between the optical evoked response amplitude and the acoustic threshold. Figure 9C shows responses to optical stimulation using the waveguides 300-μm core (total diameter 306 μm). In one animal (GP001, Figure 9), the waveguide was cut at a 45-degree angle, inserted into the scala tympani, and then rotated by 360 degrees (Figure 9D). In the air, the cut surface reflects the radiation by ∼90 degrees, and the waveguides become "side-emitting." In fluids, the difference in the refractive index between the waveguide and the water is less than

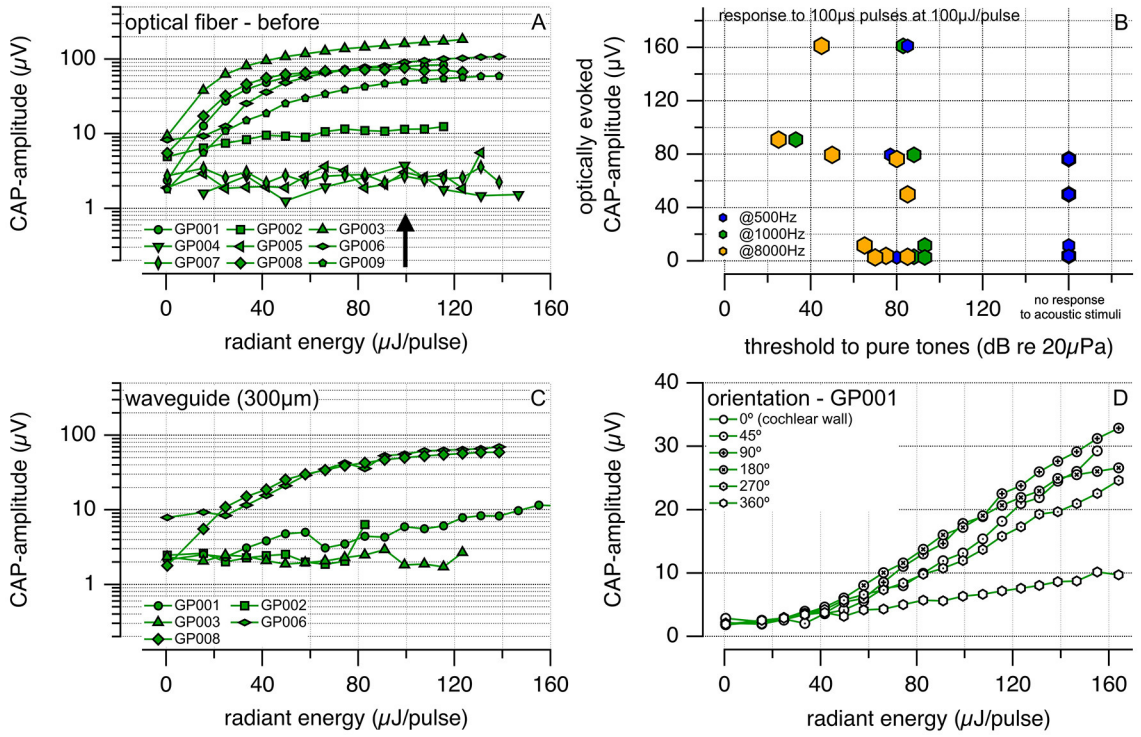


FIGURE 9
**(A)** Shows the compound action potential (CAP) amplitudes evoked optically in guinea pigs using a polished optical fiber with a 200 μm core (P200-5-VIS NIR, Ocean Optics) and coated with CYTOP. A larger radiant energy delivered to the cochlea leads to a larger CAP amplitude. **(B)** Shows the optical CAP amplitude evoked by 100-μs optical pulses at 100 μJ/pulse vs. the threshold to pure tone acoustic stimuli. Previous experiments in our and other laboratories show that laser radiation in the infrared can result in pressure pulses. If pressure pulses are responsible for the responses rather than direct neural stimulation, a correlation should exist between the amplitude evoked by a laser pulse and the animals' hearing. Deaf animals should have a smaller response amplitude than hearing animals, and the optically evoked amplitude should correlate with the response threshold to acoustic stimuli. The correlation coefficients for the laser and acoustically evoked responses are −0.62, −0.27, and −0.34 at 8,000, 1,000, and 500 Hz, respectively. **(C)** Exhibits the CAPs amplitude evoked optically using our waveguide with a total diameter of 306 μm. We employed the waveguide in those animals from **(A)** that showed optical responses. **(D)** Describes the CAPs amplitude vs. the radiant energy delivered for different orientations of the waveguide tip to the auditory neurons. The waveguide was cut at 45 degrees, inserted into the scala tympani, and rotated by a given angle after each measurement. The neural response amplitude was the smallest for the beam path pointing to the cochlear wall.

between the waveguide and air. The waveguide still emits to the side. The optically evoked auditory responses showed the smallest CAP amplitude when the waveguide's orientation was selected, and the beam pointed toward the cochlear wall.

## 4 Discussion and conclusion

Our study demonstrated that the polymer OrmoComp® is suitable for fabricating waveguides to transmit near-infrared radiation. Initially, we experimented with waveguides with a core diameter of approximately 300 μm, which was large enough to assess their mechanical and optical properties effectively. However, this size proved too large for practical use in future multi-channel optical CIs. As a result, our focus shifted to smaller waveguide diameters, and we assessed their optical and mechanical properties.

Using light to evoke auditory responses could enhance the spatial precision of stimulation in CIs, significantly improving how implant recipients perceive sound. As we advance in developing optical CIs (oCIs), selecting the optimal placement for light sources is crucial. Internal placement within the cochlea comes with challenges related to size and concerns about current leakage, as detailed in the Introduction. Meanwhile, the external placement of light sources housed within the implant casing necessitates hermetic sealing and waveguides for light delivery into the cochlea.

For waveguides, the cochlear spiral structure presents distinct design encounters. If not meticulously addressed, the geometry of the waveguides may pose an increased risk of bending losses, compromising the performance of the oCIs. It is not just about light transmission; the goal is to harmonize mechanical properties with efficient optical properties.

In this context, the design of polymeric waveguides for biomedical applications is an emerging field with few off-the-shelf options. For instance, FiberFin (Yorkville, Illinois, United States) produces polymeric waveguides designed for the visible range, which is not suitable for INS. Their core diameter is large (up to 1 mm), and they do not provide the necessary bending flexibility essential for our application, considering the small size of the human cochlea. A different vendor, Nitto Denko (Osaka, Japan), provides polymeric waveguides for medical endoscopy. Although they might have applications in other medical fields, they do not meet our requirements.

In pursuing different waveguide solutions for cochlear applications, we recognize the efforts of a research group from Germany. They have been exploring the design of polymeric waveguides intended to be used in future optogenetics-based-CIs (Helke et al., 2022). Using a wafer-level micromachining process, they have manufactured flexible waveguides using Polymethyl Methacrylate (PMMA) as the cladding and SU-8, an epoxy photoresist, for the core. This fabrication approach allows for large-scale production. However, the waveguides produced are rectangular, which can introduce challenges. From a mechanical perspective, the bending stress experienced by circular waveguides is distributed more uniformly due to their geometric form. This contrasts with rectangular waveguides, where stress distribution can be non-uniform, leading to mechanical failures in the corners and anisotropic and inhomogeneous refractive index distribution (Huang, 2003). This could result in increased bending and propagation losses.

For this reason, we have opted for circular waveguides. Nevertheless, large-scale production presents its own challenges, particularly when considering the limitations of wafer-level micromachining for such rounded geometries. We have employed a fabrication process that utilizes circular molds to address this. While addressing the manufacturing constraints, selecting the suitable material for the core in these waveguides also emerged as a critical factor. In this context, we chose the polymer OrmoComp®. This selection was influenced by its unique characteristics as an Ormocer, a material that merges the benefits of organic polymers and inorganic ceramics (Schizas and Karalekas, 2011). Its composition enables it to display glass-like properties after UV curing, contributing to its durability and stability, similar to traditional ceramics, while maintaining the flexibility typical of organic materials. The hybrid structure of OrmoComp®, which combines inorganic building blocks with organic groups, offers thermal and chemical stability and notable optical transparency, essential for effective light transmission. In addition, the biocompatibility of OrmoComp® is also a significant consideration, especially for medical devices such as future oCIs. Its compatibility with our circular waveguide molding process facilitates a more manageable and reproducible production method.

Building on these considerations, our study demonstrated that OrmoComp® is a suitable material for delivering near-infrared radiation. We initially experimented with waveguides having a core diameter of approximately 300 μm. This size not only allowed us to assess their mechanical and optical properties but also helped us to evaluate the performance during *in-vivo* optical stimulation of the cochlea in guinea pigs. These *in-vivo* experiments using our waveguides with a 300 μm core proved successful. They effectively delivered infrared light to target neurons and efficiently evoked neural responses (Figure 9B). An important observation from these experiments is the orientation of the waveguide to the auditory neurons. Optimal neural responses were achieved when the radiation was oriented correctly, emphasizing the critical role of accurate positioning, especially as we look toward designing future waveguide bundles. By conducting experiments with deafened guinea pigs, we ensured that sound did not contribute to evoking an action potential optically. No correlation was found when comparing the thresholds of optical and acoustic stimulation in these animals, highlighting the distinct mechanisms at play for each type of stimulation.

While the 300 μm core waveguide showed promising performance in optically stimulating the guinea pigs' cochlea, they were too large in diameter and stiff. Considering future multi-channel oCIs, reducing the diameter size of the waveguides became of interest. This led to an increased focus on using polyimide tubing as a cladding material. By aspirating the polymer with a syringe into the polyimide tubing, we successfully built waveguides with a core diameter of 100 μm. The method of aspirating should be conducted carefully to avoid forming air bubbles within the waveguide, which affect light propagation. The reduced diameter significantly improved our initial prototypes (injection molding). This smaller size enhances the overall mechanical compliance, making them more suitable for the human cochlea.

It is important to note that our *in-vivo* studies using guinea pigs are necessary to ensure that the waveguides are functionally capable of transmitting infrared light and stimulating the auditory neurons before advancing to a human clinical trial. In these *in-vivo* tests, the waveguides did not extend beyond the first turn of the guinea pig's cochlea due to their stiffness. We positioned them at 200 to 300 micrometers within the cochlea, focusing solely on assessing the light transmission efficiency for stimulating the auditory neurons at the cochlea base. In line with this, we used an acrylic human-sized model when evaluating the insertion forces for single 100-μm core waveguides instead of a guinea pig's model. This decision was based on the need to test the waveguides in an environment that accurately reflects the human cochlea's unique curvature, size, and length. Furthermore, the transparency of the acrylic model allows for clear visualization of the waveguide during insertion, enabling us to observe and assess any potential buckling or folding of the waveguide. It is vital to ensure its proper mechanical functioning and integrity and provide insights into how the waveguides would behave in a clinical scenario. Based on the aforementioned, the insertion forces measurements for single 100-μm core waveguides were in line with values reported for conventional cochlear electrodes arrays (Roland, 2005; Majdani et al., 2010; Schurzig et al., 2010; Kontorinis et al., 2011a,b; Miroir et al., 2012; Nguyen et al., 2012; Balster et al., 2014; Wade et al., 2014; Mirsalehi et al., 2017; Lo et al., 2018; Vadivelu et al., 2019; Hendricks et al., 2021; Snels et al., 2021; Zuniga et al., 2021; Bottcher-Rebmann et al., 2022). Considering that we inserted one waveguide at a time into the cochlear conduit to determine their single mechanical insertion behavior, we can expect insertion forces to increase when using a bundle of waveguides due to the overall larger stiffness. Therefore, a unique design of the fiber bundles should be considered, allowing individual waveguides to slide relative to each other. In this regard, it is important to note that fewer waveguides are in a cross-section of the bundle tip, decreasing the stiffness but increasing at its base (larger number of waveguides at the bundle base). In addition, to facilitate the insertion procedure, thus reducing the exerted forces, the bundle can have a pre-bended form at the tip, similar to cochlear electrode arrays. In addition to these results, we also found that force measurements at different insertion velocities exhibited similar slopes as the waveguide was introduced deeper into the cochlea (see Figure 7). From these results, we conclude that the insertion forces are mainly dominated by

bending rather than friction forces between the waveguide and the cochlear walls.

Concerning propagation losses in our waveguides, they encompassed a diverse range of wavelengths from the visible to the infrared spectrum, including 450 nm, 534 nm, 680 nm, 1,375 nm, 1,460 nm, and 1,550 nm. However, the selection was narrowed when examining bending losses, specifically omitting the 450 and 680 nm wavelengths. Our primary focus was on the potential of infrared neurostimulation (INS) for CIs, particularly given its characteristic of stimulating the cochlea without the need for genetic modifications of the spiral ganglion neurons. Propagation losses for waveguides 100-μm core were minimum at 1,375 and 1,460 nm, while 534 nm losses were about ten times greater. Bending losses over 360 degrees, the loop showed values in the range of 1 dB and below for a similar curvature radius present in the human cochlea. Previously published results on the measurements of the optical properties of OrmoComp® provide valuable data that corroborate our measurements (Heinrich, 2021; Kampasi et al., 2021). Their work has determined the optical attenuation of OrmoComp® slabs, a parameter that sets a lower limit of optical losses in waveguides made from this material. It is important to recognize that propagation losses in waveguides are composed of not only the inherent losses within the core material, such as absorption and scattering (optical attenuation), but also additional scattering losses at the cladding interface. Focusing on NIR wavelengths in our study, specifically at 1,375, 1,460, and 1,550 nm, the optical attenuation of OrmoComp® measured by Heinrich (2021) and Kampasi et al. (2021) was between 0.5–2 dB/cm. This range is consistent with our findings for these wavelengths, as detailed in the tables of our manuscript. However, in the visible spectrum, particularly between 400–650 nm, despite the optical attenuation of OrmoComp® remaining similar in these works, our waveguides exhibit significantly higher propagation losses in the visible spectrum. This discrepancy suggests a low performance of the polyimide cladding material in our waveguide design for visible wavelengths. The propagation losses we measured were considerably higher up to ten times than the attenuation values for OrmoComp® reported in the studies mentioned above.

As our research advances, we prepare to conduct further evaluations on the 100 μm-core OrmoComp® waveguides, building upon the characterizations already presented in the current work. These upcoming studies will focus on improving the light coupling using microlenses, assessing the waveguides' resilience to photobleaching and their stability in electrolyte environments similar to cochlear perilymph. Additionally, we intend to undertake a long-term study of these waveguides in an animal model such as guinea pigs and cats. This study is designed to provide insights into the waveguides' performance and biocompatibility over extended periods, essential for their potential clinical application in future oCIs.

We also plan to explore the potential for reducing the total diameter of waveguides to approximately 50 μm and even smaller. This reduction in diameter is crucial for effectively fitting the waveguides within the scala tympani of the human cochlea. Given the scala tympani's varying inner diameter—from 1.5–2.5 mm at the base to below 1 mm at the apex—we anticipate the feasibility of housing compact bundles comprising 40–50 waveguides in this region. In achieving this, we could consider using smaller microtubing with the required total and inner diameters, although this approach presents specific challenges, particularly with polyimide tubing. A promising alternative strategy involves using Nylon-6 microtubing as molds for the waveguides. The critical challenge in this approach is to remove the tubing without compromising the OrmoComp core. Nylon-6 may offer a more practical solution for dissolving than polyimide, potentially easing the fabrication process. Successfully navigating this challenge would enable us to fabricate OrmoComp® cores of the desired small diameters. To explore the waveguide's optical and mechanical properties, these cores could then be coated with several cladding materials, such as thin CYTOP layers and UV-curable resins (Evertz et al., 2021). Such investigations in cladding are crucial for ensuring efficient light transmission and mechanical stability during the insertion of the fiber bundle into the human cochlea, thereby aiming to enhance future oCIs performance.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The animal study was approved by IACUC at Northwestern University. The study was conducted in accordance with the local legislation and institutional requirements.

## Author contributions

MK, LK, and XT: Methodology, data acquisition, investigation, and writing, review & editing. JC: Methodology, data acquisition, formal analysis, investigation, and writing, review & editing. MT and KK: Conceptualization, methodology, and writing, review & editing. R-uH and C-PR: Conceptualization, methodology, data acquisition, formal analysis, investigation, project administration, writing the original draft, and writing, review & editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

C-PR and JC filed patents on the fabrication of waveguides. C-PR is a co-founder of NuroTone and co-owner of a patent on the fabrication and use of waveguides.

The remaining authors declare that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fauot.2024.1221778/full#supplementary-material

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# A novel consumer-centric metric for evaluating hearing device audio performance

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**Background and Aim:** The emergence of direct-to-consumer hearing devices has introduced confusion in making appropriate choices, highlighting the need for users to be well-informed for optimal device selection. Currently, no established metric offers insights into the sound performance of these devices. This study aimed to introduce and assess a novel consumer-centric metric (i.e., SoundScore) for hearing device audio performance.

**Method:** The SoundScore metric was created based on five dimensions of hearing device audio performance (i.e., speech benefit in quiet and moderate, speech benefit in loud, own voice perception, feedback control, streamed music sound quality). Tests were conducted under lab conditions with an acoustic manikin using two fitting protocols meant to approximate (1) real-world default device settings for a mild-to-moderate sloping hearing loss ("Initial Fit") and (2) an audiological best-practices approach ("Tuned Fit"). A total of 41 hearing devices comprising 10 prescription hearing aids (Rx-HA), 10 self-fitting over-the-counter hearing aids (OTC-SF), 8 pre-set based over-the-counter hearing aids (OTC-PS), and 13 personal sound amplification systems (PSAPs) were evaluated.

**Results:** SoundScore varied significantly between device classifications with Rx-HA yielding the highest average scores and PSAPs the lowest. SoundScore also varied with fitting method, whereby preset based devices scored lower on average than devices programmable by fitting software. Performance across the five composite sound performance metrics generally improved between "Initial" and "Tuned" fits for Rx-HA. However, this was not observed with OTC-SF. Also, no significant difference in SoundScore was found between devices of different form factors (i.e., BTE vs. ITE).

**Conclusions:** Initial findings suggest that the SoundScore can effectively distinguish between the audio performance of different hearing aids, offering consumers a valuable decision-making tool. Future studies should examine the relationship between the SoundScore and consumer hearing aid benefit/satisfaction.

KEYWORDS

**hearing aids, hearing aid sound quality, direct-to-consumer, consumer metrics, audio performance**

# Introduction

The direct-to-consumer (DTC) model in hearing healthcare is becoming increasingly popular (Taylor and Manchaiah, 2019). This is a direct result of both technological advancement and policy changes that have blurred the lines between medical and consumer-grade hearing devices. In addition, the U.S. Food and Drug Administration (FDA) created a new category of over the counter (OTC) hearing aids for adults with perceived mild to moderate hearing loss to further improve accessibility. Consequently, individuals with mild-to-moderate hearing loss have access to an array of hearing devices including prescription hearing aids (Rx HA), self-fitting OTC hearing aids (OTC-SF), preset OTC hearing aids (OTC-PS), and personal sound amplification systems (PSAPs). In the U.S., hearing aid consumers can purchase these devices through various channels (i.e., hearing healthcare providers, online vendors, in-person electronics retailers) and at diverse price points (e.g., PSAPs starting at as low as $20 with high end Rx HA costing several thousand dollars).

While the DTC movement in hearing healthcare has improved accessibility (Manchaiah et al., 2017; Tran and Manchaiah, 2018), it has also introduced confusion among consumers and hearing healthcare professionals (Manchaiah et al., 2019; American Speech-Language and Hearing Association, 2022; Chappell, 2022). New devices enter the market every few weeks, making it challenging to keep abreast of every offering, and providers likely have limited experience with DTC products as they are not a part of traditional clinical practices. These reasons may collectively leave hearing healthcare professionals ill-equipped to advise patients on device quality and suitability. More importantly, it is challenging for consumers to accurately assess device quality due to factors such as (1) the growing landscape of DTC products, (2) the range of prices, (3) companies using similar marketing claims regarding hearing benefit. Consumers who purchase these devices on DTC channels may find it extremely difficult to navigate these barriers without professional assistance as found in the traditional hearing aid model.

Professionals typically use electroacoustic characteristics such as full-on gain, frequency response, harmonic distortion, and equivalent input noise as measures to determine the quality of hearing devices. These metrics, however, are not easily accessible or comprehensible to consumers. Sound quality of hearing devices is probably the most desirable attribute that consumers would like to ascertain (Manchaiah et al., 2021) as it relates to their hearing aid benefit and satisfaction (Bannon et al., 2023). As a result, a consumer-centric metric for hearing device audio performance which emphasizes the sound performance could be invaluable for consumers to inform purchasing decisions.

Enhancing consumer-centricity in hearing healthcare, especially in approaches and communication, is crucial given the proliferation of DTC options (Brice et al., 2023; Manchaiah et al., 2023a). For example, there is a need for deeper understanding of consumer preferences and values to inform creation of products and channels tailored to their specific needs. In addition, there's a pressing demand for tools that assist consumers in their decision-making. Web-based decision aids, for instance, can guide consumers in sifting through device options, while metrics focusing on hearing device quality can inform their final product choice (Tran et al., 2023). In line with this perspective, the Hear Advisor (www.hearadvisor.com) initiative was launched, establishing an independent hearing aid testing lab. Hear Advisor uses realistic recorded audio scenes (e.g., conversations in quiet office, noisy environments) that are presented from an 8-speaker array with hearing devices placed on a Knowles Electronic Manikin for Acoustic Research (KEMAR; Burkhard and Sachs, 1975). Hearing aid output is recorded, and sound performance elements are evaluated. The culmination of this testing is the "SoundScore" metric—a straightforward 0–5 scale where a higher score denotes superior audio performance. Comprehensive details of these experiments can be found in the method section.

Developing a singular consumer-centric metric presents substantial challenges due to the myriad of variables involved, such as different hearing loss categories, diverse environments, and various hearing device settings. To streamline this undertaking, certain decisions were made regarding which variables to prioritize. For instance, the focus was narrowed down to patterns of mild-to-moderate hearing loss, a selection of frequently encountered sound environments, and uniform hearing aid settings across devices. Whenever feasible, validated objective metrics, such as the Hearing-Aid Speech Perception Index (HASPI V2), for assessing speech perception benefit was used (Kates and Arehart, 2021).

This study describes the methods and preliminary evaluation of this novel consumer centric SoundScore metric for hearing device audio performance. The specific objective was to examine the SoundScore and constituent five dimensions of hearing device audio performance (i.e., speech benefit in quiet and moderate, speech benefit in loud, own voice perception, streamed music sound quality, and feedback control) across (1) different hearing device technology categories; (2) adjustment interface; (3) fitting method (i.e., initial fit vs. tuned fit); and (4) hearing device form factor (i.e., BTE vs. ITE).

# Method

## Study design

The study used a cross-sectional laboratory experimental design (Sabin et al., 2023). The sound performance ratings for 41 hearing devices were estimated based on KEMAR recordings of 12 realistic sound environments and multi-talker scenes. The hearing devices were fit to an age-related hearing loss audiogram with mild-to-moderate high frequency sloping pattern (see Table 1; Bisgaard et al., 2010) using an "Initial" and "Tuned" Fitting. The hearing devices included Rx HA ($n = 10$), OTC-SF ($n = 10$), OTC-PS ($n = 8$), and PSAPs ($n = 13$).

## Test environment and equipment

All hearing device testing was conducted in a custom-built near-anechoic acoustic lab where all surfaces were covered with significant sound-absorbing materials, other than the floor which was carpeted. The resulting test environment was measured to be sufficiently quiet and non-reverberant with an ambient sound pressure level of 34 dB LAeq (A weighted) and 4-frequency (0.5,

TABLE 1 Mild-to-moderate N3 audiogram (Bisgaard et al., 2010).

| Frequency in Hz | 250 | 375 | 500 | 750 | 1k | 1.5k | 2k | 3k | 4k | 6k |
|---|---|---|---|---|---|---|---|---|---|---|
| Threshold | 35 | 35 | 35 | 35 | 40 | 45 | 50 | 55 | 60 | 65 |

1, 2, and 4 kHz) reverberation time of 0.059s. A KEMAR (45BA model with RA0045 ear simulators and VA tapered ear canals) was positioned at the center of the room and used for binaural hearing device recordings (see Figure 1). Surrounding KEMAR was an 8-speaker horizontal array of Yamaha HS5 Powered Monitors (45° resolution). A speaker ring radius of 1-meter was used based on an estimated critical distance of 1.5-meter, ensuring recordings at the ring center were dominated by the direct speaker sound and not room reflections.

An Antelope Orion Studio external sound card, Pro Tools software, and custom Matlab program were used for the presentation of audio scenes through the speaker ring, calibration, and recording of signal from KEMAR's eardrum microphones. For a more detailed explanation see Sabin et al. (2023).

## First and tuned fitting protocols

Hearing aids were configured to two fitting paradigms to replicate programming variations observed in the real-world. Specifically, the "Initial Fit" attempted to approximate what most people experience where real-ear measures are not performed and either basic instructions are used, or the default manufacturer recommendations are the basis for fitting (Mueller, 2014). Even a simple fitting process as this has many variables and therefore, a decision-tree flow chart was used for consistency across devices (Sabin et al., 2023). For many OTC products, this meant adjusting one primary parameter (e.g., volume control) to best match NAL-NL2 Experienced user targets (Keidser et al., 2011) for a 65 dB SPL presentation of the International Speech Test Signal (ISTS; Holube et al., 2010). For Rx HA, each respective device's fitting software was used to perform a "First-Fit" relying on manufacturer recommendations and their proprietary fitting algorithm. Device ear tip, or the acoustic coupling between device and KEMAR's artificial ear canals, was also considered and addressed in the flow chart. For DTC products this often resulted in using the default ear tip or, as was the case with Rx HA, using manufacturer recommendations based on N3 audiogram input or an on-ear hearing test.

Recordings were also made at a second "Tuned Fit" where audiologic best-practices were followed to optimize speech intelligibility benefits. In this fitting protocol, all parameters and available ear tips were adjusted to best match prescriptive targets for speech inputs at 55, 65, and 75 dB SPL. If a hearing device did not offer input specific gain adjustments, a 65 dB SPL presentation of ISTS was used for the fitting (see Figure 2). Across both fittings, the equivalent of real-ear measures (REM) was replicated on KEMAR using the output of the eardrum microphones to allow for real-time monitoring of device adjustments in custom Matlab programs [described in Sabin et al. (2023)].

## Recordings

Twelve realistic acoustic scenes from the Ambisonic Recordings of Typical Environments (ARTE) database were decoded and presented to our 8-channel 2-dimensional speaker ring (Weisser et al., 2019). A custom set of multi-talker scripts (1, 2, and 3 talkers) were also recorded with the help of voice actors (1 female and 2 males) in an acoustically treated recording studio. Each script was recorded twice with rotating actors and the associated background sounds were monitored over headphones throughout the recording process to elicit potential Lombard effects. To account for acoustic differences between environments, speech recordings were convolved using the multichannel impulse response from the ARTE database matching the reverberation levels for each corresponding acoustic scene. Individual voices were also positioned across speaker channels 1 (0 degrees), 2 (45 degrees), and 8 (−45 degrees) creating realistic spatial talker locations relative to KEMAR.

The final speech and background scenes were combined and presented following the observed environmental sound-pressure levels and signal-to-noise ratios outlined by Wu et al. (2018). All recordings were preceded by 15 seconds of isolated background scene to allow time for hearing device program switching. A total of 72 scenes were ultimately recorded for each hearing device across 12 background scenes, 3 talkers, and 2 actor rotations.

The audio quality of streamed music was also assessed by presenting five genres of royalty free music with a smartphone (iPhone 8 Plus iOS v16.7.5) to hearing devices positioned on KEMAR's ears. The music segments were 33.7 seconds in length on average and, like speech presentations, an extra 15 seconds of music was included in the beginning to allow time for program switching. Streamed music presentation levels were calibrated prior to recordings by way of a custom Matlab program and real-time spectral analysis of KEMAR's eardrum microphones. Specifically, the smartphone streamed audio levels were adjusted to be +/− 5dB of a music-based reference curve at 1 kHz (1/3 octave filter).

Finally, all audio files were diffuse field equalized to make them suitable for monitoring over headphones (i.e., removing acoustic effects of the manikin from the audio recordings). This was achieved by (1) recording uncorrelated white noise at the center of the speaker ring through KEMAR and a flat reference microphone and (2) computing a filter of the spectral differences between them. The resulting filter shape was largely in agreement with published values as illustrated in Figure 2 (Bentler and Pavlovic, 1992).

## Sound performance metrics and rating estimation

All hearing device audio recordings were analyzed across five dimensions of sound performance and scales to a 5-point scale.

FIGURE 1
KEMAR and 8-channel speaker ring in the custom-build acoustic lab. Walls seen are stretched acoustically transparent fabric over velocity-based absorption material.

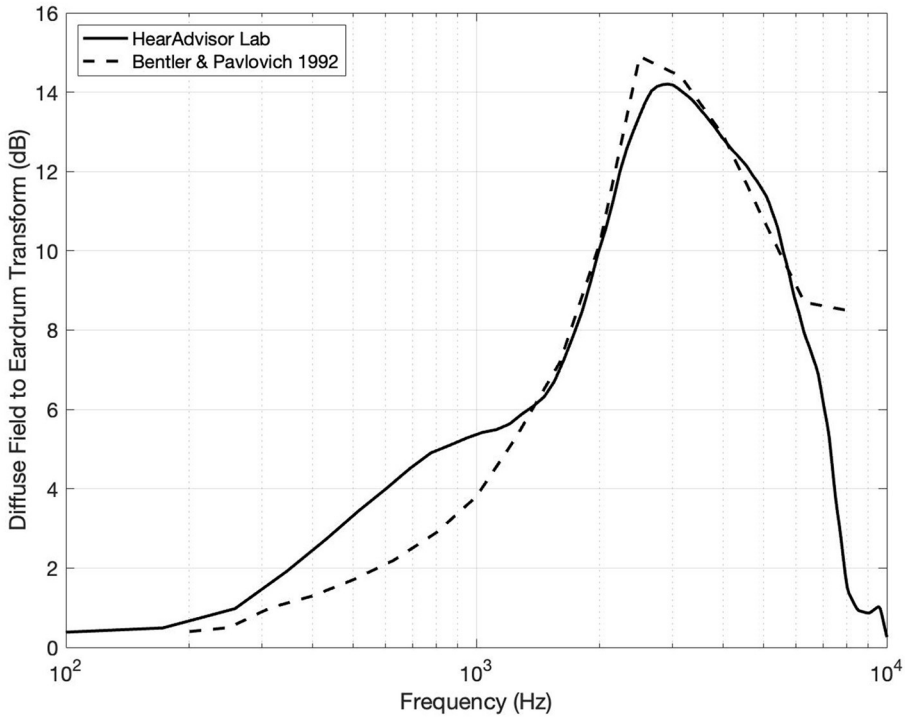


FIGURE 2
Diffuse field equalization filter compared to previously reported values by Bentler and Pavlovic (1992). Some variation is observed which can be attributed to differences in environment and recording methodology.

The first dimensions focused on predicted speech intelligibility benefits using HASPI v2 which models the impaired auditory system and has been found to predict intelligibility across a range of acoustic environments (Kates and Arehart, 2021). HASPI v2 scores were computed for each device, averaged across both ears, and separated into our (1) Speech Benefit in Quiet and Moderate and (2)

TABLE 2 Results of both forced-rank surveys from Sabin et al. (2023): (A) survey of hearing aid consumers ($n = 107$) and hearing aid professionals ($n = 95$) ranking relative importance which was used to create the 5 metric weighted average and (B) survey asking hearing aid consumer ($n = 257$) to rate "How important is it that your hearing aids sound good with minimal effort?".

| A | Speech benefit in quiet and moderate | Speech benefit in noise | Own voice not boomy | Does not squeal | Streaming music quality |
|---|---|---|---|---|---|
| Consumers avg. Rank | 3.2 | 3.1 | 1.1 | 1.3 | 1.3 |
| HCPs avg. rank | 3.5 | 2.7 | 1.4 | 1.7 | 0.7 |
| 2-Group avg. rank normalized | 0.34 | 0.29 | 0.12 | 0.15 | 0.10 |
| **B** | **Not at all important (0.0)** | **Slightly important (0.25)** | **Moderately important (0.5)** | **Very important (0.75)** | **Extremely important (1.0)** |
| Percent of sample | 1% | 4% | 15% | 37% | 43% |

This survey aimed to assess the importance of Initial Fit accuracy and was used to create a weighted average of the Initial and Tuned fitting scores.

Speech Benefit in Loud metrics. HASPI v2 values for each of these two categories were computed separately based on environmental scenes and whether the average sound pressure level was $<$ or $>$70 dB SPL, respectively.

Own Voice Perception was our third sound performance metric which aimed to estimate subjective occlusion using Real Ear Occluded Insertion Gain (REOIG). This was previously obtained during calibration to verify ear tip occlusion on KEMAR and reflects spectral differences between open ear and occluded ear (with device off). Subjective occlusion for our Own Voice Perception metric was estimated by comparing our REOIG values to those from Cubick et al. (2022) and then mapping the relationship between our objective measurements and their subjective user ratings. For devices with active occlusion compensation (AOC), extra steps were taken to account for the influence of active cancellation on own-voice sound quality. This was estimated by measuring active occlusion with an Audioscan Axiom test box and similarly mapped our findings to REOIG values and the previously mentioned user ratings. These steps are described in detail in Sabin et al. (2023).

Feedback volatility, or the likelihood of a device to squeal during everyday use, was the focus of our fourth sound performance dimension (i.e. Feedback Handling) and is a common complaint among hearing aid users (Jenstad et al., 2003). We therefore tested the feedback canceller of each device by making KEMAR recordings in two challenging real-world conditions: (1) simulating a hair scratch motion by moving hands periodically by KEMAR's ears for 10 seconds and (2) repeatedly cupping KEMAR's ears for 10 seconds. These recordings were then subjectively rated during blind listening tests and mapped to a 5-point scale.

The final dimension was Streamed Music Audio Quality which again sought to estimate subjective sound quality preferences of hearing aid users. Appropriately, the Hearing Aid Audio Quality Index (HAAQI; Kates and Arehart, 2015) was used as it employs the same model of the impaired auditory system as HASPI v2 and was designed to match sound quality judgements of individuals with hearing loss. HAAQI scores were mapped to a 5-point scale after averaging scores across KEMAR's ears and the 5 audio compositions recorded.

## Weightings and SoundScore

To increase accessibility of our findings, we sought to simply the five dimensions of hearing device audio performance and two fitting paradigms to a single easy to understand number, i.e., "SoundScore." This was achieved in three steps: (1) by combining the composite sound performance metrics using a user-centric weighted average, (2) combining the Initial and Tuned fitting paradigms in a manner that mirrors real-world user experiences, and (3) applying a normalization factor such that the top scoring hearing device received a 5.0. The specifics of this process are outlined in Sabin et al. (2023), and involved two separate forced-rank surveys of hearing aid consumers and professionals (seen in Table 2).

## Data analyses

Descriptive statistics of the sound performance ratings (i.e., SoundScore) were examined. The difference in sound performance rating across hearing device categories based on technology level were assessed using one-way ANOVA if the data met the assumption of normality or using the Kruskal-Wallis test if the data failed the assumption of normality. *Post-hoc* multiple comparisons were performed using two sample *t* test or Wilcoxon rank-sum test with Benjamin-Hochberg corrections for multiple comparisons. In the presence of heteroscedasticity Welch ANOVA followed by the Games-Howell pairwise comparison tests were used. Similar analysis was conducted to assess the significant differences of sound performance across different fitting methods.

Difference in sound performance ratings in the first fit and tuned fit for Rx HA and OTC-SF were evaluated using paired sample *t*-tests. Finally, a simple linear regression model was utilized the impact of the form factor (i.e., BTE vs. ITE) on the SoundScore. Necessary regression model assumptions, including the normality were satisfied. All analyses were performed with R statistical software (Version: 4.2.2). All tests were two tailed and performed at a threshold of 5% level of significance.

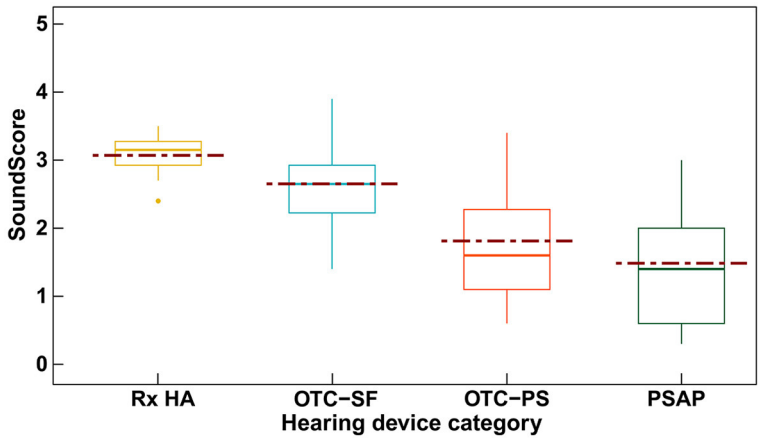


FIGURE 3
Box plot showing the SoundScore variation (median [solid line], mean [dotted line], and inter quartile range) across different hearing device categories. SoundScore values published in Hear Advisor websites include an added constant value of +1.1 to the scores provided here.

# Results

## Effect of hearing device technology categories on audio performance

Figure 3 depicts the variation in SoundScore across different hearing device categories. The highest median overall score can be seen with the Rx HA (median: 3.15, IQR: 0.35) while the lowest median overall score was seen with the PSAPs (median: 1.4, IQR: 1.4). PSAPs had the highest IQR (1.4) relative to all other categories.

Table 3 includes the mean (SD) values for different elements of audio performance ratings across different hearing device categories along with the results of the significance test among these categories. The Rx category displayed the highest mean SoundScore of 3.07 (SD: 0.3), while the PSAP category had the lowest at 1.48 (SD: 0.9). Differences in SoundScore between the hearing device categories was significant ($p < 0.001$) as illustrated in Table 3. SoundScore between Rx HA vs. OTC-PS ($p = 0.018$), Rx HA vs. PSAP ($p < 0.001$), and OTC-SF vs. PSAP ($p = 0.006$) were significantly different as shown in Supplementary Table 1. Significant differences were also observed for audio performance elements of speech benefit in quiet and moderate, speech benefit in loud, own voice sounds boomy, and overall scores for both first fit and tuned fit, but not for elements music streaming sounds good and does not feedback. Pairwise comparisons showed significant difference between Rx HA vs. OTC-PS, Rx HA vs. PSAP, OTC-SF vs. PSAP on several of these elements but no significant differences were observed among Rx HA vs. OTC-SF, OTC-SF vs. OTC-PS, and OTC-PS vs. PSAP (see Supplementary Table 1).

## Effect of adjustment interface on hearing device audio performance

Figure 4 shows the SoundScore variation across hearing devices with different adjustment interface. The highest median overall score can be seen for devices with fitting software (median: 3.15, IQR: 0.35) while the lowest median overall score was seen with the hearing devices with preset programs (median: 0.85, IQR: 0.50).

Hearing devices with fitting software (Table 4) showed the highest mean SoundScore of 3.07 (SD: 0.3) while preset-based hearing devices had the lowest mean of 0.91 (SD: 0.5). A statistically significant difference in SoundScore between different fitting methods ($p < 0.0001$) was demonstrated (Table 4). Pairwise comparisons showed a significant difference in SoundScores for devices with fitting software vs. App-based ($p < 0.01$), fitting software vs. preset-based ($p < 0.001$), and App-based vs. preset-based ($p < 0.001$) as illustrated in Supplementary Table 2.

Significant differences were also observed for audio performance elements of speech benefit in quiet and moderate (in first fit and tuned fit), speech benefit in loud (in first fit and tuned fit), own voice sounds boomy (in tuned fit), music streaming sounds good (in first fit and tuned fit), and also for overall scores (in first fit and tuned fit) across hearing devices with different fitting methods as shown in Table 4. The pairwise comparisons are provided in Supplementary Table 2.

## Effect of audiologist adjustments (tuned fit) on hearing device audio performance

Figure 5 shows the spread of first fit (green dots) and tuned fit (red dots) scores for Rx HA and OTC-SF. For Rx HA, the overall first fit score variation ($M = 2.99$, $SD = 0.4$) is reduced substantially with audiologist tuned fit ($M = 3.36$, $SD = 0.3$). However, for OTC-SF, the tuned fit overall scores ($M = 2.61$; $SD = 0.7$) does not seem to change substantially when compared to initial fit overall scores ($M = 2.36$; $SD = 0.8$). These results suggest that the Rx HA category can be fine-tuned more than the OTC-SF. In addition, the Rx HA brand may have some difference in initial fit with manufacturers proprietary software, but the audiologist can achieve similar audio performance ratings following tuned fit irrespective of the device brand and price-point.

10.3389/fauot.2024.1406362

TABLE 3 Audio performance ratings across different hearing device categories.

| Elements of audio performance | Mean (SD) across different hearing device categories | | | | Significant difference | |
|---|---|---|---|---|---|---|
| | Rx HA ($n = 10$) | OTC-SF ($n = 10$) | OTC-PS ($n = 8$) | PSAP ($n = 13$) | F or $X^2$ | *P*-value |
| SoundScore | 3.07 (0.3) | 2.65 (0.7) | 1.81 (1.0) | 1.48 (0.9) | 9.88 (df1 = 3, df2 = 37) | <0.001 |
| First Fit Scores | | | | | | |
| Speech benefit in quiet and moderate | 3.54 (0.8) | 3.27(0.9) | 1.74 (1.7) | 1.06 (1.1) | 12.31 (df1 = 3, df2 = 37) | <0.001 |
| Speech benefit in loud | 1.74 (0.7) | 1.59 (1.2) | 0.68 (0.8) | 0.74(1.1) | 11.55* (df = 3) | 0.009 |
| Own voice does not sound boomy | 2.59 (0.7) | 2.62 (1.2) | 2.88 (1.5) | 1.47 (0.8) | 4.00 (df1 = 3, df2 = 37) | 0.014 |
| Music streaming sounds good | 3.30 (0.6) | 1.37(1.8) | 1.50 (1.8) | 2.01 (2.3) | 5.02* (df = 3) | 0.169 |
| Does not feedback | 4.56 (0.5) | 4.27(0.7) | 4.47(0.9) | 4.87 (0.4) | 7.09* (df = 3) | 0.069 |
| First fit overall score | 2.99 (0.4) | 2.60 (0.7) | 1.8 (1.0) | 1.40 (0.8) | 9.98 (df1: 3, df2: 37) | <0.001 |
| Tuned fit scores | | | | | | |
| Speech benefit in quiet and moderate | 4.32 (0.3) | 3.60(0.8) | 2.01 (1.8) | 1.50 (1.5) | 20.7 (df1: 3, df2: 16.2) | <0.001 |
| Speech benefit in loud | 2.37 (0.8) | 1.89 (1.4) | 0.86 (1.0) | 1.05 (1.1) | 3.98 (df1: 3, df2: 37) | 0.0149 |
| Own voice does not sound boomy | 2.59 (0.7) | 2.23 (1.4) | 2.22 (1.4) | 1.17 (1.0) | 3.63 (df1:3, df2: 37) | 0.0216 |
| Music streaming sounds good | 3.14 (0.5) | 1.42 (1.9) | 1.64 (1.9) | 2.01 (2.3) | 3.76* (df = 3) | 0.2881 |
| Does not feedback | 4.09 (0.5) | 4.07 (0.8) | 4.11 (1.1) | 4.78 (0.5) | 6.56* (df = 3) | 0.0873 |
| Tuned fit overall score | 3.36 (0.3) | 2.73 (0.7) | 1.84 (1.0) | 1.62 (1.1) | 14.3 (df1 = 3, df2 = 16.7) | <0.001 |

Significant differences which were assessed by Kruskal-Wallis test are marked with*.

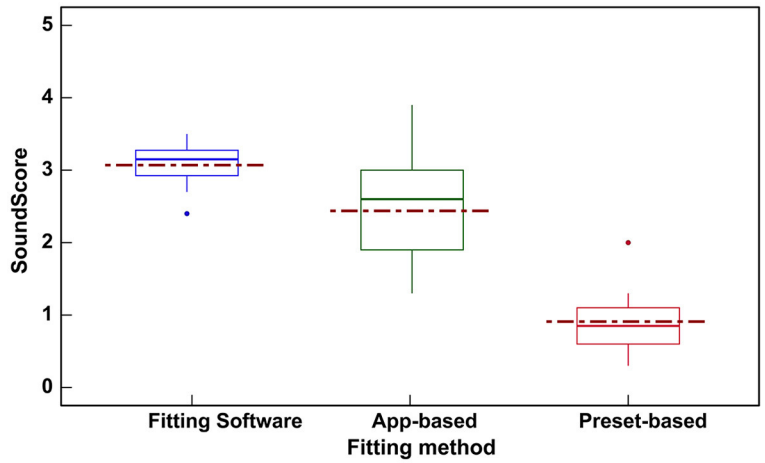


FIGURE 4
Box plot showing the variation in SoundScores (median [solid line], mean [dotted line], and inter quartile range) across hearing devices based on three different fitting interfaces. SoundScore values published in Hear Advisor websites include an added constant value of +1.1 to the scores provided here.

TABLE 4 Audio performance ratings across hearing devices based on three different adjustment interface.

| Elements of audio performance | Mean (SD) across different hearing device categories | | | Significant difference | |
|---|---|---|---|---|---|
| | Fitting software ($n = 10$) | App-based ($n = 21$) | Preset-based ($n = 10$) | F or $X^2$ | *P*-value |
| **Sound score** | 3.07 (0.3) | 2.44 (0.7) | 0.91 (0.5) | 34.95 (df1 = 2, df2 = 38) | <0.0001 |
| First fit scores | | | | | |
| Speech benefit in quiet and moderate | 3.54 (0.8) | 2.51 (1.4) | 0.8(1.0) | 13.56 (df1 = 2, df2 = 38) | <0.0001 |
| Speech benefit in loud | 1.74 (0.7) | 1.37 (1.2) | 0.21 (0.3) | 15.59* (df = 2) | 0.0004 |
| Own voice does not sound boomy | 2.59 (0.7) | 2.38 (1.4) | 1.83 (0.8) | 4.95* (df = 2) | 0.08 |
| Music streaming sounds good | 3.3 (0.6) | 2.3 (2.0) | 0.36 (1.1) | 11.06* (df = 2) | 0.004 |
| Does not feedback | 4.56 (0.5) | 4.41 (0.7) | 5.00 (0.0) | 5.49* (df = 2) | 0.06 |
| First fit overall score | 2.99 (0.4) | 2.36 (0.8) | 0.93 (0.5) | 28.74 (df1 = 2, df2 = 38) | <0.0001 |
| Tuned Fit Scores | | | | | |
| Speech benefit in quiet and moderate | 4.32 (0.3) | 3.1 (1.2) | 0.8 (1.0) | 25.33* (df = 2) | <0.0001 |
| Speech benefit in loud | 2.37 (0.8) | 1.78 (1.2) | 0.21 (0.3) | 36.70 (df = 2) | <0.0001 |
| Own voice does not sound boomy | 2.59 (0.7) | 2.05 (1.3) | 1.22 (1.1) | 3.71 (df1 = 2, df2 = 38) | 0.034 |
| Music streaming sounds good | 3.14 (0.5) | 2.37 (2.0) | 0.36 (1.1) | 10.34* (df = 2) | 0.006 |
| Does not feedback | 4.09 (0.5) | 4.17 (0.9) | 4.95 (0.1) | 5.66* (df = 2) | 0.06 |
| Tuned fit overall score | 3.36 (0.3) | 2.61 (0.7) | 0.8 (0.6) | 49.36 (df1 = 2, df2 = 38) | <0.0001 |

Significant differences which were assessed by Kruskal-Wallis test are marked with*.

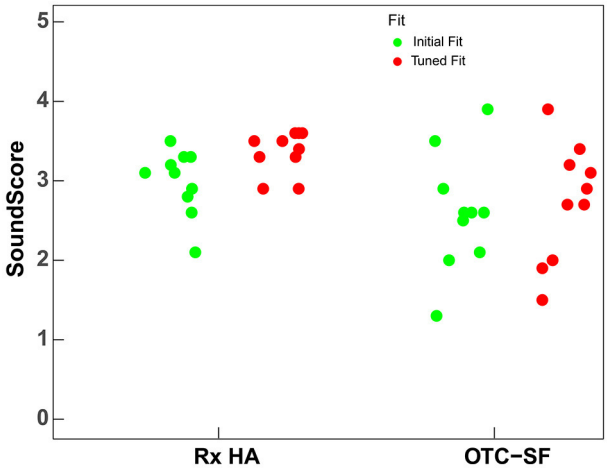


FIGURE 5
SoundScores for prescription hearing aids (Rx HA) and self-fitting OTC hearing aids (OTC-SF) at first fit and tuned fit. SoundScore values published in Hear Advisor websites include an added constant value of +1.1 to the scores provided here.

The initial fit and tuned fit scores for *overall score* and *sound performance in loud* (Table 5) were statistically significant for both Rx and OTC-SF (i.e., scored improved after tuned fit). Additionally, the initial fit and tuned fit scores for *sound performance in quiet and moderate* (scores improved after tuned fit) and *does not feedback* (scores decreased after tuned fit) scores were significantly different for Rx HA.

## Effect of hearing device form factor on hearing device audio performance

Figure 6 shows the SoundScore variation across hearing devices with different form factor. The mean and median SoundScore for BTE devices were higher (mean: 2.23, SD: 1.10, median: 2.65, IQR: 1.85) when compared to ITE devices (mean: 2.19, SD: 0.80, median: 2.10, IQR: 1.05). There was no significant difference ($t = 0.13$, $p = 0.9$) in SoundScores among hearing devices with different form factor (i.e., BTE vs. ITE). For this reason, no further analysis was performed related to the Form factor.

# Discussion

The DTC movement in hearing healthcare has expanded consumer options, allowing access to hearing devices through various service delivery models. Some early evidence suggests that various DTC hearing devices provide measurable benefit to individuals with mild-to-moderate hearing loss (Manchaiah et al., 2017; Tran and Manchaiah, 2018; Chen et al., 2022), with OTC-SF devices demonstrating comparable outcomes to Rx HA fitted by audiologists (De Sousa et al., 2023; Swanepoel et al., 2023). Despite the positive results, the expanding range of choices has

TABLE 5 Difference in audio performance ratings with first fit and tuned fit for prescription hearing aids (Rx HA) and self-fitting OTC hearing aids (OTC-SF) (*P*-value: * <0.05; ** <0.01).

| Hearing device category | Difference in audio performance ratings with first fit and tuned fit (*p*-value) | | | | | |
|---|---|---|---|---|---|---|
| | Overall score | Sound quality in quiet and moderate | Sound quality in loud | Own voice does not fit boomy | Music streaming sounds good | Does not feedback |
| Rx HA | 0.01* | 0.009** | 0.013* | 0.1 | 0.7 | 0.02* |
| OTC-SF | 0.04* | 0.06 | 0.04* | 0.1 | 0.2 | 0.3 |

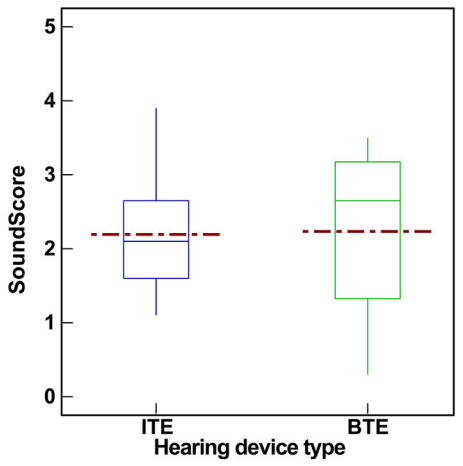


FIGURE 6
Box plot showing the variation in SoundScores (median [solid line], mean [dotted line], and inter quartile range) across hearing devices based on form factor (BTE vs. ITE). SoundScore values published in Hear Advisor websites include an added constant value of +1.1 to the scores provided here.

introduced complexities for consumers, making the navigation and selection of appropriate hearing devices challenging. Our study contributes to this growing body of literature by introducing a novel consumer-centric metric, the SoundScore, which reflects the audio performance across various DTC and traditional devices as a way to support consumer choices.

The significant variation in SoundScores among different hearing devices, as presented in our results, underscores the technology level's impact on performance. As expected, at the group level, Rx HA had the highest scores followed by OTC-SF, OTC-PS, and PSAPs. Examining the specific elements of audio performance, except for music streaming and feedback, there was significant differences between all device categories at first fit and tuned fit. Previous studies reported that certain DTC devices, such as PSAPs possess electroacoustic characteristics and simulated gains comparable to Rx HAs (Smith et al., 2016; Reed et al., 2017). Johnson et al. (2017) and Plyler et al. (2021) also reported no improvements in user performance with higher technology levels within Rx HAs. Our study however showed difference suggesting that when including DTC devices in the evaluation, technological differences become apparent and measurable. The technological nuances and their impact on audio performance become more pronounced, highlighting the importance of comprehensive metrics like the SoundScore in aiding consumers to make informed decisions.

The integration of consumer electronics with medical-grade Rx HAs has blurred the lines between device categories, creating a spectrum of devices with features from both segments. For this reason, the difference between some device categories (e.g., Rx HA vs. OTC-SF or OTC-PS vs. PSAP) may be less obvious just based on the categories. One key differentiator of the hearing devices may be the adjustment interface or commonly referred to as fitting method (Boymans and Dreschler, 2012). The current study suggests that devices equipped with fitting software yielded superior SoundScores, followed by app-based and preset-based devices. This would be expected, at least in part, due to increase in degree of freedom in the fitting software. Urbanski et al. (2021) also indicated that a more customized approach in self-fitting for OTC devices was closest to Rx HA outcomes. SoundScore differences across hearing devices in this study was also reflected in the fitting method. This is not surprising as the Rx HA devices use fitting software's, most PSAPs and OTC-PS use preset-based methods, and most OTC-SF and come OTC-PS use App-based fitting methods.

The difference in SoundScore with first fit and tuned fit was evaluated for Rx HA and OTC-SF categories. For Rx HAs, the variability in audio performance metrics, including the SoundScore and performance in various auditory environments, diminished significantly with a tuned fit. This suggests that the intrinsic characteristics of the device, such as brand, technology level, or price, are less influential than the philosophy behind the fitting rules. Conversely, the OTC-SF category showed minimal changes in sound performance following the tuning, indicating a limitation in the current app-based fitting approach. Again, this would be expected due to the fewer adjustment controls OTC-SF vs. Rx HA. This limitation could be clinically significant as it restricts hearing healthcare professionals, who are eager to assist OTC device users, from optimizing device settings to individual needs (Manchaiah et al., 2023b). Given that some consumers looking for hearing healthcare are also keen to seek support from hearing healthcare professionals (Singh and Dhar, 2023) it would be useful for OTC hearing aid manufacturers to consider enabling such adjustments through professional fitting software. This would not only empower audiologists to provide comprehensive care but could also enhance user satisfaction by ensuring that OTC devices can be tailored to the unique hearing profiles of their users.

In examining the impact of form factors on sound performance, our study found no significant difference between BTE and ITE devices. There was a difference in open (i.e., BTE) and

closed (i.e., ITE) fittings especially in terms of hearing own voice (Winkler et al., 2016), due to occlusion effect in closed fittings. In addition to some acoustics modifications, it is also possible to make gain adjustments through hearing device software to address this issue. For these reasons, it is reasonable to conclude that the sound performance may not vary as a result of form factor.

### Study limitations

This study marks an initial step in developing a consumer-centric metric for assessing the audio performance of hearing devices. However, the novel approach introduced here, along with the resultant findings, must be carefully considered within the context of study's limitations. First, our methodology involved using a single audiometric profile typical of mild-to-moderate hearing loss and a limited array of acoustic environments. While this approach enabled a degree of standardization, it inherently does not encompass the wide variability in hearing loss patterns. This limitation suggests that our findings may not fully extend to the broader hearing-impaired population. Second, while the SoundScore metric introduced here offers an innovative means to quantify audio performance, it does not encapsulate other crucial factors that inform consumer decisions. Aspects such as comfort, usability, device features, and cost are also vital to the decision-making process but remain beyond the score of this metric. Hence, the SoundScore should be considered as one of multiple factors in comprehensive decision-making framework. Third, although the study aimed to represent a breadth of hearing devices, and classification was guided by the FDA categories, some devices within OTC-PS (FDA QEG category) demonstrated features more characteristics of OTC-SF devices. This overlap indicates a potential need to refine device classification or to consider feature-based, rather than category-based, differentiation in future research. Finally, it is most important to recognize that these group-level results represent a current snapshot in time. We expect that any category differences to change as the field continues to indicate. With this in mind, we intend to evaluate new devices as they are released.

### Future directions

Early validation of our method and metric has been promising, yet further research is essential to establish the relationship between the SoundScore and actual user benefit and satisfy action. Future studies should seek to determine the SoundScore thresholds that correlate with optimal hearing aid outcomes. Additionally, defining critical difference levels for the SoundScore would enhance its precision in differentiating between devices, particularly concerning their sound performance. Such research endeavors will not only fortify the validity of the SoundScore but will also expand its utility for consumers navigating the complex landscape of hearing devices.

## Conclusions

The SoundScore, introduced in this study as a novel metric for assessing hearing device audio performance, shows promise in aiding consumers' selection process by distinguishing between devices based on technological capability. Clinically, this metric could facilitate audiologists in tailoring hearing solutions to individual needs and aid manufacturers in optimizing product design. While initial evidence supports its utility, further research is necessary to define critical thresholds that correlate with improved user satisfaction and to validate the metric's effectiveness in predicting real-world hearing aid outcomes. Ultimately, the SoundScore has the potential to streamline the decision-making process and enhance the overall quality of hearing healthcare.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

VM: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. ST: Data curation, Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. AB: Supervision, Resources, Conceptualization, Writing – review & editing, Methodology, Investigation. DS: Writing – review & editing, Methodology, Investigation. HR: Formal analysis, Writing – review & editing, Methodology, Investigation. AS: Writing – review & editing, Visualization, Resources, Methodology, Investigation, Data curation, Conceptualization.

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## Conflict of interest

VM and DS serves as Scientific Advisors for the hearX Group. DS also holds equity in the hearX Group. ST, AB, and AS are the co-founders of HearAdvisor, LLC. AS works for Bose Corporation. AB and ST are also employed by Hearing Tracker Inc.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fauot.2024.1406362/full#supplementary-material

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# Examining the psychometric properties of the Columbia Speech Quality Instrument in cochlear implant users

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**Objective:** Although speech recognition among cochlear implant (CI) users improved over the past few decades, many still report poor speech quality. Currently, there is no validated tool to measure speech quality. The objective was to examine whether a previously validated speech quality tool is applicable in the CI population using psychometric analysis.

**Design:** Cross-sectional psychometric analysis of the Columbia Speech Quality Instrument (CSQI; previously validated in normal-hearing individuals; consists of 2 original and 7 manipulated speech clips designed to accentuate selected speech characteristics) was performed in adult English-speaking CI recipients ($N = 36$). Subjects rated each clip using a visual analog scale (VAS) on 14 characteristics: cartoonish/not-cartoonish, clear/unclear, like/dislike, breathy/not-breathy, smooth/rough, echo-y/not-echo-y, tinny/bassy, soothing/not-soothing, natural/unnatural, mechanical/not-mechanical, hoarse/smooth, pleasant/unpleasant, male/female, and speech-like/not-speech-like. Main outcome measures included validity, reliability, and factor structure.

**Results:** Content validity was previously confirmed during instrument design. Construct validity by item-item correlation analysis demonstrated correlation of 12/14 items with $\geq$1 other retained item ($r \geq 0.35$, Spearman). Reliability was confirmed by internal consistency; factor analysis using two subsets selected by Scree plot and factor loading $\geq$0.4 demonstrated Cronbach alpha coefficients of 0.89 and 0.74 for factors 1 and 2, respectively. Tinny/bassy and male/female were the only characteristics that did not pass construct validity or internal consistency.

**Conclusions:** The CSQI has strong psychometric properties in the CI population; however, our findings support removal of tinny/bass and male/female characteristics from the final instrument prior to implementation in the CI population. The CSQI can be utilized in cochlear implantees to investigate effects of changes in speech processing strategies and postoperative outcomes with different devices.

KEYWORDS

**cochlear implantation, cochlear implant, hearing loss, speech recognition, word recognition, speech perception, speech quality, validated instrument**

# Introduction

Speech recognition among cochlear implant (CI) users has improved drastically in the past few decades due to improvements in hardware, software, and surgical techniques (Zwolan, 2008). Despite advances in speech recognition, many patients anecdotally report that speech quality heard through CIs remains odd and unpleasant. Although individual experiences widely vary, sounds are often described as mechanical or cartoon-like by patients. Beyond linguistic content, human speech encodes information about the speaker's age, gender, identity, accent, and emotional state, which are critical for social interactions and may be lost when speech quality is inadequate. CI users are known to struggle with gender identification (Fu et al., 2005), speaker identification (Vongphoe and Zeng, 2005), and emotion recognition (Luo et al., 2007) compared to their normal hearing peers.

To improve speech quality heard by CI recipients, a standardized method of defining and scoring speech quality is necessary to track changes among different techniques. Previous validated tools that incorporate perceived sound quality as a metric include the Hearing Implant Sound Quality Index ($HISQUI_{19}$) (Amann and Anderson, 2014) and the Speech, Spatial, and Qualities of Hearing Scale (SSQ) (Gatehouse and Noble, 2004). While the $HISQUI_{19}$ and SSQ are excellent at measuring the impacts of hearing loss and cochlear implantation on everyday activities and QOL, they do not investigate which specific characteristics of speech sound unnatural or assess how CI users describe the quality of speech they are hearing.

Our group has developed the first tool to assess speech quality and its pleasantness. The Columbia Speech Quality Instrument (CSQI) is a concise, interactive, computerized test that consists of nine speech clips manipulated to clearly portray speech qualities of interest as defined by normal hearing individuals. Participants quantify the quality of perceived speech across 14 characteristics. The CSQI was generated by a focus group of otolaryngologists, audiologists, speech pathologists with extensive experience with patients with hearing loss and CI users and previously administered to normal hearing participants for development of the initial item bank and subsequent finalized speech quality instrument, which underwent validity and reliability analyses (Chen et al., 2018). In this study, we aimed to determine whether this validated speech quality tool is applicable in the CI population using psychometric analysis to examine the validity, reliability, and factor structure of the CSQI among CI listeners; the CSQI will be useful in optimizing speech quality in cochlear implantees by quantifiably measuring changes in speech quality scores across speech processing strategies and CIs.

# Materials/methods

## Recruitment and study design

We partnered with an experienced sound/audio engineer and a full stack web developer to develop a novel web-based application based upon specifications of our prior data (Peter Karl Studios, New York, NY; WYC Technologies, New York, NY). Subjects were recruited from the Columbia University Medical Center CI program and from web-hosted prominent CI support groups. Eligibility criteria included age > 18 years, bilateral or unilateral cochlear implantation status, a minimum of 6 months since implant activation, and English literacy. Subjects had the option to complete the study in our clinic or to complete the study online at home. Subjects completing the study online at home had the option of sending their audiogram in a de-identified fashion.

All subjects were e-consented prior to participation in the study under a protocol approved by the Columbia University Irving Medical Center Institutional Review Board. Subjects tested in person were consented in person. All systems were in compliance with the institutional information security charter. After completing consent, patients were asked to complete a brief demographic survey covering their otologic history, relevant medical history, and primary language. Subjects were instructed to complete the study using direct stream to their CI, or if this was unavailable, using external speakers in a quiet room.

## Sound/audio engineering for the Columbia Speech Quality Instrument

Subjects were presented the CSQI, which consists of a series of nine audio clips previously developed and validated among normal hearing listeners (Chen et al., 2018). Each audio clip consists of a male or female speaker reading the Rainbow Passage (Fairbanks, 1960). Two audio clips contain original audio, while the remaining have been manipulated by a sound engineer using Apple Logic 9 Pro recording software (Apple Inc., Cupertino, CA) to accentuate one of the following goal qualities: bassy, cartoonish, far, garbled, mechanical, not speech, or rough. The final audio clips were as follows: original male, original female, not-speech female, bassy male, cartoonish female, far male, garbled male, mechanical female, rough male.

Following each clip, subjects rated the speech on 14 characteristics using a visual analog scale (VAS):

1. Cartoonish (10) vs. not cartoonish (0)
2. Clear (10) vs. garbled (0)
3. Like (10) vs. did not like (0)
4. Breathy (10) vs. not breathy (0)
5. Smooth (10) vs. rough (0)
6. Echo-y (10) vs. not echo-y (0)
7. Tinny (10) vs. bassy (0)
8. Soothing (10) vs. not soothing (0)
9. Natural (10) vs. unnatural (0)
10. Mechanical (10) vs. not mechanical (0)
11. Hoarse (10) vs. not hoarse (0)
12. Pleasant (10) vs. unpleasant (0)
13. Male (10) vs. female (0)
14. Sounds like speech (10) vs. does not sound like speech (0)

TABLE 1 Participant demographics of cochlear implant users.

| | |
|---|---|
| **Gender** | |
| Female | 66.7% |
| Male | 33.3% |
| **Age at survey (years)** | |
| Mean (SD) | 64.2 (14.7) |
| 31–64 | 41.7% |
| 65+ | 58.3% |
| **Years post-implantation** | |
| <1 year | 16.7% |
| 1–3 years | 52.8% |
| >3 years | 30.6% |
| **Years deafness prior to implant** | |
| Mean (SD) | 24.1 (17.8) |
| <1 year | 2.8% |
| 1–10 years | 8.3% |
| 11–29 years | 13.9% |
| 30+ years | 13.9% |
| No response | 61.1% |

## Technical specifications: application structure

The main web application was developed by an experienced full stack web developer (WYC Technologies, New York, NY). The program was written in the Python programming language and runs on the latest version of web application framework known as Django 1.11. Version 1.11 of Django is supported with security patches and upgrades until at least April 2020. It includes several open-source libraries as is typical in modern web development, but also as few as necessary to reduce complexity. The latest version of PostgreSQL is used for the application database. Network HTTPS requests are reverse-proxied by nginx, which is also used to terminate TLS connectivity.

The responsible web application browser frontend was written in JavaScript using the ReactJS framework, free, open-source, and maintained by Facebook, Inc. Several common packages were used from the NodeJS ecosystem to provide user interface functionality. All communication to the backend occurs through HTTPS connections at API endpoints that authenticate and authorize requests based on unique survey codes.

The server runs Debian 9 with GNU/Linux on Amazon Web Services EC2. The application and database both run on the server. A virtual firewall restricts all access aside from HTTP, HTTPS, SSH, and ICMP Ping requests. HTTP is only used to redirect to HTTPS. The proper TLS certificates have been generated with LetsEncrypt.

## Statistical analysis

All statistical analysis was performed using Stata 13.0. Inter-item correlation was calculated using Spearman's rank-order correlation, with moderate correlation defined as $r \geq 0.35$. Factor analysis was used to determine factor loading, and scree plot analysis was used to determine the number of factors to retain. Final factor loadings were determined by VARIMAX rotation, and items with factor loading ≥0.4 were retained. Cronbach's alpha was calculated using the built-in alpha function in Stata. Test-retest reliability was calculated via intraclass correlation using a random-effects model with a maximum likelihood estimator among participants who completed the CSQI twice within 1 week.

# Results

## Demographics

Thirty-six participants completed the CSQI, with a mean age of 64.2 ± 14.7 years (mean ± SD) at time of survey completion (Table 1). Participants were on average 2.98 ± 2.62 years post-CI implantation, and 66.7% of participants were female. Of the 14 participants who reported number of deaf years pre-implantation, the average number of deaf years was 24.1 ± 17.8 years. Eleven participants completed test-retest of the CSQI within 1 week.

## Construct validity

Construct validity was determined by inter-item correlation (Table 2). All speech quality items except Bassy were at least moderately correlated ($r \geq 0.35$) with another item in this survey. The highest correlation was found with Pleasant and Natural with a correlation coefficient of 0.81. Pleasant, Smooth, and Natural all had high correlation ($r \geq 0.7$) with each other. The lowest correlation was found with Sex ID and Bassy with a correlation coefficient of 0.04.

## Instrument reliability

Scree test identified two subsets of speech quality items for factor analysis (Table 3, Figure 1). Items with factor loading ≥0.4 were retained. Items that loaded onto factor 1 include clear/garbled, like/dislike, smooth/not smooth, echo-y/not echo-y, soothing/not soothing, natural/not natural, mechanical/not mechanical, pleasant/not pleasant, and speech-like/not speech-like. Items that loaded onto factor 2 include cartoonish/not cartoonish, breathy/not breathy, mechanical/not mechanical, and hoarse/not hoarse. Bassy/tinny and male/female (i.e., sex ID) did not load onto either factor, and mechanical/not mechanical loaded onto both factors.

Internal consistency was determined by Cronbach's alpha, which is calculated as 0.93 for factor 1 and 0.69 for factor 2. Among the 11 participants who completed the CSQI twice within a period of 1 week, test-retest reliability was determined by intraclass

TABLE 2 Inter-item correlation demonstrating construct validity.

| | Not cartoonish | Clear | Like | Not breathy | Smooth | Not Echo-y | Bassy | Soothing | Natural | Not mechanical | Not hoarse | Pleasant | Sex ID | Speech-like |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not cartoonish | 1.000 | | | | | | | | | | | | | |
| Clear | 0.202 | 1.000 | | | | | | | | | | | | |
| Like | 0.280 | **0.788** | 1.000 | | | | | | | | | | | |
| Not Breathy | **0.472** | 0.088 | 0.083 | 1.000 | | | | | | | | | | |
| Smooth | 0.298 | 0.614 | **0.661** | 0.142 | 1.000 | | | | | | | | | |
| Not echo-y | 0.241 | 0.400 | **0.415** | 0.283 | **0.525** | 1.000 | | | | | | | | |
| Bassy | 0.252 | 0.104 | 0.195 | 0.069 | 0.096 | 0.163 | 1.000 | | | | | | | |
| Soothing | 0.292 | **0.635** | **0.747** | 0.121 | **0.782** | **0.459** | 0.195 | 1.000 | | | | | | |
| Natural | **0.369** | **0.617** | **0.702** | 0.152 | **0.740** | **0.458** | 0.249 | **0.676** | 1.000 | | | | | |
| Not mechanical | **0.364** | **0.460** | **0.540** | 0.177 | **0.622** | **0.462** | 0.275 | **0.598** | **0.740** | 1.000 | | | | |
| Not hoarse | 0.330 | 0.332 | 0.238 | 0.296 | **0.402** | 0.276 | 0.098 | 0.316 | 0.336 | **0.433** | 1.000 | | | |
| Pleasant | 0.333 | **0.632** | **0.744** | 0.142 | 0.714 | **0.447** | 0.181 | **0.775** | **0.807** | **0.705** | **0.368** | 1.000 | | |
| Sex ID | 0.202 | 0.179 | 0.100 | 0.101 | 0.192 | 0.190 | 0.042 | 0.082 | 0.232 | 0.225 | **0.432** | 0.192 | 1.000 | |
| Speech-like | 0.346 | **0.524** | **0.533** | 0.199 | **0.524** | 0.311 | 0.212 | **0.457** | **0.618** | **0.519** | 0.285 | **0.514** | 0.298 | 1.000 |

All speech quality items except Bassy were at least moderately correlated ($r \geq 0.35$) with another item in this survey. Bolded numbers indicate $r \geq 0.35$.





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TABLE 3 Mean item ratings and factor loadings for final items.

| | Mean rating | SD | Factor 1 | Factor 2 |
|---|---|---|---|---|
| Not cartoonish | 0.571 | 0.364 | 0.224 | **0.596** |
| Clear | 0.347 | 0.343 | **0.756** | 0.159 |
| Like | 0.311 | 0.325 | **0.869** | 0.151 |
| Not breathy | 0.649 | 0.307 | 0.054 | **0.529** |
| Smooth | 0.404 | 0.312 | **0.791** | 0.287 |
| Not echo-y | 0.457 | 0.335 | **0.467** | 0.350 |
| Bassy | 0.471 | 0.287 | 0.144 | 0.253 |
| Soothing | 0.321 | 0.317 | **0.823** | 0.209 |
| Natural | 0.386 | 0.347 | **0.789** | 0.361 |
| Not mechanical | 0.422 | 0.346 | **0.617** | **0.475** |
| Not hoarse | 0.576 | 0.311 | 0.269 | **0.541** |
| Pleasant | 0.342 | 0.327 | **0.833** | 0.284 |
| Sex ID | 0.734 | 0.294 | 0.088 | 0.321 |
| Speech-like | 0.513 | 0.390 | **0.544** | 0.318 |
| Cronbach's alpha | | | 0.930 | 0.688 |

Scree test identified two sets of characteristics (Factor 1 and Factor 2). Items with factor loading ≥0.4 were retained and bolded above. Internal consistency demonstrated Cronbach alpha of 0.930 and 0.688 for Factors 1 and 2, respectively. ID, identification; SD, standard deviation.

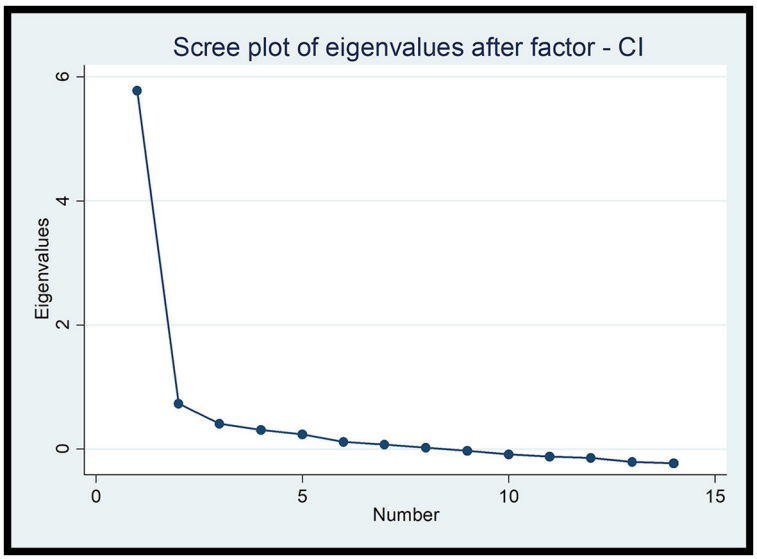


FIGURE 1
Scree plot identified two subsets of speech quality items for factor analysis. Items with factor loading ≥0.4 were retained.

correlation, which was calculated as 0.78 (95% conf. interval: 0.49–0.95, $P < 0.001$).

## Discussion

The CSQI was previously validated in normal hearing participants (Chen et al., 2018); our findings suggest that this instrument is suitable for use in the CI population. This tool fulfills the critical need for a validated instrument to assess the frequently reported complaints of speech quality in cochlear implantees. The test is short, easily completed, and self-administered on a computer, making it clinically feasible and well-suited for implementation in a broader clinical setting. Moreover, it is the first validated instrument employed to examine speech quality and its pleasantness in CI users.

Our psychometric analysis with limited re-validation of the CSQI in the CI population was determined by examining validity,

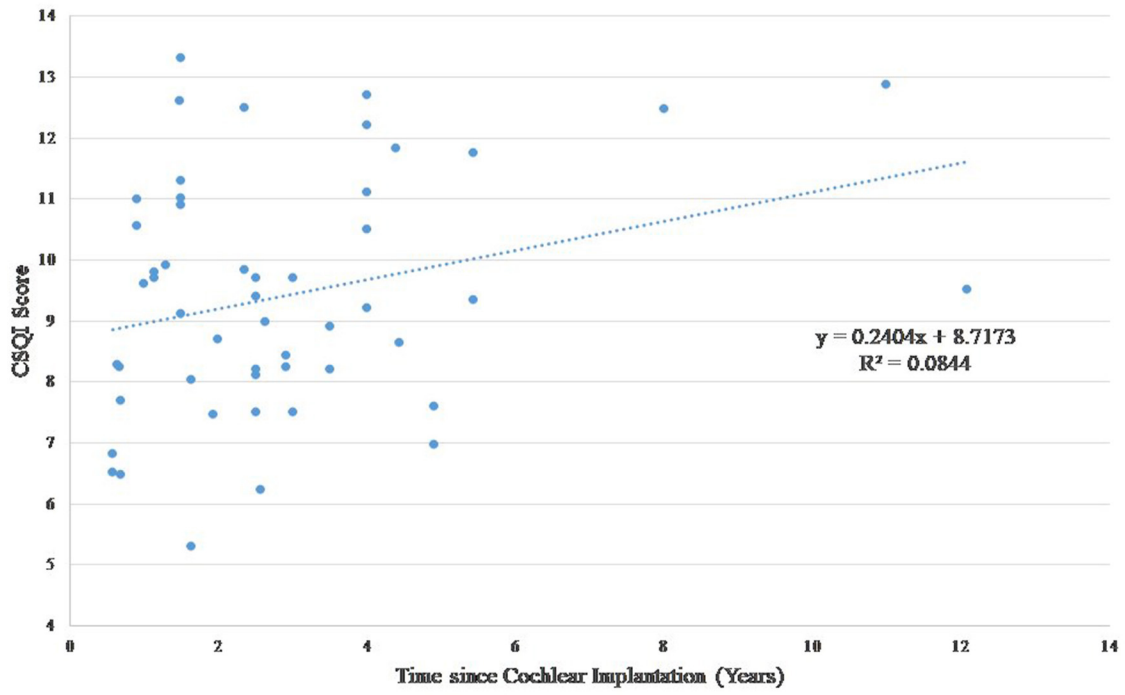


FIGURE 2
Scatterplot illustrating Columbia Speech Quality Index (CSQI) scores of all the study participants for a sample stimulus (original female) plotted as a function of time since cochlear implantation. Each circle is used to denote a unique study/participant. There is a trend of increasing CSQI scores with increased time since implantation, as participants get acclimated to their implant.

reliability, and factor structure in this population. Content validity was achieved during the design of the instrument as described in our previous report (Chen et al., 2018). Briefly, a focus group of otolaryngologists, audiologists, and speech pathologists identified 18 items to define speech quality. Speech stimuli were recorded by 2 male and 2 female voices, then modified by sound engineers to accentuate 10 goal qualities for a total of 44 speech clips. The speech clips were then presented to normal-hearing listeners and each speech quality item of each clip was rated on a 10-point visual analog scale. Based on these preliminary results, items and clips were pruned to a finalized set for the CSQI.

Construct validity was confirmed by inter-item correlation, which demonstrated 13/14 speech quality items had at least moderate correlation with another item. Among CI users, bassy/tinny was the only item that did not correlate with another item. In comparison, our previous study showed that all items demonstrated at least moderate correlation with another item among normal hearing individuals (Chen et al., 2018). This difference among the CI and normal hearing groups may be a result of abnormal pitch perception through CIs, different demographic distribution, or other confounding factors (Zeng et al., 2014). Alternatively, bassy/tinny may truly not be associated with any of the other speech quality items, and exists as a unique trait to be measured.

Reliability was determined by internal consistency and test-retest reliability. Based on a cutoff of factor loading $\geq$0.4, 12/14 speech quality items loaded onto either factor 1 or factor 2; Bassy/tinny and sex ID were the only items that did not load onto either factor, which may also be a result of altered pitch perception or changes in temporal cues and spectral cues through CIs (Fu et al., 2005; Zeng et al., 2014). Factor 1, consisting of 9/14 items, had excellent internal consistency based on Cronbach's alpha of 0.93, while factor 2, consisting of 4/14 items, had acceptable consistency based on Cronbach's alpha of 0.69. Thus, while the items within factor 1 are highly correlated, the items in factor 2 are not as closely correlated and may individually be important measures.

Although the bassy/tinny item did not demonstrate at least moderate correlation with another item or demonstrate loading on any of the two factors, many cochlear implantees anecdotally report the speech they hear as bassy or tinny. Sex ID also demonstrated near-significant loading at 0.321 for Factor 2—cochlear implantees are known to struggle with gender identification with smaller differences in mean fundamental frequency of the speaking voice (Fu et al., 2005). In addition, the mechanical/not mechanical item loaded onto both factors, indicating redundancy of the item. However, this is a common complaint by CI users, and was retained for the final set of CSQI items. Of note, results of exploratory factor analysis are solely based on data and not on any theoretical basis; thus, it is important to consider inclusion of clinically relevant characteristics such as bassy/tinny and sex ID. That said, our examination of the psychometric properties of the CSQI supports elimination of the bassy/tinny and sex ID for the cochlear implantee population. This also helps facilitate a shorter assessment with better prospects for incorporation into clinical use.

The primary limitations to this study include the sample size, variability in the demographics of our participant population,

and inability to control for listening environments (i.e., in a standardized audiology suite or soundproof). Due to the nature of the CI user population available for participation, the average age and sex distribution are skewed toward older and more female participants than the population used to validate the CSQI in normal hearing individuals. The heterogeneity of CI usage (i.e., total time spent using CI) and years of deafness prior to implantation were also not accounted for during validation of the CSQI. For example, at the time of taking the CSQI, 16.7% of participants had their CI(s) for <1 year, 52.8% for 1–3 years, and 30.6% for >3 years (Table 1). This did not account for frequency of usage of the CI; indeed, duration of daily processor use is significantly correlated with speech recognition abilities in adult cochlear implantees (Holder et al., 2020). Thus, compared to novice CI users, experienced users may be able to more easily identify the speech characteristics presented in the CSQI. Similarly, adults with prelingual deafness are known to demonstrate poorer speech outcomes and pre/post-CI improvement compared to those with postlingual deafness (Boisvert et al., 2020). In our study population, several participants were noted to had deafness since an early age (e.g., ~3–4 years of age). Our study had limited participant data regarding the etiology and status of the contralateral ear, given many were recruited online. Participants were also tested in a mix of conditions (direct stream and external speakers) based on convenience and technology limitations of participants who were doing the study at home. In instances where speakers were used, the contralateral ear was not plugged to isolate the non-CI ear. As such, there are also insufficient data to address unilateral, bilateral CI, or bimodal strategies, which are the focus of ongoing studies. These differences in demographics may affect the interpretation of the speech quality items, and may contribute to the observed differences in inter-item correlation and internal consistency. Nonetheless, our study was still able to demonstrate excellent construct validity (13/14 items were at least moderately correlated with each other) and reliability (12/14 speech items loaded on either factor 1 or 2) in CI users. Finally, cochlear implantees may experience improvement in speech quality over time as patients acclimate to their device and undergo central cortical adaption, similar to the way they experience improvement in speech perception. As such, this assessment should be employed throughout the rehabilitation process.

The novel use of an online survey method provides many advantages including accessibility and allowing users to listen in their normal hearing environment, but also introduces variability in audio device quality and ambient noise levels among participants. Although this heterogeneity of listening environments may have contributed to observed differences in speech quality, the CSQI still demonstrated construct validity and reliability of the CSQI despite the variability in these demographic factors. The online nature of the instrument also provides the advantages of reaching a larger user base in their natural listening environment thus increasing the clinical utility of CSQI. Having participants take the CSQI on a computer with speakers in a quiet room demonstrates more ecological validity (i.e., more similar to a real-life environment) and clinical feasibility than having them visit their audiologist and take the test in a sound booth. This is particularly important in the setting of the current COVID-19 environment, where it is necessary to minimize risk of exposure. As such, a study that future participants complete the CSQI at home is a practical solution.

The CSQI adds to the current options of validated tools available for improving the experience of CI users by developing a shared vocabulary to define attributes of speech, providing a library of standardized speech clips with accentuated speech characteristics, and establishing a standardized method of measuring speech quality. It is critical to ensure that vocabulary used by normal hearing individuals and cochlear implantees is consistent, as it allows providers and CI users to communicate effectively about the CI listening experience. With the CSQI, specific terms can be linked to specific qualities of speech across both normal hearing and CI participants. Similarly, the 9 speech clips within the CSQI can serve as universal standards for the speech characteristic each clip is engineered to portray, and can be used in future studies or tools.

Future efforts will be directed at using participant-reported scores per speech clip to generate an overall score to represent how pleasant and/or accurate speech quality sounds to the participant. Compiling metrics for overall performance of speech quality production will allow for numerous applications of the CSQI in research and clinical use. As a research tool, the CSQI can be used to compare new developments in CI technology, to quantifiably demonstrate if newer speech processing strategies, electrodes, devices, or other advancements can improve speech quality heard through CIs. In addition to speech recognition, improvements in speech quality as measured by the CSQI can become standard outcomes for measuring success of cochlear implantation.

We also envision the CSQI becoming implemented as a diagnostic tool in the clinic for assessing the effects of changes in CI hardware or software on perceived speech quality. Once included into the standard battery of tests that CI recipients undergo during each check-up visit, the CSQI can be trended over time to monitor the progress of either the CI user's acclimatization to the device or the modifications to speech processor settings or hardware. For example, Figure 2 demonstrates that there is improved speech quality as measured by the SCQI over time in our group of CI users. Providers can use the CSQI during in-person or virtual telemedicine visits to tailor CI recipients' program settings to maximize enjoyment of listening to speech.

## Conclusion

The Columbia Speech Quality Instrument (CSQI)—a concise and portable computerized test previously validated in normal hearing users—has strong psychometric properties in the CI population. Our findings suggest tinny/bass and male/female characteristics should be removed prior to implementation of the CSQI in the CI population. This instrument may be utilized in cochlear implantees so quantitative measurements of speech quality can be used to track changes across various electrodes, devices, and speech processing strategies to optimize listener enjoyment. The online format of the CSQI allows it to be widely distributed and accessible to a larger, more diverse user base. Future studies can examine modifiable aspects of speech to enhance CI speech enjoyment and explore differences between CI and normal hearing speech quality perception.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Columbia University Irving Medical Center Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

AL: Conceptualization, Methodology, Supervision, Writing – review & editing, Writing – original draft. MC: Data curation, Investigation, Formal analysis, Project administration, Validation, Visualization, Writing – review & editing, Writing – original draft. TH: Data curation, Investigation, Project administration, Writing – review & editing, Writing – original draft. AC: Formal analysis, Visualization, Validation, Writing – review & editing, Writing – original draft. LT: Data curation, Investigation, Project administration, Writing – review & editing, Writing – original draft. SC: Writing – review & editing, Writing – original draft. MS: Validation, Writing – review & editing, Writing – original draft. DM: Conceptualization, Investigation, Writing – review & editing, Writing – original draft. IC: Conceptualization, Investigation, Supervision, Writing – review & editing, Writing – original draft.

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## Conflict of interest

AL: Haystack Medical (Founder and Equity Owner).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fauot.2024.1362810/full#supplementary-material

SUPPLEMENTARY DATA 1
CI speech perception scores.

SUPPLEMENTARY DATA 2
Columbia SQI raw data.

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# Middle ear anatomy and implant sizes: correlates and the need for uniform implant dimensions

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**Introduction:** Conductive hearing loss describes an insufficient sound transfer of the middle ear, often caused by defects or absence of the ossicles. Depending on the specific middle ear dimensions and the kind of defect, surgeons can choose from a variety of passive implants to reconstruct the middle ear and hence restore sound transmission. However, the latter is only achieved if the optimal implant size is available and selected for each individual patient.

**Methods:** Anatomical dimensions relevant for middle ear reconstruction were assessed within high-resolution clinical imaging data of 50 patients (100 ears). The ranges of these dimensions were then compared to implant types and sizes available from different manufacturers.

**Results:** In general, total and partial prostheses seem to cover the whole range of anatomical variations. A lack of stapesplasty implants was found for particularly small anatomies. Various implant lengths of all types far exceed dimensions necessary for successful restoration of sound transmission. In some cases, implant lengths are not clearly specified by the manufacturer. Tympanic membrane and stapes axis were not in line for any of the investigated middle ears.

**Conclusion:** Clear specifications of implant lengths are crucial to allow for successful hearing restoration, and clinics often need to have more than one implant type to cover the entire range of anatomical variations they may encounter. There appears to be an unmet clinical need for smaller stapesplasty implants. Devices which allow for an angular adjustment between distal and proximal end appear to mimic the orientation of the ossicles more naturally.

KEYWORDS

**hearing loss, tympanoplasty, ossiculoplasty, stapesplasty, middle ear reconstruction, anatomical variability, sound conduction**

## 1 Introduction

The function of the middle ear is the transmission of vibrations from the tympanic membrane to the stapes footplate. In doing so, the composition of tympanic membrane, ossicles and oval window compensate for impedance differences between the air-filled outer ear canal to the fluid-filled cochlea (Pickles, 2013). In patients with conductive hearing loss, sound transmission from outer to inner ear is compromised, requiring ossiculoplasty (Kartush, 1994; Mudhol et al., 2013; Young and Ng, 2023) to surgically reconstruct the functionally impaired middle ear structures. This can be done using either autologous grafts or alloplastic passive middle ear implants (PMEIs).

Various studies have been conducted to determine requirements for PMEIs and successful ossiculoplastic surgery, the goal of which is often stated as a postoperative air bone gap of less than 20dB (Yung and Vowler, 2006; Amith and Rs, 2017). While autologous grafts were found to be advantageous for slight defects (Amith and Rs, 2017), more pronounced ossicular chain destructions are typically treated with artificial prostheses made of metal and/or plastics (Beutner and Hüttenbrink, 2009). Obvious requirements for these manufactured PMEIs include factors such as biocompatibility and bio-stability, missing bone apposition, low weight for optimal sound conduction and the avoidance of radiological artifacts (Beutner and Hüttenbrink, 2009). Different materials such as hydroxyapatite, polytetrafluoroethylene, gold and titanium are commercially employed for PMEI manufacturing, all of which fulfill the requirements stated above and were shown to yield comparable sound transmission results (Morris et al., 2004; Ringeval et al., 2004; Mojallal et al., 2009).

One factor responsible for the variability in postoperative ossiculoplasty outcomes (Austin, 1969; Kartush, 1994; Yung and Vowler, 2006; Kamrava and Roehm, 2017; Neudert, 2020) is the condition of the middle ear: if the stapes superstructure is still present, partial prostheses can be implanted to only bridge the gap between tympanic membrane and stapes head. These devices were shown to yield favorable results in comparison to total prostheses which transfer incoming sound from the tympanic membrane directly to the stapes footplate (Yu et al., 2013; Kortebein et al., 2023). Furthermore, the absence of the malleus was shown to negatively affect implantation outcomes, which is likely owed to insufficient sound transfer from outer to middle ear (Yung and Vowler, 2006).

Another factor influencing the postoperative outcomes is the placement of the implant during surgery. If the malleus is present, the distal end of the total or partial prosthesis should be placed onto the malleus handle and not directly onto the tympanic membrane (Bance et al., 2004). Furthermore, cartilage slices are typically placed between malleus/tympanic membrane and prosthesis for mechanical stability, but the thickness of these slices should not exceed 0.5 mm in order to preserve optimal sound conduction properties (Mürbe et al., 2002; Morris et al., 2004).

Finally, the selection of the functional length of the implant was shown to play a significant role in ossiculoplasty outcomes (Morris et al., 2004; Merchant and Rosowski, 2013). The middle ear anatomy varies substantially between patients (aWengen et al., 1995; Todd and Creighton, 2013; Kamrava and Roehm, 2017), which is why PMEIs are typically available in different lengths or are length adjustable. The selection of the ideal length for an individual patient is crucial: a stapesplasty prosthesis should not be inserted more than 0.5 mm into the stapedotomy to avoid contact to the utricular macula (Mukherjee et al., 2011). In case of total or partial prostheses, the implant must be long enough to establish sufficient contact to the ossicles (Lord et al., 2000), but an implant which is too long creates a static force onto the stapes footplate, which causes the annular ligament (AL) surrounding the footplate to be elongated (Figure 1). It was shown that this elongation causes the AL to become stiffer (Gan et al., 2011; Lauxmann et al., 2014), which reduces the vibrational amplitudes of the stapes footplate during sound conduction (Koike et al., 2005) and hence negatively affects

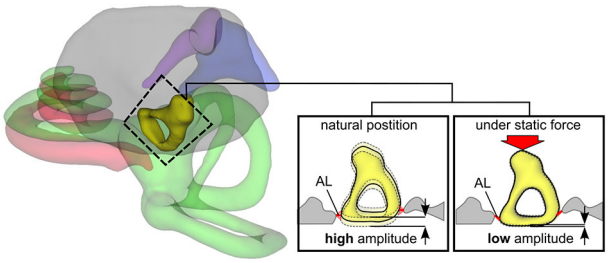


FIGURE 1
Static force onto the stapes causes pre-tension of the annular ligament (AL), resulting in substantially reduced vibrational amplitudes of the stapes during sound transmission.

sound transmission especially in the low frequencies (Bance et al., 2004; Morris et al., 2004; Neudert et al., 2016; Schär et al., 2023). The implant length for an individual patient must hence be chosen such that it is long enough to bridge the gap between the affected middle ear structures, but not too long to avoid prestress of the AL surrounding the stapes footplate.

Under consideration of these spatial constraints, the anatomical variations of the middle ear were assessed in clinical imaging data within the present study. Dimensions relevant for ossiculoplasty were compared to the ranges of PMEIs offered by different manufacturers. The goal was to assess if commercially available PMEI sizes (total, partial and stapes prostheses) sufficiently cover the anatomical variability of the middle ear.

# 2 Materials and methods

## 2.1 Imaging data

High-resolution cone-beam computed tomography (CBCT) imaging datasets of 100 ears (50 patients, 23 female, 27 male, 9–89 years old) were investigated within the present analysis. Informed consent was obtained from all patients by admission allowing the use of their anonymized data for research purposes. Each imaging dataset was obtained between 2017 and 2020 with a 3D Accuitomo 170 (Morita Group, Osaka, Japan) and had an isotropic voxel size of 250 µm. After initial investigation, 6 ears (3 patients) had to be excluded due to insufficient image quality, possibly owed to slight movements during CBCT acquisition, and an additional 5 ears (from four patients) were excluded because they were already implanted with a PMEI. Within all other imaging data, the middle ear anatomy was found to be normally developed and clearly distinguishable by an experienced ENT surgeon.

## 2.2 Fiducial placement

Assessment of the middle ear anatomy was conducted using 3D Slicer [version 4.11, www.slicer.org, (Fedorov et al., 2012)] by placing a total of 10 fiducials per ear along various structures of interest. However, only 7 of these 10 fiducials are relevant for the present study: 4 of these fiducials were placed along the edge

of the TM, 1 fiducial (F5) was placed onto the central malleus handle and 2 further points were placed along the stapes axis (F9: stapes head; F10: center of stapes footplate). Detailed depictions of these fiducials placed within the corresponding imaging data are given in the Supplementary Figure S1. All fiducials were first placed by an ENT resident and subsequently checked by an experienced ENT specialist. In addition, fiducials were placed again in 20 of the investigated ears by both the ENT specialist and an experienced neuroradiologist to investigate intra and inter observer variability respectively.

## 2.3 Computation of anatomical dimensions

The fiducials of the 89 ears included in the present investigation were then imported into Matlab (version R2018a, Mathworks, USA) to compute relevant dimensions for PMEIs. An overview of these dimensions and the fiducials used to compute the corresponding values is given in Figure 2. The TM diameters in horizontal ($TM_h$) and vertical ($TM_v$) direction were computed as the metric distances F1 to F2 and F3 to F4 respectively (Figure 2A). Furthermore, a plane was fitted to the fiducials F1-F4 by minimizing the perpendicular distances of these fiducials to the plane (least squares, see Figure 2B). This TM plane hence defines the spatial orientation of the TM in each ear. The normal vector of this plane in combination with the stapes axis, which was defined as the vector from stapes head (F9) to stapes footplate (F10), were then used to compute the angle α between TM and stapes (Figure 2B). A value of $\alpha = 0^\circ$ hence corresponds to an exact alignment of stapes axis and TM normal direction. In addition, the metric distances from central malleus handle to stapes footplate (M-SFP) and stapes head (M-SH) were computed as the distances from F5 to F10 and F5 to F9 respectively (Figure 2C). Finally, the length of the stapes S (Figure 2D) was computed as the metric distance from stapes head (F9) to stapes footplate (F10).

It must be noted here that the TM could only be clearly distinguished on 41 of the 89 ears. The complete set of anatomical dimensions described above could hence only be computed for these 41 ears. For the other 48 cases, only those dimensions could be computed which were independent on F1–F4, i.e., M-SFP, M-SH and S.

## 2.4 Passive middle ear implants

Information on available total, partial and stapesplasty prostheses and the respective dimensions was acquired using the product catalogs of different implant manufacturers:

- Audio Technologies S.r.l. (Piacenza, Italy), www.audiotechnologies.it (version CAT400 rev.00 – Oct. 2015).
- Grace Medical, Inc. (Memphis, USA), www.gracemedical.com (version LIT0041 CID6009 Rev. 2018-08).
- Heinz Kurz GmbH (Dusslingen, Germany), www.kurzmed.com (version 03/2018-M9600320).
- MED-EL Medical Electronics (Innsbruck, Austria), www.medel.com (version M00130 r4.0).
- Medtronic ENT (Jacksonville, USA), www.medtronicent.com (version UC201402426k EN).
- Olympus Corporation (Tokyo, Japan), www.olympus-global.com (version E0492509EN · 800 · 11/17 · PR · HB).
- Spiggle & Theis (Overath, Germany), www.spiggle-theis.com (stapesplasty: version F_Nitinol_E_03; total/partial: version F_MEI_E_01).

Implants were grouped by manufacturer, implant type (total, partial, stapesplasty) and dependent on whether the implant length can be adjusted.

In order to allow for direct comparisons to the assessed anatomical dimensions, the minimal and maximal functional length each prosthesis was noted. In case of some partial and stapesplasty prostheses, the functional length was not stated by the manufacturer (e.g., in case of the stapesplasty prostheses by Audio Technologies). In these cases, a 1 mm offset was subtracted from the total implant length to account for the height of the stapes head attachment of partial prostheses or the loop diameter of stapesplasty prostheses respectively.

## 2.5 Statistical analyses

All statistical evaluations were conducted in Python (version 3.7, Python Software Foundation, USA) using the Scipy library (version 1.2.1). Normal distribution testing was conducted using the Shiparo-Wilk test with 5% significance level. Pearson's correlation tests were performed to investigate interrelations between specific parameters. Significances were tested with the two-sided Mann-Whitney-Wilcoxon test with Bonferroni correction with a 5% significance level.

# 3 Results

The derived distributions of the different anatomical dimensions evaluated within the present study are depicted in Figure 3. The median angle between stapes axis and TM normal direction α was found to be 15.4°, and α did not reach 0° in any of the investigated cases. Other median values were $TM_h = 8.84$ mm and $TM_v = 9.59$ mm for the horizontal and vertical TM diameters respectively, M-SFP = 4.32 mm and M-SH = 2.19 mm for the distances from central malleus handle to stapes footplate and stapes head respectively and S = 2.97 mm for the length of the stapes. The smallest stapes was found to only be 1.90 mm long, but the respective middle ear was confirmed to be normally developed after re-investigating the images. Only the TM diameters ($TM_h$: $p = 0.261$; $TM_v$: $p = 0.651$) and stapes length S ($p = 0.171$) were found to be normally distributed. Pearson correlation testing revealed significant positive correlations between $TM_h$ and $TM_v$ ($R^2 = 0.44$, $p < 0.001$) as well as M-SFP and M-SH ($R^2 = 0.48$, $p < 0.001$) and M-SFP and S ($R^2 = 0.14$, $p < 0.001$).

In order to investigate the reproducibility of the conducted anatomical measurements, the fiducials described in Section 2.2

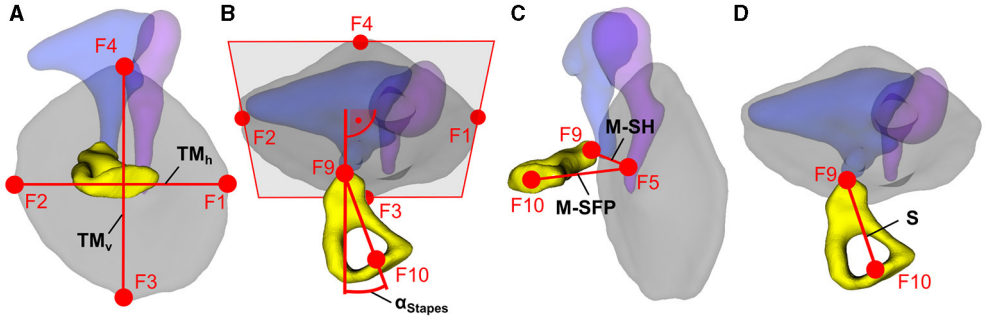


FIGURE 2
Fiducial coordinates were used to compute **(A)** the TM diameters in horizontal ($TM_h$) and vertical direction ($TM_v$), **(B)** the angle α between stapes and TM, **(C)** the distances between central malleus handle and stapes footplate (M-SFP) and stapes head (M-SH) respectively and **(D)** the length of the stapes (S).

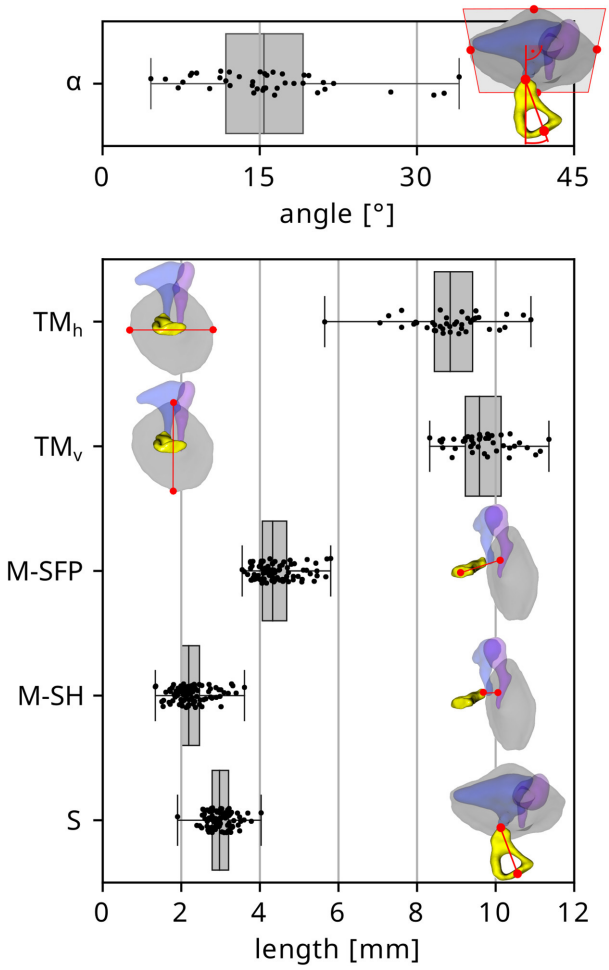


FIGURE 3
Distribution of the investigated anatomical dimensions (from top to bottom: stapes angle, horizontal and vertical TM diameter respectively, distance from central malleus handle to stapes footplate and stapes head respectively, stapes length).

were placed again in 20 of the ears investigated within this study. This was done once by the same observer who conducted the initial assessments (obs1) and then repeated by a second, independent observer (obs2). The resulting intra and inter observer deviations are depicted as Bland-Altman and box plots in Figure 4. The results show noticeable differences in individual measurements both between measurements and observers. Comparisons of the ranges of derived anatomical dimensions revealed only one statistically significant difference, which was for the vertical tympanic membrane diameter $TM_v$ between observers 1 and 2. No statistically significant differences could be observed for any dimensions relevant for the investigated prostheses (i.e., M-SFP, M-SH or S).

The subsequent step of the investigation was the extraction of the different types and lengths of available prostheses mentioned in Section 2.4. In total, 404 different implants were found and categorized. An overview these PMEIs is given in Table 1. The functional lengths offered by different manufacturers was then compared to the distributions of anatomical dimensions relevant for the respective PMEI type. In case of total prostheses, available implant lengths were compared to the distance from central malleus handle to stapes footplate M-SFP minus 0.5 mm to account for the recommended cartilage slice between implant and TM (Mürbe et al., 2002). For partial prostheses, the distance from central malleus handle to stapes head M-SH minus 0.5 mm cartilage thickness was used as the anatomical reference. In case of stapesplasty prostheses, the length of the stapes S plus 0.5 mm was used to account for the recommended insertion depth of the implant piston into the stapes footplate (Mukherjee et al., 2011).

Figure 5 shows the comparison of the corresponding anatomical reference ranges (box plot depiction on the top of each diagram, projected down in red) to the length ranges of total (Figures 5A, B), partial (Figures 5C, D) and stapesplasty implants (Figures 5E, F). Each implant type is separated into fixed (left column) and adjustable length type implants (right column). More detailed information of each individual implant offered by the different manufacturers are given in the Supplementary Figures S2–S22. For the total prostheses (Figures 5A, B), nearly all manufacturers offer implant lengths which cover the entire range of anatomical variation found within this study. In case of the adjustable length total prostheses by Medtronic, it must be noted that a minimal length is only stated for 3 of the 26 available implants. It is hence possible that the lack of implant lengths for very small anatomies depicted

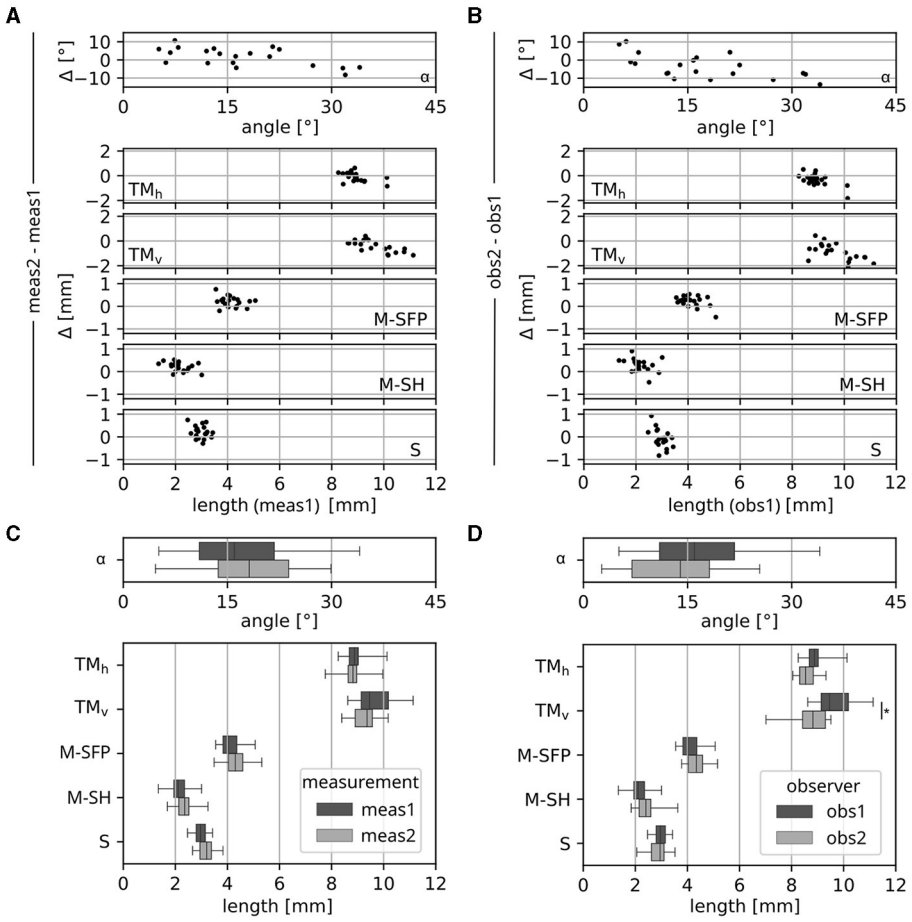


FIGURE 4
differences in dimensions as the result of 2 consecutive measurements (meas1 and meas2) by the same observer (obs1) as well as 2 measurements by two different observers (obs1 and obs2) in a subset of 20 ears, shown as **(A, B)** Bland-Altman plots to depict deviations in individual measurements as well as **(C, D)** box plots to show differences in the resulting ranges of anatomical dimensions, which were found to be not significant except for $TM_v$ between obs1 and obs2.

**TABLE 1** Number of PMEIs found for the different manufacturers.

| Manufacturer | Total protheses | | | Partial prostheses | | | Stapesplasty prostheses | | | Total # PMEIs |
|---|---|---|---|---|---|---|---|---|---|---|
| | Fixed | Adj. | Total | Fixed | Adj. | Total | Fixed | Adj. | Total | |
| Audio Technologies | 12 | 22 | 34 | 15 | 10 | 25 | 25 | 26 | 51 | 110 |
| Grace Medical | 4 | 40 | 44 | 14 | 35 | 49 | 19 | 2 | 21 | 114 |
| Kurz | 5 | 2 | 7 | 6 | 2 | 8 | 10 | 0 | 10 | 25 |
| MED-EL | 2 | 1 | 3 | 3 | 1 | 4 | 4 | 0 | 4 | 11 |
| Medtronic | 0 | 26 | 26 | 2 | 25 | 27 | 9 | 5 | 14 | 67 |
| Olympus | 4 | 8 | 12 | 4 | 11 | 15 | 18 | 5 | 23 | 50 |
| Spiggle and Theis | 2 | 3 | 5 | 3 | 1 | 4 | 10 | 10 | 20 | 29 |

Each PMEI group (total, partial, stapesplasty) is additionally divided into fixed and adjustable length type implants.

in Figure 5B is covered by some implants, but that is not distinguishable from the product catalog. It should also be noted that all manufacturers offer prostheses (adjustable and fixed) which noticeably exceed the anatomical distance they are supposed to cover.

The comparison of anatomical indication ranges and available implants lengths for partial prostheses is shown in Figures 5C, D. Although the different ranges of anatomies appear to be sufficiently covered overall, only few of the individual devices are available in all necessary sizes—especially regarding very small anatomies (cf.

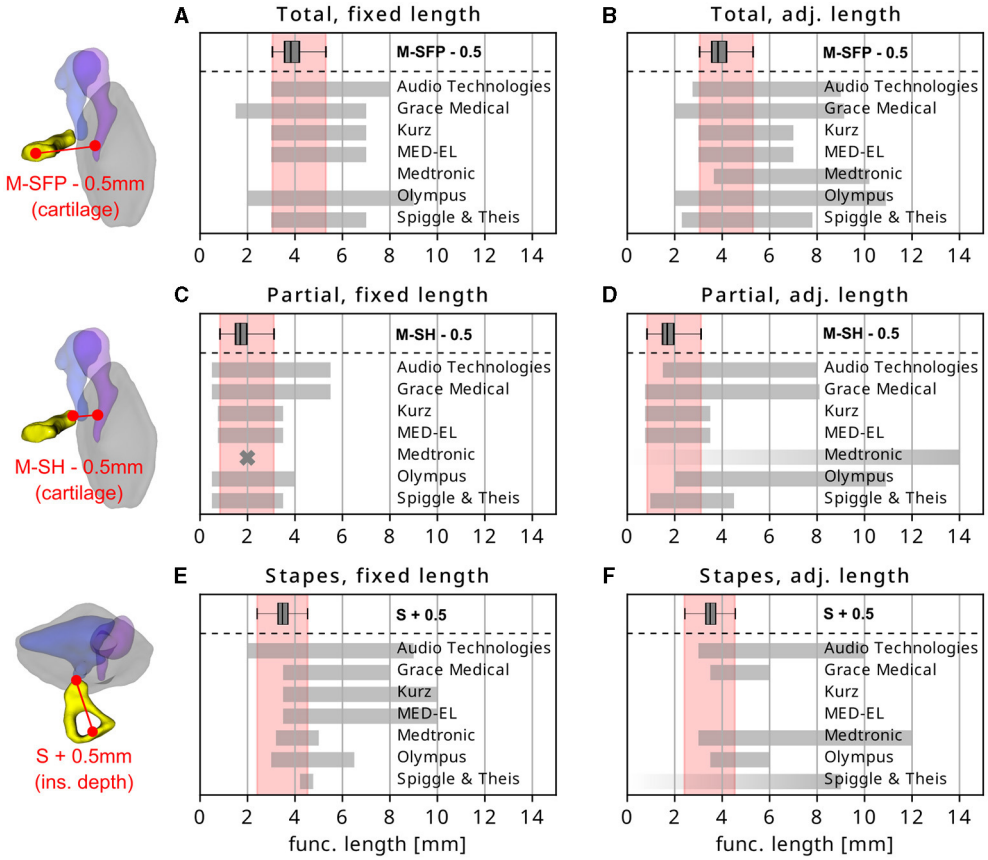


FIGURE 5
Comparison of available length ranges (in gray) of **(A, B)** total, **(C, D)** partial and **(E, F)** stapes prostheses offered by different manufacturers. Prosthesis groups are divided into (left column) fixed and (right column) adjustable length types. Each image also shows the relevant anatomical variations found within this study, the range of which is projected down in red. Fading edges of gray bars indicate that the respective length limit was not clearly stated by the manufacturer. Crosses indicate that only one specific length value is available.

Supplementary Figures S2–S22): the ratio of implants covering the entire anatomical variability to the total number of prostheses is 1/25 for Audio Technologies, 3/49 for Grace Medical, 3/8 for Kurz, 4/4 for MED-EL, 0/27 for Medtronic, 0/15 for Olympus and 3/4 for Spiggle & Theis. Furthermore, some prosthesis types of Audio Technologies, Grace Medical, Medtronic and Olympus are only available in one particular size. Also, Medtronic offers only 2 types of fixed length partial prostheses which are both only available with a functional length of 2 mm, and the lower limit of the length adjustable partial prostheses is not stated for any of the 25 available implant types.

Finally, the comparison the anatomical variability of the stapes length and available stapesplasty implant sizes shows that most of the implant manufacturers do not offer a sufficient portfolio of implant lengths. Most of the available length ranges only cover about half of the derived anatomical variability, stapes pitons for smaller anatomies can only be found within the fixed length pistons offered by Audio Technologies. Other length adjustable devices offered by Audio Technologies, Medtronic and Olympus may be applicable in these cases, but the lower limit of the corresponding length ranges is not stated in the respective product catalogs. Spiggle & Theis only offers fixed length stapes prostheses from 4.25 to 4.75 mm, which only covers the top end of anatomical indications found within this study. The company also offers length adjustable stapesplasty prostheses but does not state the bottom limit of what these devices can be shortened to.

# 4 Discussion

## 4.1 Anatomical variations

The present study demonstrated that just like the inner ear (Meng et al., 2016; Timm et al., 2018), the middle ear anatomy shows substantial anatomical variations. While this has been demonstrated in previous studies as well (aWengen et al., 1995; Todd and Creighton, 2013; Kamrava and Roehm, 2017), the present results also highlight that there is not only variability in size but also in shape. Investigation of the horizontal and vertical tympanic membrane diameters, for instance, showed that only 44% of their variance is explained by correlation of the two measures. More relevant for PMEIs are the variations observed in between tympanic membrane and stapes footplate. The distance from central malleus handle to stapes footplate (M-SFP) was shown to correlate with both distance from malleus handle to stapes head (M-SH) and stapes length (S). However, Pearson coefficients

were only $R^2 = 0.48$ and $R^2 = 0.14$ respectively. This shows that while the distance through the entire middle ear correlates with dimensions reflecting parts of this overall measure, their contribution to the overall distance varies in between subjects. Similar interrelations were derived by Todd and Creighton (2013) who investigated the correlation in size of malleus and incus. An additional degree of complexity is given by the fact that the central malleus handle is not in line with the stapes (Todd, 2008) and the angle between stapes and tympanic membrane axis (Beutner et al., 2011; Gostian et al., 2013). These factors cause the sum of the distance from malleus handle to stapes head and the stapes length to not correspond to the distance from malleus handle to stapes footplate (cf. Figure 3). So unlike cochlear implantation [where specific measurements like the basal cochlear parameters allow for accurate approximations of other parameters of interest (Schurzig et al., 2018, 2022; Breitsprecher et al., 2023)], tympanoplasty always requires the direct measurement of the dimension of interest itself, e.g., of the distance from central malleus handle to the stapes head M-SH for partial prostheses.

One limitation of the present study is the type of imaging that was employed. Although the resolution of 250 µm of the investigated images is quite high for clinical CBCT data, the images still lack the degree of clarity of the recent advances in photon-counting technology (Willemink et al., 2018; Nakamura et al., 2023) or even higher resolution imaging methods like synchrotron radiation phase-contrast imaging (Elfarnawany et al., 2017). Hence, the derived values are affected by assessment errors due to the imaging, which may reach values as high as the voxel size itself. Furthermore, the comparison of dimensions derived by different measurements and observers demonstrated a lack of reproducibility in conducting individual measurements (cf. Figures 4A, B), likely caused by the abovementioned lack of clarity in visualizing the ossicles in clinical CT imaging: the small size of the ossicles yields a blurry boundary when transitioning from bone to air, especially in case of the stapes. Small deviations in assessments between observers in combination with the small sizes of the ossicles hence cause noticeable relative deviations in anatomical dimensions between observers and measurements, exceeding the voxel size of the imaging. The employed clinical imaging technology is hence not sufficient for the assessment of patient specific ossicle dimensions, e.g., as part of the clinical planning prior to middle ear reconstruction. Hopefully, new technological advancements like photon-counting CT (Willemink et al., 2018; Nakamura et al., 2023) can help with these current, clinical limitations and enable more reliable quantitative assessments of patient specific middle ear dimensions in the future. An important finding regarding the present study is that no significant differences could be observed for the ranges of dimension relevant for the investigated prostheses (i.e., the distances from malleus handle to stapes footplate M-SFP and stapes head M-SH or the length of the stapes S) between measurements or observers (cf. Figures 4C, D). Thus, it can be assumed that the derived ranges of these middle ear dimensions are a sufficiently accurate foundation for the comparison with available PMEI lengths.

One further limitation of the present study is that all measurements were taken in normal middle ear anatomies. Consequently, the assessed middle ear dimensions may differ from those of malformed or diseased middle ears, e.g., because the tympanic membrane may be retracted. It is therefore unclear if the development of novel prostheses is justified exclusively based on the current study. It was, for instance, shown that the smallest stapes found within the patient cohort had a length of under 2 mm. The need for an accordingly small prothesis, however, can only be verified if such small dimensions can also be assessed within otosclerotic ears. Nevertheless, we believe that the assessed dimensions provide a good general foundation for what length ranges specific prostheses should cover. In the future, the anatomical part of the present study should be repeated on a large set of high-resolution imaging of pathologic middle ears to compare the spatial dimensions relevant for PMEIs.

## 4.2 PMEI specifications

Clear length specifications of PMEIs within the manufacturers' product catalogs and implant packaging are crucial for selecting the right implant for an individual patient. Unfortunately, in conducting the present study we found that these specifications are not always given. Especially in case of length adjustable implants, the bottom limit of this adjustability was often missing and—in case of some manufacturers—not stated for any available PMEIs. Furthermore, length specifications are often stated differently for different manufacturers. In fact, comparable length information across manufacturers was given only for total prostheses: the total length (TL) describes the distance from the top of the head plate to the bottom the prosthesis piston and corresponds to the anatomical distance which is supposed to be bridged by these devices, i.e., from the tympanic membrane [or malleus handle to improve audiological outcomes (Bance et al., 2004)] to the stapes footplate. In case of total prostheses, the functional length (FL), i.e., the length of the section bridging the gap of missing anatomical structures, hence corresponds to the TL of the implant.

Unfortunately, this is typically not the case for partial prostheses. In patients requiring the use of these devices, the distance which needs to be bypassed (i.e., the FL) corresponds to the distance from tympanic membrane/central malleus handle to the stapes head. This is relevant as partial prostheses typically have an adapter at the proximal end of the shaft to enable sufficient coupling of the prosthesis to the stapes head, or the prosthesis piston is hollow such that it can be placed over the stapes head and protect the implant against slipping out of place. The TL of the implant is hence strongly affected by the design of the individual prosthesis (as is depicted for $TL_1$ and $TL_2$ in Figure 6A) and does not correspond to the FL. If taking into account that prestressing the AL surrounding the stapes footplate entails substantial losses in sound transfer (Bance et al., 2004; Morris et al., 2004; Merchant and Rosowski, 2013; Neudert et al., 2016; Schär et al., 2023), length specifications of partial prostheses should hence always include the FL of the device such that surgeons can select an implant which matches the patient specific, intraoperative measurement.

Similar length specification issues occur in case of stapesplasty prostheses due to the loop at the distal end of these devices. This

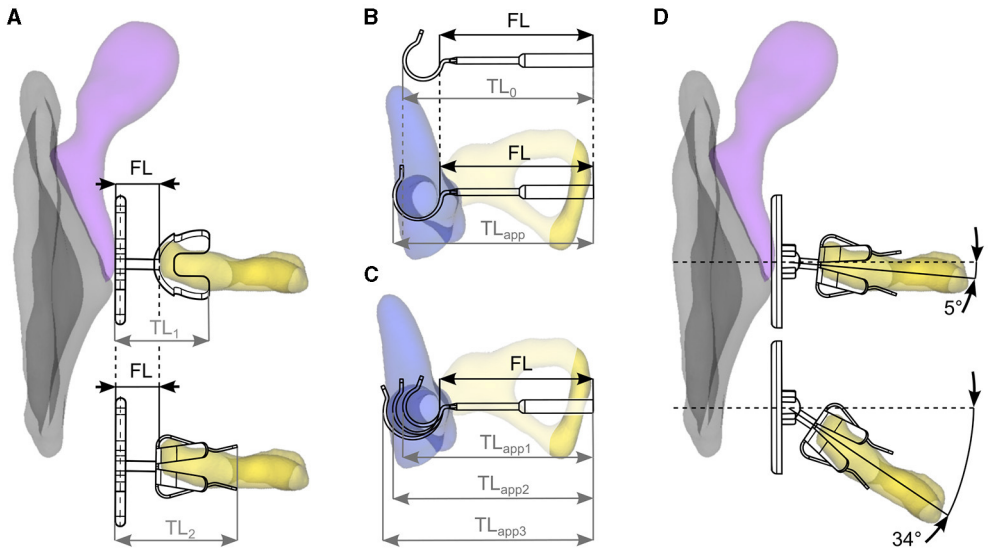


FIGURE 6
**(A)** Relevant for surgical reconstructions with passive prostheses is the functional length FL rather than total length TL as it describes the middle ear distance to be bridged independent of the prosthesis design. **(B)** The initial total length $TL_0$ of a stapesplasty prosthesis may differ from the total length after application $TL_{app}$, and **(C)** the latter is further affected by the size of the long process of the incus, highlighting the importance of FL specifications for stapesplasty prostheses. **(D)** Accommodation of the derived extrema in angular deviations between tympanic membrane axis (dashed line) and stapes axis (solid line) by a partial prosthesis design containing a ball joint.

loop is supposed to be crimped around the long process of the incus during surgery, which can be done mechanically or using shape memory alloys which wrap around the incus when heat is applied to the structure. In either case, the initial loop diameter and implant size $TL_0$ will only rarely correspond to the length after implantation $TL_{app}$ (see Figure 6B). Furthermore, neither one of these dimensions corresponds to the distance FL needing to be bridged in these stapesplasty, which ranges from the proximal end of the long process of the incus to just below the stapes footplate. An additional factor making total length specifications of stapesplasty prostheses unsuitable is the variation of the diameter of the long process of the incus (Chien et al., 2009; Tóth et al., 2013). Studies have demonstrated that this diameter can range from under 500 µm to about 1.5 mm. Depending on the size of an individual incus, the TL of a stapesplasty prosthesis after implantation can vary noticeably between subjects, as is depicted in Figure 6C. The most straightforward and reliable approach for selecting an implant length ideally suited for a particular patient is hence to measure the distance between long incus process and stapes footplate, add the desired insertion depth of the implant piston and select an implant whose FL corresponds to this specific value, making a clear statement of the respective FL value within the implant specifications mandatory.

## 4.3 PMEI sizes

One of the most obvious findings within this study is that nearly all manufacturers offer implant lengths which far exceed the derived anatomical indication ranges (Figure 5). The maximum distance from central malleus handle to stapes footplate within the study cohort was 5.8 mm, resulting in a maximum required FL of a total prosthesis of 5.3 mm if considering a cartilage slice of 0.5 mm between prosthesis and tympanic membrane. As shown in Figures 5A, B, maximally available total prosthesis lengths exceed this value by far, with the largest fixed length protheses offered by Audio Technologies (e.g., with the 8 mm AUDIO-HA® Total Prosthesis) and Olympus (9 mm Wehrs II Incus-Stapes System). Since these devices cannot be shortened, their applicability is questionable if planning to avoid excessive pretension of the AL and corresponding losses in sound conduction. One potential indication may be patients with strongly lateralized tympanic membranes, requiring an accordingly longer prosthesis to bridge the gap between outer and inner ear (Sperling and Kay, 2000).

The same holds true for partial prostheses: the maximum anatomical distance to be bridged by these devices was found to be 3.6 mm, which corresponds to a maximum FL of 3.1 mm if a cartilage slice of 0.5 mm thickness is used. With a FL of 5.5 mm, the maximum fixed length partial prostheses offered by Audio Technologies and Grace Medical are substantially longer than the anatomical indication range and should hence not be employed If wanting to avoid excessive AL pretension. Another interesting observation was made when further inspecting the fixed length partial prostheses: Audio Technologies, Grace Medical, Medtronic and Olympus offer devices which are only available in one specific length. Although most of these specific length values lie close to the center of the derived anatomical variability and are hence made for average anatomies, studies could demonstrate clearly that even small preloads onto the stapes cause severe reductions in sound transmission. Unless devices are made for specific cases like the Goldenberg CAP Prosthesis which is clearly designed for particularly small anatomies, the derived anatomical

variability suggests that implants should generally be available in different lengths.

For the fixed length stapesplasty prostheses it could be observed that Audio Technologies is the only manufacturer who offers devices which cover the entire anatomical indication range. This is owed to their Platinum Prosthesis for Stapedectomy (SPL 03.00) which is available in 2 mm and longer. All other manufacturers lack stapesplasty pistons which can—according to our study results—be safely implanted into smaller anatomies. In case of Spiggle & Theis it can only be stated that with 4.25–4.75 mm, their fixed length stapesplasty prostheses cover the smallest range of all investigated manufacturers and are only applicable in case of very long stapes lengths. The length adjustable prostheses offered by Spiggle & Theis may be applicable in all other cases but unfortunately, their product catalog is lacking the corresponding length specifications. It must be noted here that the present study was conducted with a target insertion depth of 0.5 mm of the prosthesis piston into the SFP. This value was postulated by Mukherjee et al. (2011) as the maximal insertion depth which will reliably transfer the piston movements into the perilymph without touching the utricular macula. However, another factor that must be considered in deciding on a target insertion depth are piston displacements not related to incoming sound, i.e., due to sneezing and/or atmospheric pressure changes. While inserting the stapesplasty piston 0.5 mm into the SFP was proposed to be sufficient for preventing piston dislocation due to sneezing (Fisch, 1994), research could also show that atmospheric pressure changes (e.g., when diving or flying) may displace the stapes piston by more than 0.5 (Hüttenbrink, 1988, 2003). Hence, a stapedotomy was suggested to be advisable at the posterior section of the SFP such that piston contact to the utriculus is avoided and the distance to the saccule is maximized (Hüttenbrink, 2003). In this case, the piston could be inserted beyond the 0.5 mm mark, which would shift the anatomical indication ranges (shaded areas in Figures 5E, F) toward larger values and hence create a larger overlap with currently available implant sizes. Another factor that must be addressed is that the reason for offering stapesplasty prostheses which far exceed the derived range of stapes length (plus an insertion depth of 0.5 mm and more) may have to do with manufacturers trying to not only offer devices for stapesplasty but also for malleovestibulopexy. In the latter case, the prosthesis must bridge the gap between malleus handle and SFP (i.e., a distance larger than the stapes length S), requiring accordingly longer prosthesis lengths.

A general finding regarding all length adjustable prostheses is that while the anatomical variation may be covered by nearly all manufacturers, that does not necessarily hold true for all devices offered within the respective product portfolios. This can be quantified by calculating the ratio of the number of implants covering the entire anatomical variability to all implants with sufficient length specifications. Length adjustable implants which do not cover the derived anatomical variability are offered by Audio Technologies (6/16), Medtronic (0/3) and Olympus (2/3) in case of total prostheses and Audio Technologies (0/6), Grace Medical (2/21), Olympus (0/3) and Spiggle & Theis (0/1) for partial prostheses. As mentioned before, no length adjustable stapesplasty implants were found which sufficiently cover the derived anatomical variability. These findings are highly relevant for hospitals wanting to reduce the number of locally stored implants by using length adjustable devices, as the ratios point out that the specific implant to be used must be chosen with care.

### 4.4 Angle between tympanic membrane and stapes

Within the present study, the angle between tympanic membrane and stapes α was found to lie between 4.6° and 34.0° with a median of 15.4°. A visual representation of this angular range is given in Figure 6D, and recent developments in partial prosthesis designs were aimed at accounting for this angular range by a more stable fit of the prosthesis onto the stapes (Schär et al., 2023) and a ball joint at prosthesis head (Beutner et al., 2011; Gostian et al., 2013). These ball joint prostheses are now commercially available (Clip Partial Flexibal Prosthesis by Kurz, mCLIP ARC Partial by MED-EL) and were shown to yield better results than partial prostheses without this joint (Stoppe et al., 2018; Schär et al., 2023).

## 5 Conclusion

The present study demonstrates that the middle ear anatomy shows substantial anatomical variations in size and shape. The resulting range of required implant lengths for full and partial prostheses is covered by nearly all manufacturers, but not by each implant. As for stapesplasty prostheses, there is an unmet clinical need for smaller devices to match the individual anatomy of every patient's middle ear. Passive implants with angular adjustment options between tympanic membrane and stapes appear to better adjust to the natural anatomic orientation of the ossicles.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Ethics Committee of the Hannover Medical School. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

TL: Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. MB: Writing – original draft, Visualization, Validation, Methodology, Investigation,

Data curation, Conceptualization. AW: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. AG: Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. NP: Writing – review & editing, Supervision, Resources, Project administration, Data curation, Conceptualization. US: Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Formal analysis, Data curation, Conceptualization. DS: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

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## Conflict of interest

DS and US are employed by MED-EL, one of the manufacturers of the investigated passive middle ear implants. However, the data collection and analysis was conducted independently by the Hannover Medical School, and all data is made available with the submission such that the validity of the results can be checked. Furthermore, it was derived within the present study that there is a lack of specific middle ear implant sizes (for stapesplasty) which also applies to MED-EL. The present research was hence conducted in a scientifically valid manner without any bias.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fauot.2024.1418921/full#supplementary-material

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# Best practice in audiology: context matters

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Historically, modern audiology evolved from the United States of America (USA) after the Second World War, where hearing rehabilitation programs were established across the country. Since then, audiology practice and the profession as a whole has expanded from the west to the far east and global south with considerable contextual variations. Thus, the purpose of this paper is to increase conversation and engagement on definitions and the drawbacks of a single lens approach to the use of best practice guidelines in Audiology. It is important to develop a more expansive lens as influenced by different contexts such as Africa, Asia, and South America that will in turn help facilitate a multidimensional approach to audiology practice and what is considered "best practice."

KEYWORDS

**best-practice, contextualization, evidence, guidelines, global-audiology, multidimensional approach**

## The beginning and evolution of audiology practice

Historically, mankind over the past centuries had developed different solutions to hearing and vestibular disorders amongst the different ancient civilizations of the world such as the Egyptians, Babylonians, Greeks, Hindu, Byzantine, etc. Some work was recorded as early as 1500 BC. In one of the earliest classic scientific documents, Eber's Scrolls from Egypt, there are descriptions of battle wounds on temporal bones and how they affected hearing and speech. Similarly, another Egyptian text documented a chapter on "*Medications for the hard of hearing ear*" where treatment could be found for tinnitus, dizziness and hypacusia (Hawkins, 2004). The Greek philosopher Empedocles of Agrigento in Sicily (504-433 BC), was the first to describe the cochlea, named after a seashell found in the Mediterranean region (Gitter, 1990).

Modern audiology evolved from the United States of America (USA) after the Second World War, where hearing rehabilitation programs were established across the country. From this period audiologists have been collaborating with otologists and researchers in related fields to develop techniques to determine not only the degree of hearing loss but also the site of the patient's lesion in the middle ear, cochlea or retrocochlear structures (Jerger, 2019). These techniques developed over time and expertise have become the bedrock of the key technical skills that laid the foundation for the global professionalization of Audiology.

## Global professionalization of audiology

Professionalization is described as the process of acquiring a professional status (Hoyle and John, 1995) characterized by obtaining scientific knowledge through higher education to develop disciplinary skills and competencies (Abrahams et al., 2019). Among health professions, medicine was the first Western profession to achieve wide professionalization and professional autonomy (Brosnan, 2015). Newer emerging professions, especially rehabilitation occupations such as audiology are said to have galvanized resources, status, and influence of medicine as a platform for their own professional development with an empirical, positivist frame (Abrahams et al., 2019). Professions hold the power to determine ways to think and act in their domain of expertise and that power is realized through the formal education process where students learn how to see and think about the world (Montigny, 1995; Evetts, 2014; Abrahams et al., 2019).

For Audiology, the first university program was offered at Northwestern University in the USA, in 1946 under the guidance of Raymond Carhart (Jerger, 2018). During the 1950–60's, audiology practice started emerging in community speech and hearing centers in America, geared primarily to aural rehabilitation and in medical settings audiologists began conducting hearing assessments in Ear Nose and Throat (ENT) clinics (Jerger, 2019). The 1970 and 80's saw the emergence of subspecialty areas: pediatric audiology, educational audiology, industrial audiology, cochlear implants, and assessment of balance function (University of North Carolina, 2021).

## Expanding audiology into varying contexts

Since the inception of audiology professionalization to date, audiology practice and the profession as a whole has expanded from the west to the far east and global south. With this expansion into different regions in the world and growing number of audiology professionals trained, it can be argued that to date training is heavily influenced by North American and British educational models (Tuomi, 1994; Pillay and Kathard, 2018) with limited considerations of the considerable contextual variations needed in curriculum content and clinical practice. Pre-existing evidence on ancient, diverse, indigenous, and regional contextual approaches to hearing care may be overlooked or obscured by operational training and education models that are predominantly reflective of the foundational audiology program largely from the west and global north.

Both knowledge and training should be reframed to include all of the vastly different contexts in which hearing care is provided across the various regions, including the far east and global south (Ng, 2012). This reframing is encouraged by the United Nations (UN) report on indigenous peoples' access to health services (United Nations, 2015) on the inclusion of indigenous knowledge, with content that is diverse, context specific, and relevant. These aspects may be relevant in developing curriculum and training for hearing care professionals (Khoza-Shangase and Mophosho, 2018, 2021). As such, literature on contextual relevance in the profession of audiology argues that the professionalization process may be using a single lens that views the western knowledge as the only norm, and inadvertently impact what is considered current best practice (Mignolo, 2009; Ng, 2012; Khoza-Shangase and Mophosho, 2018, 2021).

## Current best practice terminologies and descriptions

Currently most healthcare professional bodies use position statements, best practice recommendations and/or clinical practice guidelines to describe how audiology clinical services should be provided. These terminologies are used interchangeably, yet they do not always mean the same. While a clear distinction between position statements, best practice, recommendations and clinical practice guidelines is yet to be made in audiology literature, these descriptions are often used as a blueprint for clinical practice, audiology education, as well as research in audiology practice (see Table 1).

## Implementation of "*best practice*"

A good practice (method or technique) that has consistently shown results superior to those achieved with other means is often used as a benchmark. The best practices might be used as a kind of checklist against which one can directly evaluate a system's design and code. Lack of adherence to any given best practice, however, does not necessarily imply a lack of quality; they are recommendations that are said to be "best" in most cases and in most contexts, but not all. "A best practice is always subject to improvement as we learn and evolve together" (Mukherji and Albon, 2014). So, this means that guidelines are good, but not always implementable. And best practice is good to get positive results, yet if we do not follow it, it does not mean poor quality. What these definitions do is, they provide the flexibility to factor-in contextual variations such as availability of resources, priorities of different countries, needs of the population, prevailing policies, and power imbalances.

The benchmark descriptions (best practice/guidelines/position statements) are often decided by consensus approach, or evidence-based methods by a group of clinicians/academics/researchers. However, the evidence is often out of context. Therefore, when best practice is viewed from an impact outcome perspective, then contextual variations have to be factored in. "*Evidence does not make decisions, people do*" (Haynes et al., 2002). Hearing health and illness beliefs differ among populations across the world. For example, South African traditional healers often seek the source of illness (including ear-related diseases) in the supernatural realm (de Andrade and Ross, 2005). Thus, evidence-based practice needs to take into account the heterogeneity of the nature and needs of the context in order to be relevant and implementable (Scheppers et al., 2006; Narayansamy et al., 2014).

TABLE 1 Current terminologies and descriptions on "best practice."

| Term | Definition |
|---|---|
| Best practice | "*Best practice*" is defined as "...professional procedures that are accepted or prescribed as being correct or most effective" (Oxford English Dictionary, n.d.). |
| Practice guidelines | "Systematically defined set of recommended procedures based on available scientific evidence and/or expert opinion that have been designed to yield specific, well-defined outcomes" (American Association of Audiology, n.d.) |
| Evidence based practice | "Evidence-based practice (EBP), incorporating all areas of healthcare, involves the integration of the best available research evidence with clinical expertise, the clinical context and the client's preferences and goals" (Wong and Hickson, 2012, p. 3). |
| Standards | "Standard" is considered as something established by authority, custom, or general consent as a model or example (Merriam-Webster, n.d.). |

## Audiology best practice and evidence: context matters

The limitedness of context specificity in the existing models of professionalization and clinical practice in Audiology may largely be creating a single lens view to what is best practice, or evidence-based practice. Similar to other rehabilitation professions, the hearing care profession is filled with conventions especially about what is objective and/or subjective evidence (Pillay and Kathard, 2018). Some anecdotal examples of a one size fits all/single lens approach that are some of the basis for this discussion paper are described in Table 2.

### Clinical guidelines vs. practice context

If the specific example of Early Hearing Detection and Intervention Programs is considered, the guidelines given by The Joint Committee on Infant Hearing (2019) for screening, diagnosis and intervention is an aspirational guideline that many countries have adopted. However, in reality, implementing this evidence-based guideline, for example, in a country like India has been challenging. This is because India serves a population that is predominantly rural, where births are largely at primary health care clinics that are at far distances from tertiary care centers having infrastructure for hearing screening or diagnosis. Further, a significant proportion of births still occur at home (Ou et al., 2021). Also, resources (equipment, professional, and infrastructure) are allocated to the more prevalent or lifesaving conditions. Additionally, the recommended screening and diagnostic tools such as OAE and AABR have not been affordable (one time purchase cost, plus annual servicing/maintenance multiplied by the number of birthing centers).

Therefore, low-cost behavioral measures that are sensitive tools to screen more severe hearing losses (Ramesh et al., 2012) is an alternative to be considered until such time that the country can afford to detect/identify mild hearing loss. Similarly, check list based high-risk screening and behavioral observation audiometry at remote birthing centers followed by referral to tertiary care centers was found to improve screening coverage (Rajpoot et al., 2023) in a developing country setting.

Outcomes of implementation in settings where health care services are self-financed will differ considerably from publicly-funded services (Olusanya, 2012). Therefore, it is prudent for countries to develop guidelines based on existing context, with consensus among all relevant stakeholders such that it is currently feasible to improve the situation of EHDI within that setting. The impact outcomes of such implementation has the potential to eventually guide improvements in resource allocations that are closer to the evidence-base.

### Premise to contextualize audiology training

Using South Africa as an example where there are several cultures, ethnicities and belief systems, research has continued to argue for cultural contextualization for the adaptation of knowledge, methods and approach in the teaching and training of audiologists (Khoza-Shangase and Mophosho, 2018, 2021). South African researchers, Pillay and Serooe (2019) highlight the prominence and use of traditional healing as a source of hearing healthcare for many South Africans of varying spiritual, religious and cultural beliefs. However, there seems to be no acknowledgment and or openness to explore the value of traditional care models for audiology within curriculum and or research (De Andrade, 2011; Pillay and Serooe, 2019). Thus, graduates produced for practice in South African audiology through the current global north influenced curriculum are often found completely dismissing the option to even ask in case history if clients consult with traditional or cultural healers (Pillay and Serooe, 2019).

Health beliefs as a whole are not often acknowledged in guidelines used for training. If the example of South Africa is used once more, another area in audiology where contextualization would be culturally responsive is with the South African guidelines on audiological management of ototoxicity (Health Professionals Council of South Africa, 2018) that are used widely in training. Particularly, within the guidelines, there is the inclusion of the term *all* in the ototoxicity monitoring recommendation: "All patients on ototoxic medication presenting with these risk factors must be monitored …" This here is an example of how this recommendation does not consider or allow for the autonomy of patients with health—and/or illness beliefs different to the guidelines' authors.

TABLE 2 Examples of a single lens view vs. a context based view.

| Area of audiology | Case example of single lens view | Case example of a context based view |
|---|---|---|
| Education | Teaching audiology using resources, tools, books, methods and in a language that emerged from contexts that are dissimilar from where it is being taught without contextualization | Teaching audiology based on knowledge and resources that emerge from the context where it is being applied, embracing a diverse evidence base from regional/local knowledge and languages |
| Clinical | Implementing early hearing detection and intervention programs using protocols and benchmarks of a developed country with outcomes based on resource capacity | Implementing early hearing detection programs based on context based on attainable goals and available resources (professionals/costs/equipment/test environment/cultural needs) |
| Research | Reviews and feedback on research (publications/conference abstracts/grant applications) from diverse practice settings including low and middle income countries, based on perceived applicability/international appeal using an international consensus peer review method with reviewers often based in developed countries/contexts | Reviews and feedback on research enabling input from local context from where the work originates as well as a broader approach that showcases on an international level what is being done in different contexts |

## Context specific practice guidelines

Context can be described as the broad circumstances and environmental characteristics or settings (Damschroder et al., 2009) in which health care services are implemented. Therefore, apart from the training, competence, and professional influences of the audiologists, the delivery of services is influenced by a number of additional contextual factors. Local infrastructure (including test environment), social fabric, financial resources, legal and socio-political climate, are some examples of these factors that have an impact (Watson et al., 2018).

Often capability, opportunity, and motivation of professionals have been attributed to lack of compliance to professional guidelines in audiology (Goulios and Patuzzi, 2008; Watson et al., 2018; Marques et al., 2022). While guidelines are driven by knowledge, "Knowledge to Action" is not spontaneous and requires one to "Adapt knowledge to local context" (Moodie et al., 2011). While exploring why audiologists do not adhere to best practice, the lack of understanding of internal conditions for the individual hearing healthcare practitioner [and their] social and physical work environment was speculated as a possible reason (Shaw, 2012).

In low and middle income countries, hearing care services are provided by various cadres of service providers including community volunteers, school teachers, special educators, audiometrists, other allied professionals, audiologists, and even otolaryngologists. These are often based on the level of capacity of individual countries to have a specialized workforce to provide hearing care services. Therefore, a vast difference exists in audiology practices based on the local context and setting prevailing in that region. To account for some of these, many local professional bodies have developed their own guidelines (Indian Speech and Hearing Association, 2017; HPCSA, 2021; SACIG, 2022). While such practices may not meet "benchmarks," they may still cater to the ear and hearing care needs plus fill service gaps that exist in that region.

This paper would like to propose that *practice context* should be factored into audiology best practice engagements and guidelines. We propose a process of *contextualization* which according to Ernstzen et al. (2019) is based on the premise that clinical practice guidelines produced in one place, timeline and context may not be appropriate for implementation across varying contexts due to differences in the healthcare systems, socio-cultural, societal, policy and economic contexts. Therefore, contextualization requires identification of *practice context* to which existing practice guidelines must be tailored to (Siegfried et al., 2018). In the schematic (Figure 1) we propose some of the contextual factors that can influence audiological practices and have broadly classified them into (i) environment (related to the physical environment and end-users) and (ii) circumstances (related to other variables that directly influence service provision; Watson et al., 2018).

These are described with some case examples below:

- *Environment:*
  - Geography:
    - *Weather/climate*—influences travel access (e.g., snowy mountains of Bhutan, deserts of Afghanistan), working hours (which in turn alters service availability), allowable/feasible testing time and protocol (e.g., in the mountains of Bhutan having test sessions across multiple days is challenging and there will be non-compliance due to difficulty in returning as a result of long distances). Therefore, conclusive time efficient test batteries may have to be conducted in single sessions.
  - End users:
    - *Person-centered care/Patient care practices*—Is it participatory culture or top-down (medical model) or advocacy-rights based culture that prevails in the context where audiology services are provided? The dominant culture will dictate the choice of services (e.g., Deaf vs. deaf).
    - *Cultural and social fabric*—stigma around disability, language (influences test tool choices), belief systems, and local practices.
- *Circumstances:*
  - Political will:

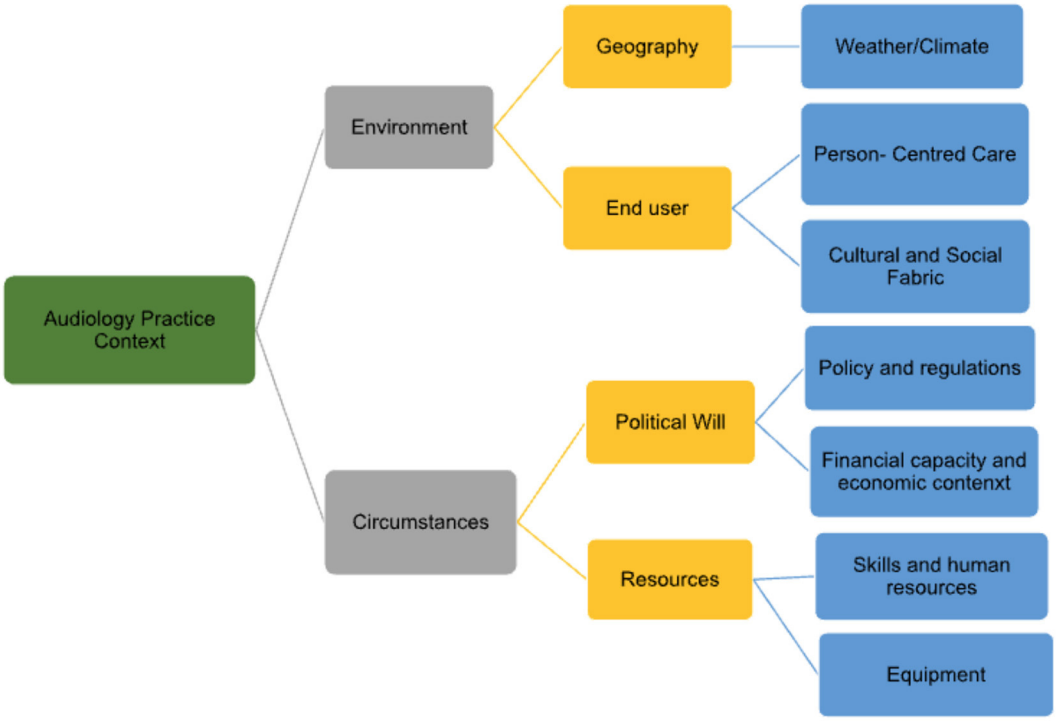


FIGURE 1
Contextual factors influencing audiology practices.

- *Policy and regulations*—will decide what benefits are provided (free hearing aids, cochlear implants, travel concessions, or educational concessions, etc.), who will receive benefits (children and adults).
- *Financial capacity and allocation/economic context*—Resources- types of schools, type of rehabilitation.
    - Equipment (e.g., otoscopy vs. tympanometry to rule out middle ear pathology).
    - Human Resources (e.g., community worker vs. audiologist performing basic hearing testing).

## Conclusion

Audiology practice and the profession as a whole has grown since the main inception era and the footprint of audiologists has expanded to reach each continent. This paper seeks to increase engagement on development of *context influenced* best practice definitions, evidence gathering and evaluation methods as well as a multifaceted regional approach to the implementation of practice guidelines. We believe that it is crucial to expand audiology and the practice thereof in each region based on the milieu such as those in Africa, Asia and South America. This expanded lens can begin with a relook at how the profession defines *best practice* and we propose that the *audiology practice context* be used as a multifactorial and multifaceted lens to *contextualize* existing best practice guidelines.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

V-GH: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. VR: Conceptualization, Project administration, Visualization, Writing – original draft, Writing – review & editing. LP: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. BV: Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Gene therapy advancements for the treatment of acquired and hereditary hearing loss

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Greater understanding of the molecular intricacies of acquired and hereditary hearing loss has spurred considerable advances in inner ear gene therapy. While approaches like cochlear amplification and cochlear implantation offer varying degrees of efficacy in restoring hearing function, there is an absence of FDA-approved pharmacotherapies targeting the underlying causes of hearing loss. Recent preclinical investigations have demonstrated promising outcomes in murine and non-human primate models, demonstrating efficient transduction and hearing recovery for both acquired and hereditary forms of hearing loss. This review provides a comprehensive analysis of the latest developments in gene therapy for hearing loss. Specifically, we focus on conditions characterized by sensory epithelium and spiral ganglion neuron dysfunction, encompassing both hereditary and acquired etiologies. We discuss recent preclinical advancements in cell-type-specific transduction strategies and highlight key findings from clinical trials exploring gene therapy interventions for hearing loss. Additionally, we address current limitations and offer insights into future directions for advancing gene therapy as a viable treatment option for individuals with hearing loss.

KEYWORDS

**gene therapy, sensorineural hearing loss, AAV vectors, clinical trials, spiral ganglion neurons, hair cells**

## 1 Introduction

Hearing loss is the most common sensory impairments in humans, affecting more than 1.5 billion people worldwide. Among those, more than 400 million children and adults suffer from severe to profound hearing loss (Collaborators, 2021). Children who are born deaf or have difficulty hearing who do not receive early intervention are at a higher risk for poor literacy outcomes and a lower quality of life (Hrastinski and Wilbur, 2016; Panda et al., 2019; Ronner et al., 2020). Hearing loss in adults has also been associated with higher rates of loneliness, anxiety, and dementia (Huang et al., 2023).

Congenital, or hereditary, hearing loss (HHL) is a well-studied and significant cause of hearing loss in children (Shave et al., 2022), while age-related hearing loss, noise-induced (NIHL), and chemotherapy-induced ototoxicity (CIHL) are significant causes of acquired adult sensorineural hearing loss (SNHL). The primary cause of functional impairment in most cases is the degeneration of sensory epithelium (outer and inner and inner hair cells [OHC/IHCs]), spiral ganglion neurons (SGNs), and the peripheral auditory nerve synapses

between them. Despite the high prevalence of these hearing disorders, there are currently no U.S. Food and Drug Administration (FDA)-approved pharmacotherapies available to prevent or reverse SNHL. Clinically, hearing amplification and cochlear implants (CI) are the only treatment options available, however they do not target the underlying molecular driver of the disease.

Gene therapy is a promising therapeutic option for hearing loss that has recently been shown to restore hearing in pediatric patients with monogenic HHL due to *OTOF* pathogenic variants (Lv et al., 2024; Simons et al., 2024). The unique anatomy of the inner ear lends itself to viral-based gene therapy, is a relatively isolated fluid compartment which lends itself to limited immunogenicity and has a small number of non-dividing target cells. The success of monogenic gene therapy is based on a multitude of preclinical studies in murine and non-human primate (NHP) models, but the focus has primarily been on IHC transduction in monogenic hearing loss. There remains a lack of information regarding treatment for SGN-degenerating conditions. Moreover, only negligible SGN transduction has been accomplished in adult mammals. This deficiency in effective targeting of SGNs limits the potential success of treatment options.

In this review, we aim to explore the use of viral vectors, delivery routes, and clinical implications of gene therapy in the mammalian inner ear. Our objective is to provide a comprehensive evaluation of the available evidence regarding cochlear HC and SGN transduction and the potential benefits and challenges associated with gene therapy for hereditary and acquired hearing loss.

# 2 Hearing loss and potential therapeutic targets

## 2.1 Monogenic, non-syndromic hearing loss

Monogenic, non-syndromic hereditary hearing loss, resulting from singular genetic pathogenic variants, is a prominent pathology within the spectrum of inherited auditory impairments/HHL. Currently, pathogenic variants in approximately 120 genes have been associated with non-syndromic hearing loss in humans (Sharma et al., 2023; Walls et al., 2024). Unraveling the genetic intricacies inherent to the normal development and function of the inner ear and vestibulocochlear nerve has been accelerating at a fast pace, opening new potential therapeutic avenues for gene therapies.

Non-syndromic hearing loss exhibits varying inheritance patterns—autosomal dominant, autosomal recessive, x-linked, and mitochondrial/maternal—with autosomal recessive predominating with more than 70% of known cases (Walls et al., 2024). In addition, de novo pathogenic variants are an important cause of HHL in patients with no familial history (Klimara et al., 2022).

Autosomal dominant, non-syndromic hearing loss (DFNA) typically exhibits heterogeneity, with both males and females being affected from early childhood to adulthood, with the onset of most cases being post-lingual (Aldè et al., 2023). Approximately 80 loci on 50+ genes have been identified, with pathogenic variants in *MYO6* (DFNA22), encoding for a crucial motor protein (Oka et al., 2020), and *TECTA* (DFNA8/12), which encodes for a tectorial membrane component named α-tectorin (Hildebrand et al., 2011), being the most identified in a European cohort (Del Castillo et al., 2022). Additionally, identified genes predominantly affect supporting cell (SC) function (*GJB2* [DFNA3A]) (Denoyelle et al., 1998; Wang et al., 2017), HC function with *KCNQ4* (DNFA2A) (Arnett et al., 2011) or SGN development and function, such as *COCH* (DFNA9) (Danial-Farran et al., 2021) and *POU4F3* (DFNA15) (Vahava et al., 1998).

Autosomal recessive, non-syndromic hearing loss (DFNB), in contrast to DFNA, is associated with severe to profound hearing loss with most patients having a pre-lingual onset, however some may present with a gradual progression of hearing loss (Sharma et al., 2023). Approximately 85 causative genes have been identified and associated with DFNB, with the *GJB2* (DFNB1A) pathogenic variants the most common at an estimated 60% of DFNB cases (Sloan-Heggen et al., 2016; Del Castillo et al., 2022; Walls et al., 2024). *GJB2* encodes for connexin 26 (a gap junction protein) in SCs that is crucial for maintaining potassium homeostasis in the HCs. Other causative genes include *OTOF* (DFNB9) (the most studied gene in gene therapy clinical trials), *TMC1* (DFNB7/11), *GJB6* (DFNB1B), *MYO7A* (DFNB2), and *SLC26A4* (DFNB4) (Doll et al., 2020; Del Castillo et al., 2022). Specifically, *OTOF* encodes for otoferlin, a synaptic protein involved in glutamate release from the HCs, thus allowing for electrical conduction of the SGN and propagation of auditory stimuli.

X-linked and mitochondrial inherited pathogenic variations make up a small proportion of non-syndromic hearing loss and have been elegantly discussed elsewhere (Vona et al., 2015; Sloan-Heggen et al., 2016; Walls et al., 2024).

Taken together, non-syndromic hearing loss is a prime candidate for gene therapy applications. By targeting and correcting the specific pathogenic variation responsible for inner ear dysfunction, there is potential to restore normal hearing function. These approaches hold potential to provide treatments tailored to individual patients, representing a significant advancement in the field of audiology and otology. Clinical trials for these applications will be discussed further below.

## 2.2 Syndromic hearing loss

Syndromic hearing loss is characterized as SNHL that occurs as part of a larger syndrome, often characterized by additional sensory and developmental dysfunction involving the neurological, cardiovascular, renal, and ocular systems. As with non-syndromic causes, most syndromic hearing loss causes are hereditary and can be linked to genetic pathogenic variants that are passed in an autosomal dominant, autosomal recessive, x-linked, or mitochondrial inheritance pattern. Moreover, specific genes, like *SLC26A4*, have been identified in both syndromic and non-syndromic hearing loss (Honda and Griffith, 2022). While there are a numerous conditions associated with syndromic hearing loss, a few have been well characterized in the literature including Usher, Pendred, and Jervell and Lange-Nielsen. Additional syndromes like neurofibromatosis type two-related schwannomatosis are also associated with syndromic hearing loss but are not primarily characterized by intrinsic inner ear dysfunction (Ren et al., 2021; Mohamed et al., 2023).

Usher syndrome is characterized by bilateral SNHL and retinitis pigmentosa with and without vestibular symptoms (Bonnet et al., 2016; Toms et al., 2020; Delmaghani and El-Amraoui, 2022). In Usher syndrome there is extensive genetic heterogeneity, with three clinically important phenotypes (Type 1, 2, and 3), with further subclassifications of the types based on the causative pathogenic variant, i.e. Usher syndrome Type 1B and *MYO7A* (Bonnet et al., 2016). The causative genes are broadly associated with ciliary function and are highly expressed in the inner ear and eye, which may explain the clinical phenotypes. Type 1 Usher syndrome (USH1) presents as congenital SNHL, vestibular dysfunction, and impaired visual acuity in adolescence (Blanco-Kelly et al., 2015). A genotype-phenotype relationship has been identified for USH1 with the predominate cause being a pathogenic variant in *MYO7A* (Le Quesne Stabej et al., 2012; Bonnet et al., 2016). *MYO7A* encodes for a crucial myosin motor protein that establishes the tip-link tension between the HC stereocilia, allowing for mechano-electrical transduction (Bonnet et al., 2016; Li et al., 2020). *USH1C*, another causative gene for USH1, encodes for the protein harmonin. It has been the focus of recent preclinical studies for gene therapy using antisense oligonucleotides (Pan et al., 2017; Wang et al., 2020). Harmonin is involved in the tip and lateral links of HC stereocilia and acts as an anchoring scaffold protein. Without tip and lateral links, the HC stereocilia cannot function properly, inhibiting mechano-electrical transduction and causing SNHL. Type 2 Usher syndrome (USH2) is clinically similar to USH1, although notably lacks vestibular findings in most patients. Similar genotype-phenotype relationships were identified and suggest *WHRN* and *USH2A* as causative genes (Le Quesne Stabej et al., 2012; Blanco-Kelly et al., 2015; He et al., 2020). *WHRN* and *USH2A*, which encode for whirlin and usherin, respectively, are components of the ankle-link protein complex which is crucial for the normal development of HCs (Wang et al., 2023a). Additionally, USH2 is the most common subtype of Usher syndrome, responsible for almost half of all confirmed cases (Bonnet et al., 2016). Type 3 (USH3) is unique in that the onset of hearing loss is post-lingual, with ophthalmologic findings presenting later in life (Delmaghani and El-Amraoui, 2022). Vestibular findings may also be found in USH3 but are clinically heterogenous (Delmaghani and El-Amraoui, 2022). This type of Usher syndrome is mainly associated with *CLRN1*, encoding for a protein that modulates the transduction efficiency of the excitatory ribbon synapses between HCs and SGNs.

Pendred syndrome is characterized by bilateral, congenital SNHL with an enlarged thyroid gland (goiter) often found in adolescence (Wémeau and Kopp, 2017). Histologically, inner ear malformations include an enlarged vestibular aqueduct (Honda and Griffith, 2022; Saeed et al., 2023). Genetic analysis has demonstrated that pathogenic variations in *SLC26A4*, *FOXI1*, and *KCNJ10* may be causative (Wu et al., 2022). *SLC26A4* encodes for pendrin, a non-specific anion and base (importantly $HCO_3^-$) exchanger protein in the epithelial cells of the inner ear. Pendrin dysfunction may lead to electrolyte and osmotic disturbances, causing enlargement of the vestibular aqueduct and loss of endocochlear potential, thereby causing SNHL.

Patients with Jervell and Lange-Nielsen syndrome (JLNS) develop congenital bilateral SNHL and cardiac arrhythmias due to ion channelopathy resulting in prolonged QT syndrome (Schwartz et al., 2006). Patients with JLNS have a high mortality rate due to risk of ventricular arrythmias, specifically Torsades-de-Pointes (Goldenberg et al., 2006). Pathogenic variations in *KCNQ1* and *KCNE1*, potassium channel-encoding genes, have been identified as causative for JLNS (Vojdani et al., 2019; Walls et al., 2024). These channels are required for potassium movement across the stria vascularis, forming the endocochlear potential.

Currently, preclinical and clinical studies have focused on the non-auditory dysfunction associated with these syndromes, for example, the majority of USH-related studies have focused on ocular gene therapy (Nuzbrokh et al., 2021). Additional studies targeting the inner ear would benefit these patients with SNHL.

## 2.3 Noise-induced hearing loss

NIHL has emerged as a prevalent form of auditory impairment caused by prolonged or acute exposure to acoustic stimuli. Moreover, NIHL is the primary preventable cause of hearing loss (Le et al., 2017). NIHL may be caused by both the classical high intensity exposure (i.e., gunshot, blast exposure, etc.), primarily associated with hair cell degeneration, and more moderate long-term noise exposure (i.e., occupational associated), which might be associated with cochlear synaptopathy and damage to the ribbon synapses. Exposure to high intensity exposure noise, whether singular or continuous, poses a risk for temporary or permanent hearing damage. Temporary NIHL manifests as a reversible temporary threshold shift (TTS), in the absence of neuronal cell death, whereas permanent NIHL leads to permanent threshold shift (PTS) often accompanied by sensory and neuronal cell death within the auditory system (Kujawa and Liberman, 2009; Early et al., 2022). PTS is often due to damage to the HCs, classically for high intensity exposure, and subsequent SGN degeneration (McGill and Schuknecht, 1976; Kujawa and Liberman, 2009). Additionally, exposure to high-intensity noises is thought to cause the HCs to release excess glutamate (Puel et al., 1998), which can lead to excitotoxicity of SGNs, while further impairment to hearing is due to destruction of the ribbon synapses between IHCs and SGNs (Kujawa and Liberman, 2009; Lin et al., 2011; Wagner and Shin, 2019; Hu et al., 2020). Finally, exposure to high-intensity noises can cause damage to the myelin sheath that surrounds the SGNs, also contributing to hearing loss (Brown and Hamann, 2014), particularly the processing of complex sounds in competing background noise. Therefore, in addition to HCs, therapeutic approaches aimed at treating NIHL should focus also on peripheral ribbon synapses and SGNs.

## 2.4 Cisplatin chemotherapy-induced hearing loss

Hearing loss as a side effect of cancer treatment can severely impact the patient's quality of life. Cisplatin is a commonly used chemotherapeutic agent and causes significant ototoxicity in up to 80% of adults and 50% of pediatric patients (Moke et al., 2021). The exact mechanism of cisplatin ototoxicity is still under active investigation, however damage to the stria vascularis and disruption of cochlear energy metabolism, which can then lead to

loss of the sensory epithelium, has been implicated in cisplatin- and carboplatin-induced pathophysiology (Liu et al., 2021; Wang et al., 2023b). Additionally, cisplatin has been shown to increase the secretion of cytotoxic inflammatory molecules (So et al., 2007) and creation of reactive oxygen species (Yu et al., 2019), thereby causing DNA damage, all which lead to activation of apoptotic pathways in the cells of the stria vascularis, HCs, and SGNs (Breglio et al., 2017; He et al., 2022). Interestingly, studies have demonstrated that HC and SGN loss may occur at different time points (van Ruijven et al., 2004, 2005). The set of studies published by van Ruijven et al. demonstrated that cisplatin interferes with SGN function and causes aberrant loss of SGNs, resulting in the elevation of compound action potential and auditory brainstem response (ABR) thresholds, as well as detachment of the myelin sheath of the type-I SGNs (a sign of degeneration) within 1 week of treatment initiation (van Ruijven et al., 2004, 2005). Moreover, the early time point (<1 week) of SGN degeneration and malfunction following cisplatin treatment indicates the importance of the timing of therapeutic intervention (van Ruijven et al., 2004, 2005; Yu et al., 2019).

# 3 Gene therapy for hearing loss

Human gene therapy for hearing loss involves introduction of genetic material into target cells to address diseases associated with dysfunction of HCs, SGNs or SCs caused either by pathogenic genetic variations or external factors. Gene delivery may be accomplished using viral and non-viral vectors. Among these, viral vectors, particularly adeno-associated viruses (AAVs), have emerged as the most extensively studied and efficacious vectors. AAVs show significant promise because of their higher rates of transduction efficiency than non-viral delivery, lack of pathogenicity, persistence of gene expression, availability of various serotypes (which specifies cellular tropism), and low risk of insertion mutagenesis due to lower host DNA integration (Pupo et al., 2022).

There are three main types of viral vector-based gene therapy: gene editing, gene silencing, and gene replacement (Wang et al., 2019; Petit et al., 2023). Gene replacement involves adding a functional gene into cells with defective or missing copies, aiming to restore normal cellular function (Petit et al., 2023; Lv et al., 2024). Gene editing enables precise modification of genetic material, often utilizing the CRISPR-Cas9 or base editing systems (Noh et al., 2022; Petit et al., 2023). Meanwhile, gene silencing inhibits the translation of a gene into proteins, achievable through mechanisms such as antisense oligonucleotides (Wang et al., 2020; Petit et al., 2023). Of these approaches, gene replacement of a pathogenic variant is the most widely used for treating HHL.

## 3.1 Gene therapy targets for hereditary hearing loss

Gene replacement is the primary therapeutic approach studied in murine models of genetic hearing loss. The genes *VGLUT3* (Akil et al., 2012; Zhao et al., 2022a; Mathiesen et al., 2023), *GJB2* (Yu et al., 2014; Iizuka et al., 2015; Guo et al., 2021), *GJB6* (Miwa et al., 2013; Crispino et al., 2017; Zhang et al., 2022), *MSRB3* (Kim et al., 2016), *TMC1* (Askew et al., 2015; Gao et al., 2018; Nist-Lund et al., 2019; Wu et al., 2021a; Marcovich et al., 2022), *KCNQ1* (Chang et al., 2015), USH-associated genes (*USH1C* (Pan et al., 2017), *USH1G* (Emptoz et al., 2017), *WHRN* (Chien et al., 2016; Isgrig et al., 2017)), *OTOF* (Akil et al., 2019b; Al-Moyed et al., 2019; Rankovic et al., 2020; Tang et al., 2023; Zhang et al., 2023; Qi et al., 2024a,b; Wang et al., 2024), *STRC* (Shubina-Oleinik et al., 2021), *LHFPL5* (György et al., 2017), *PJVK* (Delmaghani et al., 2015; Lu et al., 2022), *KCNE1* (Wu et al., 2021b), and *SYNE4* (Taiber et al., 2021) have all been studied for their efficacy and safety as preclinical, viral vector-mediated, gene replacement therapeutic targets.

Viral-mediated gene suppression and editing are other approaches that have been studied as a treatment for deafness related to *TMC1* (György et al., 2019b; Yoshimura et al., 2019), *KCNQ4* (Noh et al., 2022), and *MYO6* (Xue et al., 2022). Noh et al. utilized CRISPR/Cas9 to edit *KCNQ4*, while Gyorgy et al. utilized CRISPR/Cas9 to disrupt and suppress the mutant allele associated with *TMC1*. Liposome-mediated delivery (Tao et al., 2023) and systemic delivery of antisense oligonucleotides (Lentz et al., 2013; Wang et al., 2020) have also been studied for both syndromic and non-syndromic HHL.

These studies demonstrated excellent transduction efficiency, low toxicity, and variable recovery of auditory function in animal models. Gene replacement therapies targeting *OTOF* and *SLC17A8*-related deafness have been highly successful in a number of preclinical models, with hearing restored to wild-type (WT) ABR thresholds (Akil et al., 2012; Qi et al., 2024b). A few studies, however, did not demonstrate recovery of the ABR Wave 1, suggesting poor survival of SGNs despite general ABR threshold improvement (Akil et al., 2019b; Zhao et al., 2022a). Moreover, some studies involving AAV-mediated *TMC1* and *OTOF* gene replacement demonstrated near complete hearing recovery to WT thresholds in neonatal mice but reported mixed success in adult mouse models (Nist-Lund et al., 2019; Zhang et al., 2023). It is important to note that these efficacy studies were primarily conducted on neonatal mice, which generally, showed better response than mature models. This raises concerns for potential applicability to adult-onset hearing losses. The murine inner ear does not fully develop until around the 2$^{nd}$ week of postnatal life, whereas the human cochlea develops from gestational week 4 to approximately gestational week 30 (Kamiya et al., 2001; Johnson Chacko et al., 2019). Therefore, studies on mature mice may better represent the translational capability for treating postnatal human patients. The neonatal inner ear appears far more amenable to efficient AAV-mediated gene transfer than the adult inner ear (Transduction ranged from 100% of IHCs and ~75%% of SGNs in neonatal mice to 100% of IHCs but <20% of SGNs in adult mice) (Duarte et al., 2018; Richardson et al., 2021). Those studies that utilized mature murine models for functional gene therapy studies are summarized in Table 1.

## 3.2 Gene therapy targets for acquired hearing loss

### 3.2.1. Gene therapies for NIHL

In acquired hearing loss, the focus is primarily on preventing the degeneration of sensory HCs and SGNs, or regenerating

TABLE 1 Preclinical gene therapy studies for hereditary hearing loss in mature (≥postnatal day 12) murine models.

| Gene (deafness) | Viral vector | Delivery route | Gene therapy application | Mouse model | Hearing results | References |
|---|---|---|---|---|---|---|
| *SLC17A8*/VGLUT3 (DFNA25) | AAV2/1 | RWM | Replacement | VGLUT3 -/- | Recovery to WT ABR thresholds | (Akil et al., 2012) |
| | AAV-PHP.B | CSF | Replacement | SLC17A8 -/- | Recovery to WT ABR thresholds except at high frequencies | (Mathiesen et al., 2023) |
| | AAV8 | PSCC | Replacement | VGLUT3 -/- | Recovery to WT ABR thresholds except Wave 1 | (Zhao et al., 2022b) |
| *GJB2* (DFNB1A1) | AAV/Anc80 | RWM + CF | Replacement | $Sox10iCre^{ERT2}$; $Gjb2^{flox/flox}$ | Increased protein but no hearing recovery on ABR | (Guo et al., 2021) |
| | AAV1 | CO | Replacement | $Cx26^{fl/fl}$P0-Cre | Increased protein but no hearing recovery on ABR | (Iizuka et al., 2015) |
| *TMC1* (DFNB7/11 and DFNA36) | AAV/Anc80L65 | RWM | Replacement | $Tmc1^{\Delta/\Delta}$;$Tmc2^{\Delta/\Delta}$ | No hearing recovery on ABR | (Nist-Lund et al., 2019) |
| | AAV-PHP.B | Utricle | Replacement | $Tmc1^{\Delta/\Delta}$ | No hearing recovery on OAE or ABR | (Wu et al., 2021a) |
| | AAV9 | RWM + CF | Suppression-RNAi | $Tmc1^{Bth/+}$ | Partial recovery in young mice ($p < 84$). No recovery in hearing when injected p > 84 days | (Yoshimura et al., 2019) |
| *USH1C* (Usher Type 1 C) | AAV/Anc80L65 | RWM | Replacement | Ush1c c.216G>A | No hearing recovery on OAE or ABR | (Pan et al., 2017) |
| *OTOF* (DFNB9) | AAV2 quad Y-F capsid | RWM | Replacement | OTOF -/- | Recovery to WT ABR thresholds except Wave 1 | (Akil et al., 2019b) |
| | AAV-PHP.B | PSCC | Replacement | OTOF -/- | Partial hearing recovery | (Tang et al., 2023) |
| | AAV-OTOF | PSCC | Replacement | $OTOF^{Q939*/Q939*}$ | Recovery to WT ABR thresholds | (Qi et al., 2024a) |
| | AAV1 | RWM | Replacement | OTOF -/- | Partial hearing recovery | (Zhang et al., 2023) |
| | AAV-PHP.B | RWM | Replacement | OTOF -/- | Partial to full recovery to WT threshold | (Wang et al., 2024) |
| | AAV/Anc80L65 | PSCC | Replacement | $OTOF^{p.Q939*/Q939*}$ | Partial to full recovery to WT threshold | (Qi et al., 2024b) |

DFN, deafness; AAV, adeno-associated virus; RWM, round window membrane injection; PSCC, posterior semicircular canal injection/canalostomy; RWM + CF, round window membrane injection with canal fenestration; CSF, cerebrospinal fluid delivery; CO, cochleostomy; RNAi, RNA interference; Δ/Δ, homozygous mutant allele targeting exon 8 and 9 of *TMC1*; bth, genetic variant of *TMC1* that causes progressive hearing loss; WT, wild type; ABR, auditory brainstem response; OAE, otoacoustic emissions.





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damaged inner ear cells. There are multiple potential targets, and neurotrophins (NTs), proteins that support the growth, survival, and differentiation of hair cells and neurons, are one such avenue to restore or prevent hearing loss.

NTs activate signaling pathways critical for maintaining neuronal function and plasticity (Zigmond et al., 2012) and facilitate proper development of the auditory system (Harasztosi et al., 2020). Among these, brain-derived neurotrophic factor (BDNF), and NT3 are the most well characterized due to their role in cochlea development, with a substantive number of studies also demonstrating the therapeutic potential of glial cell-derived neurotrophic factor (GDNF). A distinction must be made between the developing and mature mammalian cochlea as there are notable differences in both NT availability and receptor expression between the two ages (Johnson Chacko et al., 2017). Specifically, the high affinity receptors for BDNF and NT3, TrkB and TrkC, are strongly expressed in the cochlea from birth to adulthood, but the BDNF ligand itself notably decreases with age (Johnson Chacko et al., 2017). In contrast, GDNF is not present at birth, but appears in the first postnatal week and into adulthood along with its receptor, GFR1a (Stöver et al., 2000). In addition to temporal differences, whether there may be spatial differences in receptor availability along the tonotopic axis of the cochlea and on certain cell types, is yet to be studied. These factors, combined with the interchangeability/cross-reactivity of some NT ligands and receptors, necessitate further studies for the selection of ideal NTs.

Despite these complexities, local exogenous delivery of AAV vectors expressing NTs may provide protective and/or regenerative effects on both SGNs and HCs in the cochlea. Local delivery of the NT proteins themselves has been extensively studied through the use of osmotic minipumps for delivery into the scala tympani (Khalin et al., 2015). However, this delivery method is not likely to be an effective long-term strategy due to transient protection of SGNs due to the relatively short half-lives of the proteins. The protective effects of NTs on SGNs appears to only last for the duration of treatment. These findings have been widely confirmed by studies in other neuronal systems (Montero and Hefti, 1988; Gillespie et al., 2003). Additionally, indwelling cannulas pose significant risk for infection and is a burdensome to the patients. Because it is a one-time treatment, viral vector mediated NT delivery is therefore being intensively investigated (Ramekers et al., 2012). Moreover, Mukherjee et al. demonstrated that local delivery of AAV2 (quad Y-F capsid)-mediated BDNF can recover noise-induced BDNF gene downregulation, ABR wave I amplitude reduction, and synapse loss in a guinea pig model (Mukherjee et al., 2022). Furthermore, AAV-BDNF may be protective in murine models of *GJB2*-related deafness (DFNB1A) (Takada et al., 2014). Additionally, Hashimoto et al. has showed that AAV-mediated overexpression of NT-3, another NT, in the cochlea following canalostomy injection can provide protection against noise-induced synaptopathy, possibly through the enhancement of synaptic function and the preservation of ribbon synapses between IHCs and SGNs (Hashimoto et al., 2019). However, only AAV-NT3 delivered prior to noise exposure was effective at improving synapse survival. This was corroborated by Bowers et al. who found that NT-3 transduction utilizing a herpes simplex type 1 viral vector attenuated the loss of SGNs following cisplatin therapy (Bowers et al., 2002). Furthermore, Leake et al. provided evidence that AAV-mediated NT gene therapy, specifically using either AAV2-hBDNF can effectively enhance the survival of cochlear SGNs in neonatally deafened cats (Leake et al., 2019). These studies collectively indicate the potential of AAV-mediated NT delivery transduction in the inner ear. However, NT3 delivered onto the RWM without use of a viral vector has shown success in mice, demonstrated improved ABR Wave 1 thresholds and moderate regeneration of the cochlear HC-SGN interface (Suzuki et al., 2016).

Additionally, Fukui et al. demonstrated SGN peripheral fiber growth and epithelial expansion after adenovirus mediated BDNF gene therapy in mature (P28) *POU4F3*-/- mice, suggesting potential virus-mediated regenerative capacity (Fukui et al., 2012). These findings were corroborated in a deafened murine model that demonstrated SGN fiber regrowth into the basilar membrane following viral-mediated BDNF delivery (Shibata et al., 2010).

Studies have also demonstrated the therapeutic potential of AAV-mediated GDNF expression for mitigating and/or reversing hearing loss in various animal models with NIHL and ototoxicity-mediated hearing loss/CIHL (Shoji et al., 2000; Chen et al., 2003; Shibata et al., 2007; Liu et al., 2008). Not surprisingly, utilization of very high titers of AAV-GDNF of $1.8 \times 10^{11}$ to $3.6 \times 10^{11}$ vg (1–2 μL injected) has been reported to cause toxicity in neonatal animals, denoting the importance of sensible dosing strategies, particularly when considering scaling up to larger mammals (Akil et al., 2019a). The study by Leake et al. showed an interesting difference in the efficacy of AAV2-BDNF and AAV5-GDNF. While both vectors elicited a neurotrophic effect on SGN survival in neonatally deafened cats, AAV5-GDNF caused undesirable ectopic fiber sprouting whereas AAV2-BDNF was not associated with ectopic sprouting. Given the lack of an AAV5-BDNF group, it is impossible to draw a clear conclusion about the toxicity of GDNF. Both vectors utilized strong, constituently active promoters (the AAV5 vector utilized the hybrid cytomegalovirus/chicken beta-actin (CBA) promoter and AAV2 utilized the CAG promoter), however the titer differences are significant. AAV2-BDNF was injected at a titer of $3 \times 10^{12}$ vg/mL (10 μL injected), while AAV5-GDNF was injected at a titer of $1.8 \times 10^{14}$ vg/mL (10 μL injected). The higher dose of the AAV5-GDNF may explain the adverse events reported in this study (Leake et al., 2019). Moreover, an important factor that is often overlooked is that AAV5 has the capacity to transduce antigen presenting cells in the brain which can lead to a full immune response when a non-self-protein is expressed, whereas AAV2 only transduces neurons, which are not antigen presenting (Samaranch et al., 2017). The Akil et al. (2019a) and Leake at al. (2019) studies involved expression of a human GDNF protein in cats and mice, so it is therefore possible that serotype selection and expression of a non-self-protein could have contributed to these findings. Of note, an immune response following transduction of antigen presenting cells has also been reported with AAV9 (Ciesielska et al., 2013; Samaranch et al., 2014). The human cochlea contains various types of peripheral glial cells that envelop the cochlear nerve, the cell bodies in the spiral ganglia, and the peripheral processes in the osseous spiral lamina. Careful selection of a viral serotype with selective tropism for HCs and SGNs that does not require a high titer for efficient

transduction with minimal tropism for antigen presenting cells will be important. Taken together, these results indicate that viral vector mediated NT delivery holds promise for the treatment of acquired hearing loss, but caution is warranted regarding serotype and dose selection.

### 3.3.2 Gene therapy strategies for CIHL

NTs are not the only potential targets, with viral-mediated delivery of apoptotic inhibitors into the cochlea of rats treated with cisplatin leading to an attenuation of HC degeneration and overall improved ABR thresholds, if administered prophylactically (Cooper et al., 2006). While this study did not perform immunohistochemistry for SGNs specifically, the ABR threshold improvements suggests at least moderate SGN survival (Cooper et al., 2006). Subsequently, the injection of this viral vector through the round window membrane (RWM) in a follow-up study by Chan et al. showed a decrease in efficacy in high-frequency, basal OHCs (Chan et al., 2007). However, administering the treatment vector 2 months prophylactically may pose challenges in clinical scenarios. Bu et al. demonstrated the success of AAV treatment at the same time as cisplatin therapy using a viral vector that expresses c-Myb, a transcription factor involved in cell survival (Bu et al., 2022). The authors found that co-treatment of cisplatin with AAV gene therapy decreased OHC loss in the basal turn of the cochlea, which is known to be commonly affected by cisplatin therapy (Bu et al., 2022). These findings underscore the potential of AAV-mediated gene therapy for preserving auditory function in patients at high risk for noise exposure or undergoing chemotherapy treatments with high ototoxicity.

## 4 Advantages and challenges of delivery of therapeutics into the inner ear—preclinical studies

The delivery of gene therapies into the inner ear requires careful consideration of various factors, including the delivery route, transduction efficiency, potential for immune responses and cellular tropism. Both infection, the ability of the virus to enter and survive in the cell, and transduction, the ability of the viral vector to introduce genetic material into the cell, are important components of transduction efficiency for gene therapy. The inner ear is comprised of two main fluids, perilymph and endolymph (Glueckert et al., 2018). However, these fluid compartments are not as isolated and immunologically privileged as previously thought (Keithley, 2022). First, the inner ear is highly vascularized with arterial flow from the labyrinthine artery but is sequestered by the blood-labyrinth barrier (Mei et al., 2020). Perilymph is connected to the cerebrospinal fluid (CSF)-containing space via the cochlear aqueduct, while endolymph circulates to/from the endolymphatic sac, where it is theorized to interact with the peripheral lymphatic system (Glueckert et al., 2018; Salt and Hirose, 2018). Additionally, the neural component of the inner ear provides a direct route to and from the cochlear nucleus, olivary complex and auditory cortex (Salt and Hirose, 2018).

Viral vectors have been administered via either intracochlear (RWM, cochleostomy) or intralabyrinthine (posterior semi-circular canal (PSCC), endolymphatic sac, utricle, and oval window/stapedectomy) pathways (Figure 1). Despite the success of these delivery routes in neonates, accessing the labyrinth directly is complex, and can lead to the damage and further degeneration of HCs and SGNs. Therapeutic delivery outside of the bony labyrinth, i.e., trans-tympanic and systemic injections, have had minimal success in adult models of hearing loss so far (Shibata et al., 2017). While AAV transduction of HCs has been extensively reported in neonates, most studies report low SGN transduction efficiency. The available data on SGN transduction are summarized in Table 2. The delivery routes, methods used, and other notable factors of delivering therapeutic agents to the inner ear are discussed below through the lens of AAV studies in the cochlea of healthy mice.

## 4.1 Round window injection

### 4.1.1 Delivery route

The most studied delivery route to the cochlea is through the RWM, which provides access to the perilymph fluid and cells of the cochlea. Due to the relatively low calcification of the temporal bone in neonatal mice vs. adults, the otic bulla may be pierced utilizing various techniques. In neonates, the bulla can be accessed with only a needle (Richardson et al., 2021), although drilling with a scalpel or a diamond drill is required for adult mice (Yoshimura et al., 2018). After gaining access to the otic bulla, the RWM can be easily penetrated using a variety of injection techniques (discussed further below). This method of accessing the RWM is similar to that used in other species like guinea pigs and even large mammals like NHPs (Wang et al., 2012; György et al., 2019a; Ivanchenko et al., 2020; Andres-Mateos et al., 2022). Micromanipulators with a micropump syringe attached to the micropipette allow for the highest level of control during the injection, although pressurizing the system with a Hamilton syringe has been done in other preclinical model studies (Richardson et al., 2021). For NHPs, a cortical mastoidectomy must be performed to expose the facial recess to allow for RWM access (György et al., 2019a,b; Ivanchenko et al., 2020; Andres-Mateos et al., 2022). György et al. (2019a) and Ivanchenko et al. (2020) have successfully used a 29-gauge needle to make the incision through the RWM. To inject the solution, a Hamilton syringe may be attached to the needle with a silicone tube. RWM delivery is associated with operative risks, most notably damage to the facial nerve, that must be considered when translating these findings into human studies. Approaches into the middle ear space where the RWM can be accessed with an intratympanic injection do not require a mastoidectomy.

While RWM delivery provides direct access to the perilymph in the scala tympani, care must be taken to avoid damaging the surrounding structures. Because the inner ear is not entirely a closed-fluid system, transient increases in pressure following injection of the viral vectors can lead to further HC and SGN degeneration. The closed bony cochlea is sensitive to pressure fluctuations and fluid shifts, which may be significant when performing a RWM injection. To combat this, multiple investigators have opted to create openings in the PSCC, to expose

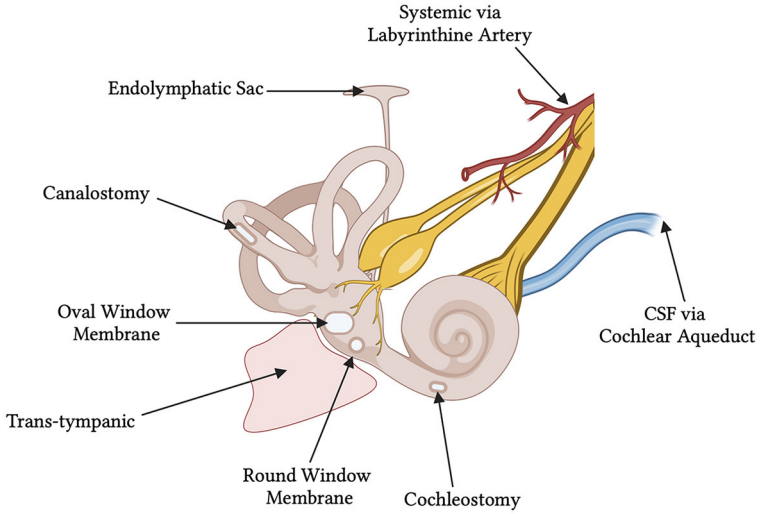


FIGURE 1
Schematic of the various delivery routes for gene therapy to the human inner ear. At the time of this review, the round window membrane has been utilized in two published clinical trials. The ossicles have been removed from the diagram showing an empty middle ear space and free oval window membrane. CSF, cerebrospinal fluid.

TABLE 2 SGN transduction based on delivery route and viral vector in murine models with healthy cochlea.

| Delivery route | Viral vector | Age of model | Transduction rates | References |
|---|---|---|---|---|
| RWM | Anc80L65 | Neonatal | ~75% across all turns of the cochlea | (Duarte et al., 2018) |
| | | Neonatal | ~50% with apex to base gradient | (Richardson et al., 2021) |
| | AAV-S | Neonatal | >75% transduction across all turns of the cochlea | (Ivanchenko et al., 2021) |
| | AAV1-5, 7, and 8 | Mature | AAV1 and 5 demonstrated most efficient transduction, % NR. | (Liu et al., 2005) |
| | AAV-PHP.B | Neonatal | Efficient transduction, % NR. | (György et al., 2019b) |
| Canalostomy | AAV-PHP.eB, AAV-ie, Anc80L65, AAV2, and PHP.s | Mature | Anc80L65 demonstrated most efficient transduction, % NR. | (Zhao et al., 2022b) |
| | AAV2/Anc80L65 | Mature | <10% across all turns of the cochlea | (Suzuki et al., 2017) |
| Cochleostomy | Exo-AAV1 | Neonatal | Robust transduction, % NR | (György et al., 2017) |
| | AAV1, AAV2, AAV5, AAV6, and AAV8 | Mature | AAV8 demonstrated transduction in 6 out of 10 mice, % NR. | (Kilpatrick et al., 2011) |
| CSF Delivery | AAV2/8, AAV9, and AAV2/Anc80L65 | Mature | Anc80L65 demonstrated efficient transduction, % NR. | (Blanc et al., 2020) |

AAV, adeno-associated virus; RWM, round window membrane injection; PSCC, posterior semicircular canal injection/canalostomy; RWM + CF, round window membrane injection with canal fenestration; CSF, cerebrospinal fluid delivery; CO, cochleostomy; NR, not reported.

perilymph and allow for the dispersion of excess pressure (Suzuki et al., 2017; Yoshimura et al., 2018; Richardson et al., 2021). Regardless of technique used for fenestration of the canal, all investigators observed the efflux of perilymph fluid before injecting the viral vector through the RWM. For NHPs, fenestration of the oval window is favored over the PSCC, as it is thought to allow for fluid displacement and create a general flow of the administered vector toward the helicotrema (Andres-Mateos et al., 2022). A transcanal approach to RWM with stapes fenestration is has been demonstrated to be safe in the *OTOF* clinical trials (ChiCTR- 2200063181). Accessing the perilymph fluid through RWM injections, with or without further bony fenestrations, has the potential to deliver the viral vectors into the central nervous system via the cochlear aqueduct which connects the perilymph and is connected to the CSF. However, this may likely only an issue in rodents where the aqueduct remains patent, compared to in humans where the patency is theorized to decrease with age. Some investigators have minimized this risk by using HC-specific promoters (Ranum et al., 2023; Wang et al., 2024).

### 4.1.2 Cochlear hair cell transduction

AAV delivery with the RWM injection has been well explored, providing high transduction rates for HCs although SGN rates

vary significantly based on vector serotype. Here, we briefly discuss the use of commonly studied AAVs, including Anc80L65, AAV9-PHP.B, and AAV2, in the transduction of HCs and SGNs.

Anc80L65, an ancestral capsid discovered through computational approaches, is one of the most promising serotypes in inner ear gene therapy and has been predominately studied using RWM injections. This vector was first described by Landegger et al. (2017) demonstrating robust transduction of the IHCs and OHCs when injected at P1in mice. In this study, Anc80L65 injected at a dose of $1.7 \times 10^9$ vg in 1 μL outperformed AAV1, 2, 6, and 8, at lower doses than AAV1 and AAV2 ($3.5 \times 10^{10}$ vg in 1 μL and $6.0 \times 10^9$ vg in 1 μL). Interestingly, the authors noted Anc80L65 transduction in the contralateral uninjected cochlea in a subset of animals and cerebellar transduction, possibly reaching these areas via the cochlear aqueduct (Landegger et al., 2017). In an additional study utilizing neonatal mice, the Anc80L65 vector successfully transduces over 90% of IHCs across all cochlear turns with a relatively low titer ($1.40 \times 10^9$ vg in 1 μL) (Yoshimura et al., 2018). In non-neonatal mice (P49), the transduction rate of IHCs was near 100%. No information is available regarding Anc80L65 mediated transduction of the cochlea when administered to mice >3 months old, when they are considered mature adults equivalent to humans aged 20 years old. Similarly, in guinea pigs, OHC transduction by Anc80L65 decreased from 90% to near <70% from base to apex at a titer of $8.5 \times 10^9$ vg in 5 μL) (Wang et al., 2022). Further studies are needed to determine whether increased titers can facilitate transduction of OHCs throughout the cochlea in older mice and guinea pigs. The apex-to-base gradient of HC transduction with Anc80L65 has also been observed in adult NHPs aged 3–4 years. Andres-Mateo et al. noted a near 100% transduction rate of IHCs at the apex with a sharp decline to around 20% transduction rate at the base. In addition, transducing NHP OHCs was much less successful (<5 positive OHCs observed in the 3,000 Hz section) and also exhibited the apex-to-base gradient of transduction (Andres-Mateos et al., 2022). The cause of this discrepancy is unknown; however, it is hypothesized that the decrease in basal OHC transduction is due to difficulty of the vector in crossing Reissner's membrane (from the scala vestibuli), requiring the vector to travel to the scala tympani where the vector can cross the basilar membrane. Another explanation is that viral tropism changes as a result of cell surface receptor differences between the base and apex, affecting the AAV's entry into the cell. Additionally, due to the tonotopic organization of the cochlea, the intrinsic cellular differences (metabolic activity, gene expression profiles, morphology, etc) between the apex and base as well as cellular specificity (tropism) of the vector itself could lead to the transduction gradient observed.

The AAV9-PHP.B vector has a modified capsule to increase transduction and reduce immunogenicity compared to the original AAV9 (Deverman et al., 2016). It has been demonstrated to effectively infect neonatal mouse HCs, with studies reporting between 60%−80% effectiveness for IHCs and between 40–60% for OHCs (György et al., 2019a; Ivanchenko et al., 2020). Infection of AAV9-PHP.B following RWM injection in a mature cochlea has been studied in *OTOF* -/- mice, and this approach demonstrated an infection rate of 80 to near 100% of IHCs (Wang et al., 2024). Two studies in juvenile NHPs have demonstrated transduction of HCs between 90–100% at relatively high doses of above $3–7 \times 10^{11}$ vg (10–20μL injected), but there is a steep decline in transduction efficiency of ∼50% at lower titers at $1 \times 10^{11}$ vg (10μL injected) (György et al., 2019a; Ivanchenko et al., 2020).

AAV serotype 2 (AAV2) is the most extensively characterized vectors clinically for central nervous system disorders due to its high efficiency transduction of neurons (Christine et al., 2009; Pearson et al., 2021). In addition, AAV2 is one of the most common serotypes used in pseudotyping to create recombinant AAVs (rAAV), including the Anc80L65 discussed previously. Yoshimura et al. found that in neonatal mice, the transduction efficiency of HCs with AAV2 is titer dependent. The authors observed near 95% IHC transduction efficiency across all turns of the cochlea with a high titer of $3.9 \times 10^{10}$ vg (1μL injected), however this was reduced to <20% at titer of $1.4 \times 10^9$ vg (1μL injected) (Yoshimura et al., 2018). Using similar rAAVs at a titer of $1.0 \times 10^{12}$ vg/mL (5–10μL injected onto the gelfoam), Wang et al. reported that the rAAV2 introduced through digestion of the RWM transduces almost 100% of IHCs in a guinea pig at the apex but was not successful at transducing IHCs at the base. In addition, <20% of the OHCs of the guinea pig were transduced at the apex and close to 0% at the base (Wang et al., 2012). In the direct comparison of AAV9 and AAV2/Anc80L65 done by Yoshimura and colleagues, the Anc80L65 vector was clearly the more effective at transducing HCs in the neonatal mice at the same titer, although this study notedly lack a reporting of SGN transduction (Yoshimura et al., 2018). Additionally, Landegger et al. demonstrated that Anc80L65 was superior to AAV2 even when injected at a significantly lower titer (Landegger et al., 2017).

A variety of naturally occurring AAVs and novel AAV capsids have been used in inner ear gene therapy, including: AAV5, AAV8, and AAV-inner ear (AAV-i.e.,). The novel capsid AAV-i.e., described by Tan et al. (2019) successfully transduces almost all IHCs and a majority of OHCs across the neonatal mouse cochlea at a titer of $1 \times 10^{10}$ vg (1.5 μL injected), but not at $3.6 \times 10^9$ vg (1.5 μL injected). This novel rAAV utilizes varying peptide sequences, including a peptide from the AAV.PHP.eB vector. Notably, this study observed high rates of transduction of cochlear support cells and vestibular cells, however the authors found that Anc80L65 was more efficient at transducing both HCs and SGNs in the neonatal model (Tan et al., 2019). Despite the success of the AAV-i.e., in neonatal mice, there were no complementary studies evaluating transduction efficiency completed in adult mammals. In a study conducted by Liu et al., AAV1-5, 7, and 8, were analyzed for their success rate in transducing adult mice HCs and SGNs (Liu et al., 2005). Out of the seven vectors used, AAV3 was the best at transducing IHCs. However, SGN rates have not been addressed in most publications, despite them being one of the vitally impacted cell types.

### 4.1.3 Spiral ganglion neuron transduction

SGN transduction rates after RW delivery vary considerably across studies and are often not reported in other studies. Duarte et al. reported a high level of SGN transduction (74%) with Anc80L65 across the cochlea in neonatal mice (Duarte et al., 2018). Interestingly, the dose used by Duarte et al. (2018) ($2.2 \times 10^8$ vg in 1μL) was significantly lower than that of Richardson et al. (2021)

($9.23 \times 10^8$ vg in 1μL) who reported worse SGN transduction rates of approximately 50% with an apex-to-base decreasing gradient. The utilization of the RWM injection compared to a canalostomy injection might explain the difference in transduction rates seen in the study by Suzuki et al. (2017). It is likely that the RWM technique offers greater transduction of SGNs as compared to canalostomy. However, the studies by Richardson et al. and Duarte et al. may suggest a negative correlation with titer and SGN transduction with RWM injections.

SGN transduction is <20% in adult mice with Anc80L65 (Richardson et al., 2021). In NHPs and guinea pigs, SGN transduction was even lower, with no transduction being detected at vector doses of $2.5 \times 10^{11}$ vg (30 μL injected) and $27.69 \times 10^8$ vg (3 μL injected), respectively (Richardson et al., 2021; Andres-Mateos et al., 2022). Moderate titer levels of $2.2 \times 10^{11}$-$8.33 \times 10^{12}$ vg/mL were utilized in these studies. It is unclear whether a higher titer could lead to higher SGN transduction in adult mammals, although in our experience higher titer Anc80L65 preparations have not been available via commercial suppliers.

Other vectors which have performed well in HC transduction, include AAV-PHP.B, which exhibits low SGN transduction rates even in neonatal mice. Moreover, the rates vary greatly in juvenile NHPs even with similar titers of $3–3.5 \times 10^{11}$ vg (Ivanchenko et al. only injected 1.2μL v. Gyorgy et al. who injected 10μL) (György et al., 2019a; Ivanchenko et al., 2020). A study by Liu et al. comparing AAV1-5, AAV7, and AAV8 via RWM delivery, demonstrated that the AAV5 vector more efficiently transduced SGNs than the other serotypes (Liu et al., 2005). This finding is consistent with robust neuronal transduction observed with AAV5 with direct brain administration (Samaranch et al., 2017). Moreover, rAAV2 infused via RWM digestion in a guinea pig demonstrated >90% transduction efficiency for SGNs at the 1st turn of the cochlea and retained >80% throughout the whole cochlea (Wang et al., 2012). However, the age of the animals are unknown. Thus far it appears that Anc80L65 most potently transduces SGNs via RWM injection, although questions remain regarding the applicability to adult mammals including the effect of increasing titer.

## 4.2 Canalostomy

### 4.2.1 Delivery route

Canalostomy can be used to create an opening in one of the semicircular canals, most often the PSCC due to the ease of access in rodents (Suzuki et al., 2017; Zhao et al., 2022b). The rationale behind this approach is that by accessing the semicircular canals, and not the cochlea itself, there may be less iatrogenic hearing loss caused by the injection procedure. A postauricular incision and blunt dissection allow for exposure of the bone overlying the PSCC in neonatal mice. Fenestration of the PSCC and direct injection can then be accomplished. To puncture the bone overlying the PSCC, 25–29-gauge hypodermic needles and a Bonn micro probe have been described (Suzuki et al., 2017; Tao et al., 2018; Isgrig et al., 2019; Zhu et al., 2021). For vector delivery, both polyimide and polyethylene tubes connected to glass micropipettes and Nanoliter Microinjection Systems have been used. Suzuki et al. connected the polyimide and polyethylene tubes in series for injection (Suzuki et al., 2017). To minimize perilymph leakage, many preclinical studies have utilized cyanoacrylate glue to seal the injection site. However, due to the small size of the PSCC and limited viewing window, there is a possibility for the injection needle to pierce the membranous labyrinth in addition to the bony labyrinth. This would then expose the vector to the endolymph and perilymph, instead of just the perilymph. Although canalostomy has been successfully used in a number of preclinical studies, one study reported that the procedure significantly increased the ABR threshold, which was also affected by perilymph leakage and speed of injection (Zhu et al., 2021). The PSCC is not as easily accessible in NHPs and humans due to its anatomic location and requires a mastoidectomy. The lateral/horizontal semicircular canal (LSCC) would be more easily accessible following a mastoidectomy in NHPs and humans, however a canalostomy of the LSCC has not been well studied in preclinical murine models due to anatomic constraints.

### 4.2.2 Cochlear hair cell transduction: adeno-associated viral vectors and titers

Similar to other delivery strategies, canalostomy delivery of AAV2/Anc80L65 transduces 100% of IHCs in mature mice (aged 6 to 10 weeks) (Suzuki et al., 2017; Tao et al., 2018). Anc80L65-injected cochleae also demonstrated a 70% OHC infection rate in these mice (Suzuki et al., 2017). Moreover, Isgrig et al. found that AAV2.7m8, a novel synthetic vector, transduced over 80% of IHCs and 70% of OHCs in neonatal mice, without causing an increase in ABR thresholds compared to non-injected control mice (Isgrig et al., 2019). Both Anc80L65 and AAV2.7m8 outperformed the other studied AAV serotypes including AAV1, AAV2, AAV8BP2, AAV8, AAV9, AAV.PHP, and AAV.ie (Suzuki et al., 2017; Tao et al., 2018; Isgrig et al., 2019; Zhu et al., 2021; Zhao et al., 2022b). However, the efficiency of AAV2.7m8 following a canalostomy vector infusion compared to the other vectors could be confounded due to the differing age of the models studied.

### 4.2.3 Spiral ganglion neuron transduction

Suzuki et al. (2017) demonstrated <10% SGN transduction with using AAV2/Anc80L65. Additionally, Zhao et al. (2022b) demonstrated that AAV-PHP.eB, AAV-i.e., AAV/Anc80L65, and AAV-PHP.S, but not AAV2, were able to infect SGNs at a moderate rate, despite no formal measurements. Other studies examined SCs but did not address SGNs.

## 4.3 Oval window

The oval window is another entry point to deliver gene therapy vectors into the inner ear. However, it is mainly accessible in humans and NHPs. In mice, the oval window is covered by the stapedial artery, limiting the oval window's use in preclinical models of gene therapy for hearing loss. Although, Wang et al. (2022) was successful in transducing the inner ear of guinea pigs (>75% of IHCs) following oval window injection. Currently, the oval window has been limited to sites of fenestration, not injection,

in NHP, preclinical studies (Ivanchenko et al., 2021; Andres-Mateos et al., 2022). The clinical trial CGF166, discussed below, is the only clinical trial that utilizes this route.

## 4.4 Cochleostomy

### 4.4.1 Delivery route

The cochleostomy delivery route provides direct access to the endolymph fluid in the scala media. Injection of viral vectors directly into the endolymph may assist with the transduction of HCs and SCs that are bathed in it. To perform cochleostomy in adult mice, the otic bulla must be surgically exposed before drilling into the bony portion of the lateral wall (Chien et al., 2015; Shu et al., 2016). Two approaches have been described, one being a similar surgical approach to the RWM injection site with a postauricular incision (Shu et al., 2016), and the second being a more caudal incision extending from the mandible to the clavicular area (Chien et al., 2015). As described earlier, the otic bulla may be perforated using a surgical drill at the space between the basal turn of the cochlea and the RWM. Once the periosteum at the base of the cochlea is removed, the scala media may be accessed without damaging the membranous portion of the lateral wall with the drill. In neonatal mice, the otic bulla can be pierced directly without need for drilling (Shu et al., 2016). Despite the ease of access to the endolymphatic fluid in the scala media of both models, the site of the injection invariably can lead to damage to the surrounding structures, including the stria vascularis. Destruction of the delicate cochlear structures during the injection and surgical approach, paired with leakage of the endolymph following breach of the scala media, can lead to the potential loss of endolymph, reduction of the endocochlear potential, and cellular injury (Kilpatrick et al., 2011; Chien et al., 2015; Shu et al., 2016). It is important to note that the scala media is a smaller fluid compartment compared to the perilymphatic space, limiting the volume of vector that can be administered.

### 4.4.2 Cochlear hair cell transduction

AAV administration via cochleostomy has resulted in promising infection rates of both HCs and SCs, despite reports of moderate postoperative hearing loss due to iatrogenic trauma (Chien et al., 2015). In a direct comparison of RWM to cochleostomy delivery with AAV8 in mice aged 1–2 months, Chien et al. (2015) demonstrated modest infection rates of HCs and SCs between the two injection techniques, with IHCs vastly predominating (∼30% of IHCs compared to ∼12% of OHCs and SCs in cochleostomy). The infection rates were modest ∼ 30% of IHC transduction at the base with a sharp reduction toward the apical turns of the cochlea at early time points following vector infusion, by 4 weeks the majority of HCs (only 32 IHCs per 400 mm-section examined were remaining) in the basal turns of the cochlea had died in the cochleostomy cohort. This loss of IHCs and OHCs was reflected hearing function of the mice, with the cochleostomy cohort demonstrating over a 20 dB increase in high-frequency ABR thresholds compared to the RWM cohort. These findings are corroborated in a study by Shu et al. (2016) that studied the infection rates of numerous AAVs via cochleostomy delivery in both neonatal and adult mice. In this study, the adult mice demonstrated extensive loss of OHCs at the basal turns of the cochlea, regardless of vector serotype. However, this did not occur in neonatal mice, who demonstrated minimal changes in ABR thresholds, suggesting the mature cochlea is more susceptible to iatrogenic injury during cochleostomy delivery. While the findings of Kilpatrick et al. may initially appear contradictory, as they indicate no significant changes in post-injection ABR of mature mice at low frequencies, a notable increase in ABR threshold (>20 dB) was observed in the high frequencies (Kilpatrick et al., 2011). This increase suggests potential damage to the basal turn HCs, aligning with the conclusions drawn by Shu et al. and Chien et al.

Both AAV8 and Anc80L65 serotypes have transduced the inner ear with high efficiency via cochleostomy delivery (Kilpatrick et al., 2011; Chien et al., 2015; Shu et al., 2016; Gu et al., 2019). Anc80L65 infected near 100% of IHCs and 90% of OHCs across all turns of the cochlea in neonate mice, however, infection of SC was <30% at the same titer (Gu et al., 2019). AAV8 and Anc80L65 vectors have been delivered by cochleostomy in a number of notable preclinical studies in murine models of NSHL investigating deafness associated with *GJB2* (Iizuka et al., 2015), *MYO6* (Xue et al., 2022), *KCNQ1* (Chang et al., 2015), and *LHFPL5* (György et al., 2017). These studies demonstrated significant hearing recovery in neonatal mice, with the *KCNQ1* -/- mice demonstrating complete recovery comparable to WT mice ABR thresholds.

### 4.4.3 Spiral ganglion neuron transduction

Kilpatrick et al. studied the infection rates of AAV1, AAV2, AAV5, AAV6, and AAV8 on SGNs in both healthy, WT mice and ototoxic drug-exposed, deafened mice (Kilpatrick et al., 2011). AAV8 infected SGNS in 6 out of 10 (60%) healthy WT mice aged 2 to 12 months, with an approximately 35% infection rate reported across all AAV serotypes studied. Furthermore, the infection rate of SGNs using all AAVs increased in the deafened cohort, with an average of 52% of mice demonstrating SGN infection. However, this study did not quantify SGN transduction itself, but counted the number of mice that demonstrated green fluorescent protein (GFP) expression in the SGNs following transduction with the AAV-GFP vectors of varying serotypes. György et al. (2017) studied exosome mediated AAV delivery via a cochleostomy procedure and demonstrated significant transduction of SGNs as well. Similarly, these authors did not quantify the SGN transduction, although representative images suggest robust (>75%) transduction efficiency.

While the cochleostomy procedure in mice has only demonstrated moderate SGN infection rates, it has been additionally studied in adult guinea pig models following viral vector delivery to both the scala tympani (perilymph) and scala media (endolymph). Studies administering AAV2 (Budenz et al., 2015; Pfingst et al., 2017) and rAAV8 (Chen et al., 2018) expressing NT-3 demonstrated variable SGN transduction efficiency from near 0% to >75% in at least one turn of the cochlea. Moreover, Chen et al. demonstrated significant ribbon synapse survival rates following noise-induced toxicity with rAAV8-NT-3 (Chen et al., 2018).

## 4.5 Additional approaches to the endolymph

### 4.5.1 Delivery route

Administration of the vector through the endolymphatic sac and the utricle are two additional routes that provide access to the endolymph. However, these studies have not been as extensively studied as canalostomy delivery. The utricle, an otolith organ, is theorized to allow access to the endolymph while avoiding the iatrogenic cochlear damage associated with canalostomy. This route has only been studied in young (postnatal age $\leq$ 16 days) mice where the utricle could be pierced directly with the injection needle (Lee et al., 2020) so questions remain about the translatability to large mammals.

The endolymphatic sac can be accessed following drilling to expose both the dura and the sigmoid sinus. The vector can subsequently be administered directly into either the endolymphatic duct or sac (Yamasoba et al., 1999).

### 4.5.2 Inner ear transduction

Lee et al. (2020) demonstrated near 100% infection of IHCs and OHCs in all turns of the cochlea following utricle injection of AAV9-PHP.B in young mice, which was more efficient than their RWM injection controls at an average of 80%−90%. At P16, AAV9-PHP.B outperformed Anc80L65 in terms of IHC transduction efficiency, especially at the basal turns of the cochlea (Lee et al., 2020). Consistent with these findings, AAV9-PHP.B utricle injections by Wu et al. (2021a) in *TMC1* -/- mice demonstrated similar HC transduction rates.

Direct adenoviral vector injection into the endolymphatic duct/sac has proven feasible in a study by Yamasoba et al. (1999). Cochlear transduction was only noted in the mice that exhibited intraoperative swelling of the endolymphatic sac during the injection, suggesting a successful injection technique. While the HC transduction was not quantified, the authors noted infection of HCs that bordered the endolymph, in addition to infection of the vestibular end organs (Yamasoba et al., 1999). Both the utricle and endolymphatic sac injection are technically more challenging than other delivery methods, with a higher risk of iatrogenic hearing loss associated with the delivery process.

## 4.6 Brainstem and cerebrospinal fluid delivery

Given the challenges in effective HC and SGN transduction particularly across the tonotopic axis of the adult mammalian cochlea with cochlear delivery, and the connection between CSF and inner ear, CSF delivery has been investigated recently to deliver genes to the inner ear.

Given that it is difficult to limit CNS transduction following injection into the CSF, hair cell-specific promotors, such as *MYO7* have been investigated to limit transduction to hair cells. Blanc et al. reported that injection of viral vectors (AAV2/8, AAV9, and AAV2/Anc80L65) into the cisterna magna (CM) of mature mice results moderate transduction of IHCs bilaterally, however the efficiency differs across the tonotopic axis (Blanc et al., 2020). AAV2/Anc80L65 was the most efficient serotype, transfecting nearly 90% of the IHCs at the base but close to 0% at the apex. Moreover, a significant portion of the SGNs were transduced, however the percentage transduction was not reported. Auditory and vestibular studies revealed that the CSF delivery did not affect hearing or vestibular function compared to the cochleostomy approach (Blanc et al., 2020). In another study by Mathiesen et al. (2023), AAV-PHP.B-CBA-VGLUT3-WPRE injected in the cisterna magna injected at a relatively high dose of $2.27 \times 10^{11}$ vg (10 µL of a $2.27 \times 10^{13}$ vg/mL solution) restored hearing in *SLC17A8* -/- mice, which lack vesicular glutamate transporters and are therefore unable to release the neurotransmitter, in all frequencies except 40 kHz. The authors report minimal off-target *VGLUT3* transgene expression in the brain (specifically the cortex, hippocampal CA2 region and cerebellum) and no expression in the liver. These findings are contradictory to many rodent and NHP studies which have consistently demonstrated widespread brain and spinal cord transduction following CSF delivery of AAV-PHP.B (Liguore et al., 2019; Arotcarena et al., 2021; Chatterjee et al., 2022). Moreover, this study was conducted utilizing mice aged 4 to 15 weeks old (P28-P105) at the time of injection, suggesting CSF delivery as a potential route for transduction of mature cochlea (Mathiesen et al., 2023).

Notably absent from this study was an assessment of presence of viral vector genomes in the liver, assessment of spinal cord transduction and screening of dorsal root ganglia (DRG) for an immune response. A recent meta-analysis of AAV delivered by CSF for CNS indications revealed DRG pathology in 83% of NHP regardless of the AAV serotype or promoter used (a total of 213 NHP which received intracisternal AAV) (Hordeaux et al., 2020). Those findings are consistent with those by Samaranch et al. who observed widespread brain, spinal cord and DRG transduction with intra-CM delivered AAV9 and AAV7 in NHPs (Samaranch et al., 2013). Consistent with Mathiesen et al., Samaranch et al. did not report any significant peripheral organ transduction, however transduction of both astrocytes and neurons was reported.

Efficient cochlea transduction following CSF delivery has also recently been reported in NHPs by Ranum et al. (2023) who explored cochlear transduction following intracerebroventricular injection of AAV9, and novel capsid variants of AAV1, 2, and 9. The AAV1 and AAV2 capsid variants, AAV1.RPG.mNG and AAV2.HDG.mTFP, transduced nearly all IHCs. Alteration of the AAV9 capsid appeared to affect transduction efficiency along the cochlea tonotopic axis in rhesus macaques. Cochlea transduction with AAV9.eGFP was strongest at the apex, while animals injected with the AAV9 capsid variant AAV9.KGG.eGFP demonstrated strongest gene expression at the base. This finding suggests that the apex to base transduction gradient observed in many studies could be due to varied expression of receptors required for viral entry into the cell across the tonotopic axis of the cochlea. Interestingly AAV9 performed better at IHC transduction in the rhesus macaque compared to the African green monkey, further implicating cellular physiological differences in transduction efficiency (Ranum et al., 2023). No SGN transduction was reported in this study, however it is possible that use of serotypes with high neuronal tropism (e.g., AAV5 or AAV-PHP.B) could improve SGN transduction with this delivery route.

Taken together, these studies suggest CSF delivery through CM and intracerebroventricular injections is an efficient delivery method for gene therapy to the inner ear. However, caution is warranted regarding the potential for off-target delivery to other organs, particularly when considering upscale to larger mammals and humans. Additionally, significantly more vector is required for CM injections compared to intracochlear injections due to potential to dilute the vector within the CSF. A relatively high dose of $2.27 \times 10^{11}$ vg and $4.7 \times 10^{11}$ vg (both in 10μL) was used in the functional and GFP studies (Mathiesen et al., 2023). Development of novel AAV serotypes specifically designed to target inner ear cells and de-target peripheral organs is an essential next step to see this route of administration enter clinical applications.

In addition to CSF delivery, injection of viral vectors directly to the brainstem may represent another potential route. AAV vectors exhibit natural tropism and route of axonal transport (anterograde, retrograde, and bi-directional) to specific cell types, which can be further modified through genetic engineering to allow for transport of genetic material along axonal pathways (Gao et al., 2002; Cearley and Wolfe, 2007; Salegio et al., 2013). The use of AAV vectors for axonal transport is a robust method that can achieve transgene expression in brain regions beyond the direct site of injection in adult NHPs (Samaranch et al., 2017; Naidoo et al., 2018). Anterograde transport involves entry of the AAV vector into cell bodies at the infusion site. Intact virions are transported along axons that originate within the site of vector delivery, are released at the axon terminal, and then transduce neighboring cells that synapse onto the dendrites (Salegio et al., 2013; Green et al., 2016). In contrast, retrograde transport requires uptake of the AAV vector by axonal projections, followed by transport to the distally located soma where it transduces the host cell nucleus, allowing for identification of neurons that project to a specific brain region (Salegio et al., 2013; Green et al., 2016). Harnessing axonal transport of AAVs to transduce various regions of the brain has also been shown as effective and safe in human trials for various diseases (Pearson et al., 2021; Rocco et al., 2022). Brainstem delivery of AAV into the cochlear nucleus could therefore use both anterograde and retrograde transport to infect the cochlea using the efferent and afferent cochlear nerve fibers, respectively (Figure 2). The brainstem delivery route has yet to be studied for its efficacy for transducing the cells of the inner ear. However, given the success with axonal transport in adult mammals within the brain, it could be expected that brainstem delivery might be a prime method for improving SGN transduction. The brainstem delivery route is a more invasive delivery route, however intraparenchymal AAV delivery has a clinical track record of safety, including in the upper brainstem in regions in close proximity to the Superior Olivary Complex and Cochlear Nucleus (Pearson et al., 2021). Gadoteridol co-infusion with AAV, and intraoperative MRI allows for real-time infusion of vector, and precise cannula placement avoiding major blood vessels and nuclei responsible for vital life functions (Lonser et al., 2020). Moreover, surgical biopsies of tumors from the proposed regions of the brainstem are routinely performed in patients with low morbidity (Lonser et al., 2020). The benefits in quality of life therefore present a potential case for development of this approach for some forms of hearing loss (Lonser et al., 2020; Pearson et al., 2021).

### 4.7 Consideration of promoters

Promoter selection is an important consideration when designing a gene therapy as gene expression in non-target cells can cause an immune response or significantly alter cellular homeostasis and result in undesirable clinical effects. While the majority of preclinical and clinical studies have opted to use strong, constitutively active promoters such as cytomegalovirus (CMV), the chicken beta-actin (CBA), and the combination CMV-enhancer/CBA promoter (CAG) promoters (Liu et al., 2007; Gu et al., 2019; Rambeau et al., 2024), hair cell specific promoters have shown great promise to limit gene expression to HCs for diseases which only affect HCs (Lv et al., 2024). CMV, CBA, CAG, elongation factor 1α (EF-1α), and hair-cell specific promoters such as Myo15 and Myo7a have all shown durable gene expression in the inner ear. A comparison of the CAG promoter and Myo7A promoters by Liu et al. (2007), showed that the CAG promoter elicited the highest expression in IHCs, while the Myo7A promoter demonstrated the most specific expression of HCs. The constitutive CMV and the CAG promoters have both demonstrated robust gene expression in HCs and SCs in preclinical studies (Gu et al., 2019; Rambeau et al., 2024). Moreover, Myo15 was demonstrated to direct gene expression in IHCs and OHCs effectively, showing promise in the development of a treatment of HHL in *OTOF*-/- models (Wang et al., 2024) and is also being utilized in a clinical trial initiated by Eye and ENT Hospital of Fudan University which has demonstrated remarkable safety and efficacy in patients with *OTOF* pathogenic variants thus far (Lv et al., 2024). Given that AAVs induce persistent gene expression in target cells, a balance must be struck between the strength and cell specify of the promoter, AAV titer and serotype such that transgene expression levels are as close as possible to physiological levels for the disease being treated.

## 5 Gene therapy clinical trials for hereditary hearing loss

### 5.1. Non-genetic targets

Significant progress has been made over recent years in the clinical development of gene therapies for congenital hearing genetic disorders, however little progress has been made in the translation of therapies for adult-onset hearing loss or treatment for non-genetic causes of hearing loss.

A Phase 1/2 clinical trial sponsored by Novartis Pharmaceuticals for severe-to-profound unilateral or bilateral hearing loss without a known genetic cause was completed in 2021 (Clinicaltrials.gov Identifier: NCT02132130). This study included 22 patients who received CGF166, a recombinant adenovirus (rAd5) to deliver *ATOH1* to the inner ear via the oval window injection. Based on preclinical studies, it was expected that forced *ATOH1* expression in HL patients may transdifferentiate remaining SC to functional HC, leading to rescue of HL. At baseline, the 22 patients had a recorded average pure tone audiometric threshold of 69.3 dB (±15.4). At the culmination of the study, the 19 remaining patients (2 lost to follow-up) had an average PTA of 78.7 dB (±18.8), demonstrating hearing status that did not show significant improvement following treatment. There were no

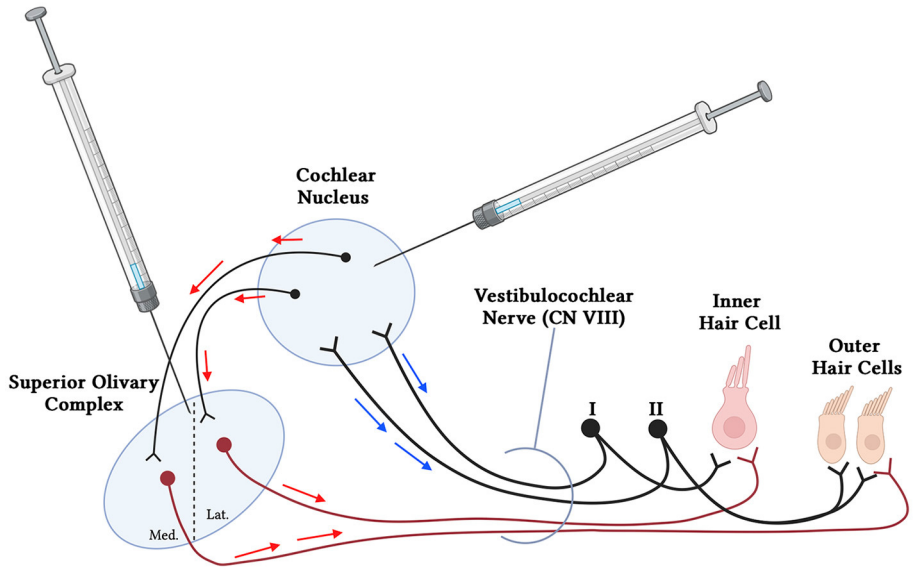


FIGURE 2
Simplified schematic of proposed brainstem delivery of viral vector to the cochlea using anterograde and retrograde transport. Viral vectors may be administered using MRI-guided intraparenchymal injections to the cochlear nucleus in the brainstem. The AAVs may utilize both anterograde (red arrows) and retrograde (blue arrows) transport through the afferent (Type I and II spiral ganglion neurons) (black), interneurons to the Superior Olivary Complex, and efferent neuronal fibers (maroon) to reach both the inner and outer hair cells of the cochlea. Additional neurons communicating with and from the cochlear nucleus and superior olivary complex have been removed for simplicity.

serious adverse events noted. The reasons for failure of this trial are unclear but could include inefficient gene delivery across the cochlear axis, choice of vector, titer, patient inclusion criteria and lack of reinnervation of HCs with SGNs. The gene target *ATOH1* is a key regulator for HC regeneration, however, is not associated with SGN regeneration. Therefore, patients with profound hearing loss with secondary degeneration of the ribbon synapses and SGNs may not benefit.

## 5.2 Genetic targets

There have been exciting breakthroughs for gene therapy for genetic congenital HHL in pediatric patients. Gene therapy clinical trials for *OTOF*-related (DFNB9) deafness are currently enrolling by Akouos/Eli Lilly and Company, Decibel Therapeutics/Regeneron, Sensorion, Otovia Therapeutics, as well as universities and research centers. A summary of clinical trial data is shown in Table 3.

The Akouos/Eli Lilly and Company AK-OTOF-101 trial (Clinicaltrials.gov Identifier: NCT05821959) commenced enrollment of pediatric subjects aged 2 to 17 years in a Phase 1/2 trial in September 2023, subsequent to receiving Investigational New Drug (IND) approval from the FDA in 2022. This trial employs AAVAnc80-hOTOF, a dual AAVAnc80 vector approach incorporating 6 kB of human otoferlin cDNA controlled by an unnamed, ubiquitous promoter, with the aim of producing functional otoferlin in the inner ear. A dual-vector system is utilized as the size of the *OTOF* gene surpasses the packaging capacity of most AAVs. Utilizing two AAV cassettes, each containing different segments of the *OTOF* coding sequence, facilitates the *in vivo* assembly of a full-length otoferlin protein. Because of the size of the *otoferlin* gene, a dual vector approach is utilized in all the clinical trials for *OTOF*-related deafness. The downside of this approach is that it necessitates two vectors to enter each cell in order to produce functional protein and also exposes the patients to a greater viral load than if a single AAV was used. Vector delivery is performed via RWM injection with concomitant fenestration of the stapes footplate using a patented needle device. Intracochlear administration of AK-OTOF to 3-week-old *OTOF* -/- mice yielded both short-term (15 days) and long-term (>6 months) hearing restoration, as evidenced by ABR threshold reductions (Hickox et al., 2021; Gao et al., 2023). Subsequent analysis revealed robust (20%−80% of IHCs) human otoferlin expression in the IHCs of injected mice. However, the efficacy of ABR restoration in *OTOF* -/- mice was contingent upon pre-injection distorted product otoacoustic emissions (DPOAE) levels and, therefore, the age of the model. Less than 20% of *OTOF* -/- mice aged 7.5 months or older exhibited recovery of OAEs, irrespective of preoperative hearing level. Additionally, among mice aged 7.5 months with no baseline OAE, representative of severe hearing loss, none achieved hearing levels comparable to control WT mice. Safety studies conducted on *OTOF* -/- mice and NHPs revealed no significant adverse findings associated with intracochlear injection of AK-OTOF (Hickox et al., 2022). The NHP studies revealed minimal vector persisting in the liver, spleen, and lymph nodes at 6 months post injection. However, organ weights and brain histopathology, representative of systemic pathology, were normal at this time frame (Hickox et al., 2022; Gao et al., 2023). Regarding human subjects, preliminary reports demonstrate that one patient (11 years-old) with profound hearing loss demonstrated significant hearing recovery at 30 days post injection, reaching thresholds

TABLE 3 Summary of available human clinical trial data regarding viral vector gene therapy for hearing loss.

| Sponsor | Trial Name (Clinicaltrials.gov identifier) | Gene target | Viral vector | Delivery route | Preclinical studies results | Clinical trial results |
|---|---|---|---|---|---|---|
| Akouos/Eli Lilly | AK-OTOF-101 (NCT05821959) | OTOF | AAV/Anc80 | RWM + CF | Neonatal mice: improved DPOAE threshold. Adult mice: no improvement | Began enrollment in second half of 2023. Preliminary: one patient exhibited significant recovery in ABR threshold at 30 days. |
| Decibel Therapeutics/ Regeneron | CHORD (NCT05788536) | OTOF | AAV1 + Myo15 | RWM + CF | Three neonatal mice models: ABR thresholds improved to WT levels. | Pending. Began enrollment first half of 2023. |
| Sensorion | OTOF-GT/SENS-501 (Identifier pending) | OTOF | rAAV2 + quadY-F capsid | RWM + OWF | Neonatal mice: Hearing recovered to WT thresholds | Pending. Begins enrollment in second half of 2024 |
| Otovia Therapeutics | OTOV101 (NCT05901480) | OTOF | NS | RWM | Neonatal mice: Hearing recovered to WT thresholds. | 2 patients: Improvement of hearing thresholds in 2/2 patients. Additional studies enrolling now. |
| Eye and ENT Hospital at Fudan University | AAV1-hOTOF (ChiCTR-2200063181*) | OTOF | AAV1 | RWM + OWF | Neonatal mice- full recovery on ABR. Adult mice- partial recovery on ABR | 5 out of 6 subjects experienced significant, long-term hearing recovery |
| Novartis Pharmaceuticals | CGF166 (NCT02132130) | ATOH1 | rAAV5 | OWM | NS | 19 patients experienced no hearing recovery |
| Institut Pasteur | TREATGENE (NCT03996824) | N/A | Unspecified | *Ex vivo* | NS | Pending. Began enrollment in the first half of 2019 |

AAV, adeno-associated virus; RWM, round window membrane injection; PSCC, posterior semicircular canal injection/canalostomy; RWM + CF, round window membrane injection with canal fenestration; CSF, cerebrospinal fluid delivery; CO, cochleostomy; NS, not stated.

of 35 and 60 dB on the ABR (Simons et al., 2024). Moreover, no serious adverse events or toxicity were recorded.

Decibel Therapeutics'/Regeneron's CHORD trial (Clinicaltrials.gov Identifier: NCT05788536), is a phase 1/2 trial which began in May 2023, is actively enrolling pediatric subjects (<18 years) with biallelic *OTOF* pathogenic variants. This study cohort mirrors that of AK-OTOF-101, with a notable inclusion of infants aged 6 months. Employing the DB-OTO dual AAV1 vector system featuring a hair cell-specific promoter, Myo15, and the human *OTOF* v5 transgenes, the CHORD trial aims to address *OTOF*-related deafness, DFNB9. Preclinical investigations utilized murine models, including Q828x, R1934Q, and Deaf5, and utilized treatment with a dual AAV vector system, administered via PSCC injection (Chung et al., 2023; Valayannopoulos, 2023). The Q28x murine model ($OTOF^{Q28x/Q28x}$) hosts an orthologous, functionally null allele that represents the pGln829* pathogenic variant found in Latin American and Spanish populations (Migliosi et al., 2002). The R1394Q and Deaf5 murine models are missense mutations, significantly decreasing gene function, in the p.Arg1934Gln and p.Ile318Asn loci, respectively (Longo-Guess et al., 2007; Kim et al., 2018). Four weeks post-injection, all Otoferlin-deficient models treated with AAV1-Myo15-myc-mOTOF demonstrated ABR levels comparable to WT mice, while vehicle-treated *OTOF* -/- controls exhibited no detectable ABR. Immunohistochemical analysis further revealed over 50% transduction of IHCs in all mouse cochleae. Notably, in NHPs, RWM injection of AAV1-Myo15 (DB-OTO) with LSCC fenestration, demonstrated no serious adverse events or immunological reactions when dosed based on total perilymph volume (Koehler et al., 2023; Valayannopoulos, 2023). Furthermore, NHP studies utilizing DB-OTO showcased transduction of over 75% of IHCs, with minimal vector dispersion observed in the brain and spinal cord. Results from this trial have not yet been released.

Sensorion's OTOF-GT/SENS-501 program is poised to commence enrollment of pediatric patients aged 6 to 36 months for a phase 1/2 clinical trial in the second half of 2024. OTOF-GT employs a dual vector AAV cassette system encapsulated within a recombinant AAV2 quadY-F capsid, addressing the challenge posed by the *OTOF* gene's size, which surpasses the packaging capacity of most single-cassette AAV therapies. Surgical intervention will involve the administration of OTOF-GT via the RWM concurrently with stapedectomy/oval window fenestration, as outlined in their NHP studies (Rambeau et al., 2024). Preclinical investigations of OTOF-GT utilized a dual AAV2 vector, recombinant AAV2 quadY-F capsid, and chimeric CAG promoter for *OTOF* coding sequence delivery. Notably, modifications to the AAV2 capsid, informed by previous studies on the retina, were implemented to enhance gene transfer efficiency (Petrs-Silva et al., 2011). *OTOF* -/- mice injected at P10 exhibited hearing recovery similar to WT mice up to 54 weeks post injection, the last measured time point. Subsequent analysis of cochleae from mice injected at P17 and P30 revealed significantly higher numbers of ribbon synapses in transduced IHCs compared to non-transduced counterparts (Akil et al., 2019b). However, the number of ribbon synapses in *OTOF* -/- mice remained markedly reduced compared to age-matched WT mice, regardless of transduction status (Akil et al., 2019b). WT NHP preclinical studies (N=6/dose) demonstrated IHC transduction, yet no significant changes in ABR or DPOAE were observed. Suggesting no viral-mediated ototoxicity or iatrogenic damage. Additionally, viral vector biodistribution in NHPs was predominantly confined to the injected ear structure (Rambeau et al., 2024).

A study sponsored by Otovia Therapeutics based in Jinan, Shandong, China began enrolling subjects in mid-2023, and the investigators recently published a report of two cases (Qi et al., 2024a). This study utilized a dual vector AAV system, termed OTOV101 (also termed AAV-OTOF), which used a hair cell-specific promotor. A 5-year-old participant received a unilateral injection of the AAV-OTOF, while an 8-year-old participant received bilateral injections (Qi et al., 2024a). The viral vector was administered through the RWM following a mastoidectomy (Figure 3). At around 1 month post injection, the 5-year-old participant's ABR threshold was near 30 dB HL, comparable to the hearing of a similar patient with no pathogenic *OTOF* variants. Further, at 3 months post injection, the patient was able to respond to voiced questions without the use of any assisted amplification devices in the injected ear. The 8-year-old patient with bilateral injections demonstrated similar improvements in ABR thresholds, reaching near 30 dB and 50 dB in the right and left ears respectively, at 3 months post injection. This 8-year-old participant is the oldest documented patient to have experienced improvement in hearing following intracochlear gene therapy, to our knowledge. No systemic toxicities or serious adverse events were noted in these two patients. The Otovia therapeutics-sponsored study (Clinicaltrials.gov Identifier: NCT05901480) is set to continue participant enrollment until the end of 2024 with an estimated enrollment of five patients. However, the Otovia Therapeutics study will not pursue the mastoidectomy approach as was used in the first two patients, but instead administer the vector through the tympanic membrane/external auditory canal approach.

The first in-human gene therapy clinical trial for a hearing disorder was recently completed. Results from a single-arm, single-center study based at the Eye and ENT Hospital of Fudan University, which began enrollment in December 2022, were recently published (Lv et al., 2024). This study utilized AAV1-hOTOF, a dual vector AAV system with a Myo15 promoter. Preclinical studies on AAV1-hOTOF demonstrated a dose-responsive effect on hearing preservation following RWM injection in neonatal *OTOF* -/- mice (Zhang et al., 2023). The high dose *OTOF* -/- group ($6 \times 10^{10}$ vg/cochlea) exhibited ABR thresholds similar to WT mice injected with vehicle controls, and otoferlin protein was detected in all turns of the cochleae of these mice. When AAV1-hOTOF was injected in adult mice, those that received doses $>3 \times 10^{10}$ demonstrated long-term (>6 months) partial recovery in hearing levels. Moreover, the safety of AAV1-hOTOF was examined when RWM injection in WT mice led to no difference in ABR function, behavior, or pathology (Zhang et al., 2023). In NHPs, no toxicity following a high dose of AAV1-hOTOF was noted. However, viral genomes were detected at minimal levels in the brain, spinal cord, and liver (Zhang et al., 2023). These preclinical studies supported the clinical trial data that were published in *The Lancet* in early 2024 (Lv et al., 2024). Six subjects (Average age: 4.1 years, Range 1.0 to 6.2 years) diagnosed with DFNB9 and complete hearing loss (no ABR at baseline, 3/6 had pure-tone audiometry recordings (all greater than 100 dB), and 4/6 had unilateral CI) were prospectively enrolled in the study. The participants were administered $9 \times 10^{11}$ vg/cochlea ($n = 1$) or $1.5 \times 10^{12}$ vg/cochlea ($n = 5$) of AAV1-hOTOF unilaterally via a transcanal RWM injection with stapes fenestration. Concurrent systemic corticosteroids and antibiotics were administered. There were no serious adverse events or dose-limiting toxicities noted throughout the 26-week-long study. Moreover, vestibular function ($n = 4$) and otoscopic examination ($n = 6$) were normal at the long-term follow up (>26 weeks). Five out of six participants exhibited significant long-term (>26 weeks) hearing recovery (at least 10-dB threshold reduction on the ABR) that was first detected between 4–6 weeks post injection. Additionally, speech perception in 3 of the 4 CI users was also significantly improved. Overall, this prospective study of six patients demonstrated significant hearing recovery in 5/6 participants with no serious adverse events at the long-term follow-up. This clinical trial is groundbreaking with extremely promising results. Moreover, this trial suggests that success in animal models can be translated to similar degrees of success in human models, paving the way for rapid clinical translation of other gene targets.

To our knowledge, there are no active gene therapy clinical trials involving for deafness related to other genetic pathogenic variants, such as *GJB2*, or gene delivery of neurotrophic factors for the treatment of NIHL and CIHL. However, Decibel Therapeutics is conducting an IND-enabling study, AAV.103, that will evaluate the safety of AAV vectors for *GJB2*-associated deafness in preparation for human trials.

# 6 Limitations and future directions

## 6.1 Model age on transduction efficiency

Given the fundamental differences in the timing of inner ear development and onset of hearing between rodent models and humans, there may be limited success in the translation of gene therapy treatments from mice to humans. The age of the preclinical model presents a significant limitation in inner ear transduction and the translation of gene therapy for adult humans. Neonatal mice exhibit high transduction efficiency in both HCs and SGNs, due to, in part, the regenerative capacity of the cells during early development. In mice, the HCs are mostly matured by P7, a process that starts as early as embryonic day 14 (Kolla et al., 2020). While the IHCs and OHCs may be distinct at P7, the ribbon synapses do not reach adult configuration until at least P14 when the cochlea matures (Michanski et al., 2019). In humans, IHCs begin to develop in gestational week 10 (GW10), with the fetus able to respond to low frequency tones at GW19 (Hepper and Shahidullah, 1994; Johnson Chacko et al., 2019). Fetal response to all frequencies, representing IHC maturation and mature connections between the HCs, ribbon synapses, and SGNs, was observed at GW35, demonstrating complete cochlear maturation embryonically (Hepper and Shahidullah, 1994). The later GW35 timepoint may better represent maturation of neural components, as studies have demonstrated IHCs and OHCs across all turns of the cochlea at GW24, a much earlier timepoint (Kelley, 2007; Johnson Chacko et al., 2019). In addition to cochlear maturation, the critical time period for auditory development varies between humans and mice. The murine critical period ends at approximately P28 while the human critical period extends through the first few years of life (Kral, 2013). Due to this maturation timeline, gene therapy for mature models must overcome substantial hurdles, particularly concerning SGNs, where transduction efficiency can

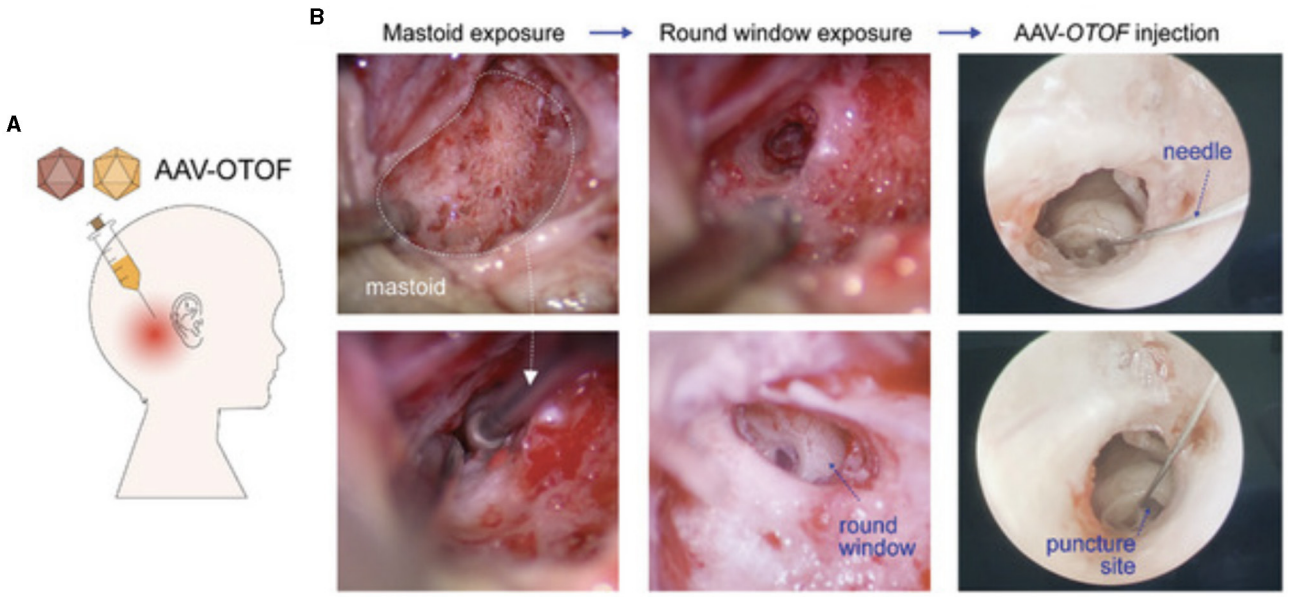


FIGURE 3
**(A)** Schematic of experimental design for injecting viral vectors in human patients. **(B)** Representative intraoperative images during the mastoidectomy procedure and subsequent AAV injection through the round window membrane (Figure reproduced from Qi et al. (2024a,b) under the open access license agreement; https://creativecommons.org/licenses/by/4.0/).

plummet to as low as 10% in mature mice (Table 2). Additionally, variation in transduction efficiency is pronounced in both IHCs and OHCs, with notable apex-to-base gradients complicating uniform therapeutic delivery. These challenges are attributed to age-related changes in cellular physiology, expression of receptors required for AAV entry, including the transient regenerative capacity of cochlear cells, which do not become fully quiescent and developed until around the 2$^{nd}$ week of postnatal development. This age limitation underscores the need for innovative approaches to enhance transduction efficiency and bridge the gap between neonatal and mature models in gene therapy research.

## 6.2 Target patient population and appropriate animal models

An important consideration for future clinical trials is identifying the ideal patient population to study and subsequently determining the availability of suitable animal models. This currently presents a major challenge for gene therapy advancements. While rare HHL diseases like Usher syndrome and *OTOF*-related deafness have provided valuable proof-of-principle studies, they affect a relatively small number of patients. Moreover, the therapeutic window for intervention is narrow, as demonstrated in studies showing minimal success in mature preclinical and clinical models. Additionally, the ideal patient population requires a specific auditory profile, having absent ABR but intact DPOAE, indicating the presence of IHCs available for transduction, and preferably without CIs. However, this patient population is almost non-existent in the United States, as congenitally deaf individuals typically receive CIs early in life (most by 1 year of age), and those who do not, often opt for communication using American Sign Language (ASL). These patients within the culturally Deaf community are less likely to desire gene therapy approaches to mediate hearing loss. While genetic mouse models are valuable for testing viral transduction efficiency and hearing restoration, NHP models are better suited for assessing clinical feasibility. Unfortunately, there are almost no models of hearing loss in NHPs, leading to reliance on studies using GFP to only index infection and transduction rates instead.

To maximize the impact of gene therapy interventions, it is crucial to expand the target population to include adult patients with non-genetic forms of hearing loss, such as NIHL and age-related hearing loss (presbycusis), which account for the majority of cases of SNHL. Consequently, approaches that are gene-agnostic, such as NTs like GDNF and BDNF, and potentially even transcription factor ATOH1, are likely to be the future focus of research and development in the field of gene therapy for acquired hearing loss.

## 6.3 Auditory nerve damage

Auditory neuropathy may consist of damage or dysfunction of any portion of the pathway from the cochlea to the brain, with HCs, ribbon synapses, and SGNs representing the major anatomical components. As discussed previously, pathogenic variants in genes such as *SLC17A8* and *OTOF* have implications as targets for SNHL related to auditory neuropathy, with *OTOF* being extensively studied. However, current studies have demonstrated inefficient infection rates of SGNs (Table 2) and have instead focused on HC transduction. This limitation severely affects the translational

capacity of these studies for use in SNHL associated with degeneration of the SGNs with or without cochlear damage. NT delivery using viral vectors have established a neuroprotective role following NIHL and CIHL but have yet to demonstrate significant regenerative capacity.

## 7 Conclusion

Recent advancements in both preclinical studies and clinical trials have highlighted the potential of gene therapy in treating sensorineural hearing loss. Notably, HHL, particularly associated with pathogenic variants in the *OTOF* gene, has emerged as a focal point of clinical discoveries. The first clinical trial for HHL has demonstrated robust hearing recovery in pediatric subjects, marking a significant milestone in the field.

However, gene therapy for degenerative conditions such as NIHL and CIHL is still in its early stages. Addressing these gaps necessitates a focus on mature models, with a specific emphasis on enhancing SGN transduction. Further preclinical investigations are essential to bridge these disparities. Despite these challenges, the rapid progress in utilizing gene therapy for both acquired and HHL holds great promise for improving patient outcomes.

## Author contributions

BD: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. EB: Conceptualization, Writing – review & editing. YR: Conceptualization, Data curation, Writing – review & editing. JN: Conceptualization, Data curation, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Knowledge, attitudes, and practices of Australian allied hearing-healthcare professionals: survey on comorbid hearing loss and cognitive impairment

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**Purpose:** As hearing loss is a modifiable risk factor of dementia, allied hearing-healthcare professionals (AHHPs) frequently see older patients who are affected by both conditions. However, little is known about how well Australian AHHP's understand the complexities of providing care to patients with comorbid hearing loss and dementia, as well as their associated views and practices. Thus, the current study used a survey to explore the knowledge, attitudes, and practices (KAPs) of Australian AHHPs in managing comorbid patients.

**Materials and methods:** A cross-sectional design was used, wherein a KAP survey was developed and distributed to eligible AHHPs via Qualtrics. Data were analysed with descriptive statistics and binary logistic regression.

**Results:** 101 Australian AHHPs met inclusion criteria (2.5% of approximately 4,000 invited AHHPs), and participated in the study. Although participants generally possessed a high level of knowledge for the association between hearing loss and cognitive impairment, their specific knowledge and practices in relation to cognitive screening tests and referral pathways was limited. Participants also expressed mostly positive attitudes towards their role in assisting patients with comorbid hearing loss and dementia. Furthermore, our results suggested that some KAPs relevant to comorbid patients differed based on sex, qualification, and ethnicity.

**Conclusion:** This study identified gaps in the knowledge and practices of Australian AHHPs with regard to the complexities of addressing comorbid cognitive impairment and hearing loss. These findings will help to develop training programs to empower AHHPs to deliver optimal healthcare services to comorbid patients.

KEYWORDS

**dementia, audiology, KAP survey, quality of care, health service delivery**

# 1 Introduction

Dementia is a progressive disorder characterised by cognitive impairments that severely affect independence and activities of daily living mostly in those aged 60 years and over (1), and was estimated to affect up to 472,000 Australians in 2021 (2). Mild Cognitive Impairment (MCI), meanwhile, is characterised by cognitive impairment(s)—namely of memory and/or executive functions—that are debilitating but not sufficiently detrimental to an individual's independence (3); it is generally considered a prodromal state for dementia. MCI has received increasing scientific interest due to the potential for early intervention and the lack of effective treatments for more advanced dementia (4). Furthermore, it is estimated that up to 40% of MCI and dementia cases could be prevented or delayed by addressing associated modifiable risk factors. Of these factors, hearing loss has the highest population attributable risk factor of 8.2% (5).

Indeed, hearing loss is itself a major chronic illness, significantly affecting an estimated 403.3 million people globally in 2019 (6). Of those affected, 62.1% are aged 50 years or over, with sharp increases in prevalence after the age of 60 (6). Furthermore, untreated hearing loss is associated with emotional loneliness (7), social isolation (8) and depression (9). Several studies have also found hearing loss to be associated with cognitive impairment (10–12) and dementia (13–16), with hearing loss of mild, moderate, and severe degrees increasing dementia rates by two, three, and five times, respectively (13). Numerous studies also show that hearing intervention, either with hearing aids (17, 18) or cochlear implants (19–21), decelerates cognitive deterioration. However, findings from randomised-control studies such as the ACHIEVE (22) and HearCog (23) are awaited to provide further insight into whether hearing intervention prevents, or reduces, the rate of cognitive decline in hearing-impaired older adults.

In the context of clinical practice, several authors have encouraged the inclusion of hearing assessment in memory clinics, or of cognitive screening in hearing clinics (24–26). Recent work has also indicated that audiology patients may themselves be amenable to undertaking cognitive screening in audiological practice (27). Moreover, the addition of hearing and cognitive assessment to memory and hearing clinics, respectively, could help improve both the identification of hearing loss in cognitively-impaired patients and the identification of cognitive impairments in hearing-impaired patients. The latter is of particular importance, as many cognitive assessments have historically been verbally-loaded, resulting in poorer performance in those with hearing loss (28, 29).

Accordingly, it would seem vital that Allied Hearing Healthcare Professionals (AHHPs; e.g., audiologists, audiometrists, etc.) be proficient in some forms of simple cognitive assessment. In Australia currently, AHHPs provide diagnostic assessments across audiological, neurological, and rehabilitation services, which include providing hearing-aid prescriptions, fittings, counselling, assistive listening devices, and implantable devices (30). Furthermore, the scope of practice developed by the three Australian practitioner professional bodies stipulates that AHHPs undertake assessment of patients' cognitive function and adapt test procedures to patients with complex cognitive needs (30). Similar stipulations have been made internationally, such as with the American Speech-Language-Hearing Association's requirement that AHHPs screen for cognitive disorders and undertake case-finding for dementia (31).

However, the above stipulations are only prescriptive; that is, they have not addressed the feasibility and acceptance of such cognitive testing within audiological practice and not been supported with the provision of any training or educational programs. Furthermore, there is limited literature on the knowledge, attitudes, and practices of AHHPs' use of cognitive screening assessments or their understanding of the association between hearing loss and cognitive impairment. In a UK-based study, Leroi et al. (32) investigated Allied-Health professionals across three main specialties (memory clinicians, optometrists, & audiologists), namely through a focus group and Knowledge-Attitude-Practice survey (KAP). Results showed that all specialties valued interdisciplinary assessment and collaboration, due to the high comorbidity of sensory and cognitive disorders in their respective patient populations; they also agreed on the need for interdisciplinary collaboration to develop new screening assessments for patients affected by comorbid sensory and cognitive impairments. However, results also demonstrated that there was low confidence within each specialty in undertaking assessments from other disciplines. An equivalent study has not been conducted in Australia.

The current study therefore aimed to assess Australian AHHP's knowledge, attitudes, and practices relevant to assessing comorbid hearing loss and cognitive impairment, with the further aim of consequently informing optimal healthcare services for patients with comorbid cognitive impairment and hearing loss in the future. An online self-report KAP survey was developed to be suitable for Australian AHHPs. The knowledge section of the KAP survey generally asked what AHHPs knew about the effect of cognitive impairment on their patients and practice, as well as the administration of cognitive screening tests and referral pathways. The attitude section, meanwhile, asked about AHHPs' attitudes towards their role in identifying cognitive impairment, administering screening tests, referring patients with possible cognitive impairment, and the challenges related to these factors. Finally, the practice section asked about whether AHHPs were discussing the link between hearing loss and cognitive impairment with their patients, conducting cognitive screening tests, and making forward referrals for medical assessment and management.

# 2 Materials and methods

## 2.1 Study design

This study used a cross-sectional design. A KAP survey developed for Australian AHHPs was used to elucidate their knowledge, attitude, and practices regarding the provision of care for hearing-impaired older adults with suspected cognitive impairment. Ethics approval for this project was received from the University of Western Australia (reference no: 2021/ET000434).

## 2.2 The KAP questionnaire

### 2.2.1 Development and contents

All survey questions were developed based on discussions with the project team, consisting of a psychologist, a general practitioner, audiologists from Ear Science Institute Australia's Lions Hearing Clinics, geriatricians, and geriatric psychiatrists from Western

Australia Centre for Health and Ageing. The questionnaire consisted of five sections: demographic information, knowledge, attitude, practice, and training (see full questionnaire in Supplementary material).[1] The demographic section contained questions about the respondent's sex, ethnic or cultural background, country of residence, years in profession, and audiology-specific qualifications. The knowledge, attitudes, and practice sections included questions on the respondent's awareness, views, and practice regarding the delivery of hearing-healthcare services to patients with potential cognitive impairment. Meanwhile, the training section included ranked questions on the format and content of training resources desirable to the respondents. Most questions were answered using a 5-point Likert scale (e.g., "Managing clients with cognitive impairment can be challenging" – *strongly disagree* [0], *disagree* [1], *neutral* [2], *agree* [3], *strongly agree* [4]; "I have used formal cognitive screening tests as part of my practice" – *never* [0], *rarely* [1], *occasionally* [2], *frequently* [3], *very frequently* [4]), though some questions were either binary (e.g., "I have used formal cognitive screening tests as part of my practice" – *no* [0], *yes* [1]) or multiple-choice (e.g., "I decide to do a cognitive screening test on older clients based on: [choose all that apply]" – a. client's age; b. client reporting memory issues; c. carer/family reporting memory issues; d. inconsistent hearing assessment results; e. other); some questions also allowed for open-ended elaboration (e.g., "Please describe how you decide to conduct a cognitive screening test"). Lastly, ranked questions were used in the training section (e.g., "Please indicate your preference [with 1 = first preference, 4 = last preference] for the kind of training that would help to empower you to work with clients with hearing loss and cognitive impairment:" – __ online course/workshop; __ in-person course/workshop; __ book/journal article; __ clinical guidelines/tip sheets).

After initial development, the survey was reviewed by a focus group of approximately ten audiologists from Lions Hearing clinics (Western Australia). Upon providing written informed consent, a 90 min facilitated discussion took place, with participant responses being recorded in a written log. Participants first shared their general reflection about the whole survey, and then addressed individual questions in terms of their clarity and usefulness. Relevant questions were subsequently revised according to the focus group's feedback. Finally, five audiologists pilot-tested the survey to assist in eliminating issues, which included verifying feasibility regarding survey length, layout across different devices, and ease of completion.

### 2.2.2 Participants and survey delivery

The survey was sent via the Qualtrics survey platform (Qualtrics, Provo, UT) to email accounts of currently practising, registered members of Audioloy Australia (AudA), the Australian College of Audiology (ACAud), and Hearing Aid Audiometrist Society of Australia (HAASA), which collectively form the main hearing-healthcare professional bodies in Australia—though, note that registration is not compulsory to practice. The total number of AHHPs who received an invitation email was estimated to be approximately 4,000, which comprised approximately 3,000 AudA members, 816 ACAud members, and 141 HAASA members.

Emails invited recipients to participate in the survey and provided a hyperlink. Participants were required to firstly read a participant information form, and then to provide informed consent if they wished to proceed with the survey. A total of two weeks was given for participants to complete the survey online, with a reminder being sent a week before the survey closed. Once started, the survey had no time limit. For data to be included in analyses, participants had to have: (1) provided informed consent; (2) been living in Australia; and (3) completed more than 20% of the survey.

## 2.3 Data analysis

Data were visualised using Python (Version 3.10.5, Python Software Foundation) and analysed using SAS software (Version 9.4, copyright © 2016 by SAS Institute Inc., Cary, NC, United States). Frequencies and percentages are provided for demographic data (sex, ethnicity, experience, and qualification), as well as each Likert item in the knowledge (all except K12), attitude (all except A7 & A8), and practice (all except P4, P5, P11 & P12) sections; multiple-choice items are presented in bar-graph format, while dichotomous-choice items are discussed in-text. Responses to open-ended items (i.e., P4b, P5b, P7a, P12a, and T1a) are provided in the Supplementary material (see footnote 1); note that there were few responses to these items. Likert-item responses are also presented graphically to demonstrate the balance of agreement across items. In order to determine whether odds of agreement for each Likert item statistically differed between categories of the demographic variables (e.g., sex: male vs. female), binary logistic regression was performed; accordingly, Likert-scale data were dichotomised into positive (i.e., "*strongly agree*" to "*agree*"; "*very frequently*" to "*frequently*"; "*always*" to "*very often*") and negative (i.e., "*strongly disagree*" to "*neutral*"; "*never*" to "*occasionally*"; "*never*" to "*sometimes*") categories. These binary logistic regression analyses were performed at the item level, as the items did not form distinct knowledge, attitude, and practice factors; please see the Supplementary material (see footnote 1) for a report of the exploratory factor analysis performed on our data. The Firth method was used in instances of quasi-complete separation (i.e., knowledge questions 1, 2, 6, and 12; attitude questions 1, 3, and 6; and practice questions 3 to 6). Odds ratios (*ORs*), 95% confidence intervals (95% *CIs*) and *p*-values are provided. Statistical significance was considered at the 5% level. Power calculation indicated a sample size of 351, given a population of 4,000, confidence level of 95%, and margin of error of 5%.

# 3 Results

## 3.1 Participants' demographic information

Of 4,000 invitations, we received 117 responses (response rate of ~2.9%), with 101 meeting inclusion criteria (~ 2.5% of initial invitations). Note that two participants who did not specify their sex were excluded from analysis, as this group size was not large enough to be analysed. In addition, 15 participants failed to complete the entire survey, with 10 of these participants failing to complete over 20%; further, two participants were outside Australia, one did not consent to complete the survey, and two responses were undeleted test previews. Consequently, after taking

1 https://osf.io/t2vgh/

all exclusions and inclusion criteria into account, sample sizes of our analyses ranged between $N = 101$ and $N = 85$ across items. As shown in Table 1, most participants in the final sample were female, identified as Caucasian, held a postgraduate qualification in audiology, and possessed more than 10 years of experience working in the field.

## 3.2 Knowledge

### 3.2.1 Descriptives of knowledge items

As seen in Figure 1, respondents generally showed high awareness of the potential comorbidity between hearing loss and cognitive impairment (K1, $N = 101$), the existence of objective hearing loss assessments for patients with cognitive impairments (K2, $N = 101$), and the need to increase clinic session time and provide alternative care options for comorbid patients (K3, $N = 101$). High awareness was also seen for the need to provide instructions for hearing-aid use in written/visual forms (K6, $N = 100$), how to initiate referral pathways for comorbid patients requiring further hearing loss assessment (K9, $N = 97$), and the need to obtain valuable information through family/carers and their attendance at clinic sessions (K10, $N = 96$).

Conversely, respondents' awareness was mixed for cognitive screening tests that account for hearing loss (K4, $N = 101$), how to incorporate cognitive-support needs in hearing rehabilitation (K7, $N = 99$), and referral pathways for comorbid patients requiring additional cognitive assessment (K8, $N = 98$). Respondents also had more mixed awareness of how to accurately identify cognitive impairments (K11, $N = 96$), and most respondents disagreed that they had the training and expertise to administer cognitive screening tests (K5, $N = 101$). Finally, this section's binary-choice question showed that two-thirds of participants (66.7%) were unaware that all Australian adults over 75 years old were administered a cognitive screening test by their GP (K12, $N = 96$).

TABLE 1 Demographics of survey participants.

| Demographics | Number (%) |
|---|---|
| **Sex** | |
| Female | 77 (76.23%) |
| Male | 24 (23.77%) |
| **Ethnicity** | |
| Caucasian | 68 (67.33%) |
| Asian | 16 (15.84%) |
| European | 10 (9.90%) |
| Other | 7 (6.93%) |
| **Qualification** | |
| Postgraduate* | 64 (63.37%) |
| Bachelor Degree† | 14 (13.86%) |
| Diploma/Certificate† | 23 (22.77%) |
| **Years' experience** | |
| >10 | 64 (63.37%) |
| 5–10 | 20 (19.80%) |
| 2–5 | 9 (8.91%) |
| <2 | 8 (7.92%) |

*Masters or Doctorate, † or equivalent qualification.

### 3.2.2 Binary logistic regression of knowledge items and demographic variables

Binary logistic regression with sex as the predictor identified that females were significantly less likely to agree than males (19.4 and 54.1% respectively) that their training was sufficient to administer and interpret a cognitive screening test (K5; $OR = 0.20$, 95% $CI$ [0.07, 0.54], $p < 0.002$, $N = 101$, $df = 1$). Similarly, females were less likely than males (30.6 and 62.5% respectively) to agree that they knew how to incorporate structured cognitive support needs in hearing rehabilitation (K7; $OR = 0.26$, 95% $CI$ [0.10, 0.69], $p < 0.007$, $N = 99$, $df = 1$). Females were also significantly less aware than males (25.3 and 61.9% respectively) that all adults in Australia over the age of 75 are administered a cognitive screening test by their GP (K12; $OR = 0.22$, 95% $CI$ [0.08, 0.6], $p < 0.004$, $N = 96$, $df = 1$).

Further binary logistic regressions with qualification as the predictor showed that those with a bachelor's degree or equivalent were less likely to agree than those with postgraduate qualifications (78.5 and 95.3% respectively) that hearing-device instructions for those with cognitive impairment should be supplemented with written/visual forms (K6; $OR = 0.18$, 95% CI [0.03, 0.97], $p = 0.046$, $N = 100$, $df = 1$). Lastly, binary logistic regression using ethnicity as a predictor showed that Asian participants were significantly more likely (73.3%) than those of other ethnicities (14.2%) to indicate awareness of how to initiate formal referral pathways for comorbid patients who need further assessment of their memory (K8; $OR = 16.49$, 95% CI [1.48, 182.91], $p < 0.023$, $N = 98$, $df = 1$).

Two additional findings of interest marginally failed to meet statistical significance in our binary logistic regressions with qualification and years of experience as predictors, respectively. For the former, those with a bachelor's degree were less likely (85.7%) than those with a postgraduate degree (98.4%) to know that clients with cognitive impairments require more time and alternative tests (K3; $OR = 0.11$, 95% $CI$ [0.0, 1.01], $p < 0.052$, $N = 101$, $df = 1$). For the latter, participants with 5 to 10 years' experience were less likely to know (22.2%) than those with over 10 years' experience (48.4%) how to incorporate structural cognitive support needs in their practice (K7; $OR = 0.30$, 95% $CI$ [0.09, 1.02], $p < 0.055$, $N = 99$, $df = 1$). All other binary logistic regressions with knowledge items were non-significant.

## 3.3 Attitude

### 3.3.1 Descriptives of attitude items

Figure 2 shows the percentage of responses for each Likert item within the attitude section of the survey. Strong agreement was found for the perceived value of asking patients about memory issues (A1, $N = 96$), difficulty of managing patients with cognitive impairments (A3, $N = 96$), and role of AHHPs in identifying cognitive impairments in patients with hearing loss (A4, $N = 96$); there was also high agreement that AHHPs should refer patients with cognitive impairments to other health professionals for follow-ups (A6, $N = 96$). Respondents had more split agreement in their confidence to ask older patients if they had memory issues (A2, $N = 96$); those who were more confident then showed split agreement on their confidence to have an in-depth discussion with patients about their memory issues

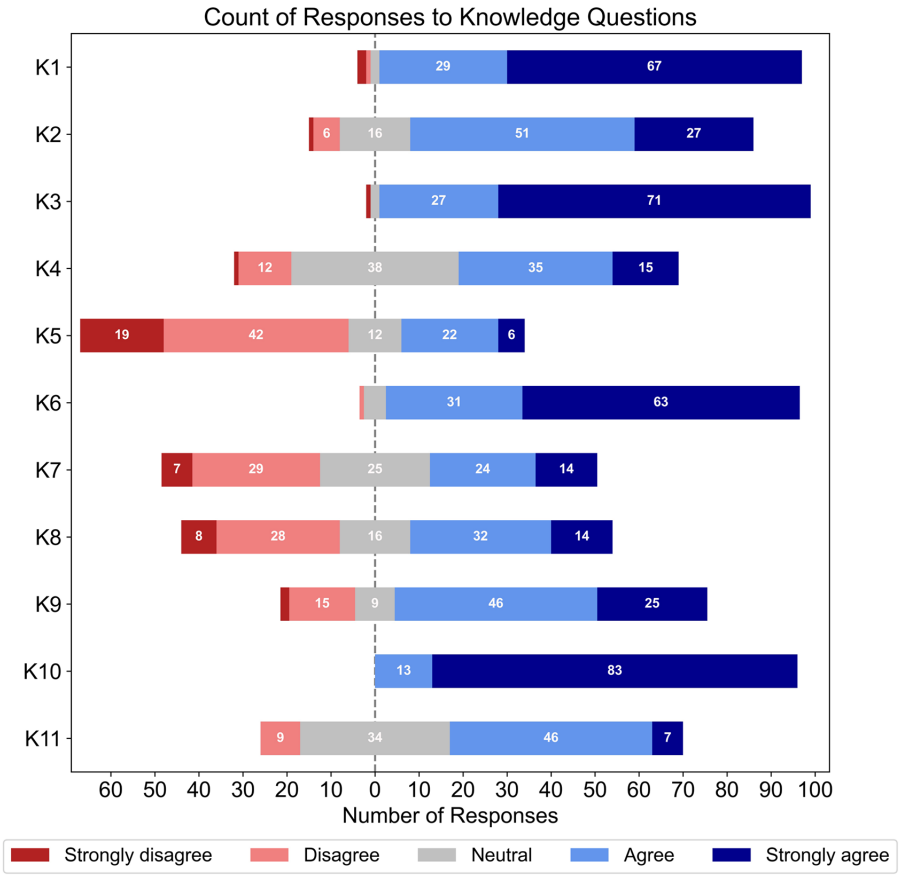


FIGURE 1
Frequencies of responses to each Likert-based item in the knowledge section; note that the total number of responses for each item varied (K1 – K5, $N = 101$; K6, $N = 100$; Q7, $N = 99$; K8, $N = 98$; K9, $N = 97$; and K10 – K12, $N = 96$).

(follow-up question A2a, $n = 60$). Mixed agreement was also found for the appropriateness of AHHPs administering cognitive screening tests to patients with hearing loss (A5, $N = 96$).

As shown in Figure 3, when listing reasons why patients with hearing loss and MCI may experience challenges in using hearing aids (A7, $N = 95$), just over two-thirds of participants (69.2%) listed all reasons; consisting of memory deficits (i.e., forgetting to use or take out device; changing the batteries; misplacing device), and cognitive issues (i.e., unable to indicate if device is broken; trouble following instructions during a clinic session). The remaining half of respondents gave an approximately equal amount of responses for other combinations of the options provided, with most having memory deficits included in their answers. However, when rephrased to ask what reasons patients with hearing loss and dementia may experience challenges in using hearing aids (A8, $N = 95$), 96.8% listed all reasons specified above—see Figure 4.

### 3.3.2 Binary logistic regression of attitude items and demographic variables

Binary logistic regression with sex as the predictor found that females were less confident (56%) than males (85.7%) to ask patients if they had memory issues (A2; $OR = 0.21$, 95% CI [0.05, 0.78], $p < 0.020$, $N = 96$, $df = 1$). Further binary logistic regressions with qualification as the predictor showed that those with a bachelor degree agreed less (64.2%) than those with a postgraduate degree (90.1%) about the value of asking patients about their memory during assessments (A1; $OR = 0.20$, 95% $CI$ [0.05, 0.78], $p < 0.022$, $N = 96$, $df = 1$). Participants with a bachelor's degree were also less likely to agree (57.1%) than participants with a postgraduate qualification (83.6%) that AHHPs have a role to play in identifying cognitive impairments in those with hearing loss (A4; $OR = 0.26$, 95% $CI$ [0.07–0.91], $p < 0.037$, $N = 96$, $df = 1$). All other binary logistic regressions with attitude items were non-significant.

## 3.4 Practice

### 3.4.1 Descriptives of practice items

Figure 5 shows the percentage of responses for each Likert item within the practice section of the survey. Over two-thirds of respondents spoke to their clients about the association between hearing loss and cognitive impairment, with approximately a quarter doing so sometimes (P1, $N = 95$). Most respondents did not conduct cognitive screening as a part of their practice (P4, $N = 95$) and most occasionally or rarely recommended objective hearing assessments if they suspected a patient's cognitive impairment affected their hearing loss tests (P3, $N = 95$). Approximately half of the respondents frequently/very frequently talked to patients about how their cognitive

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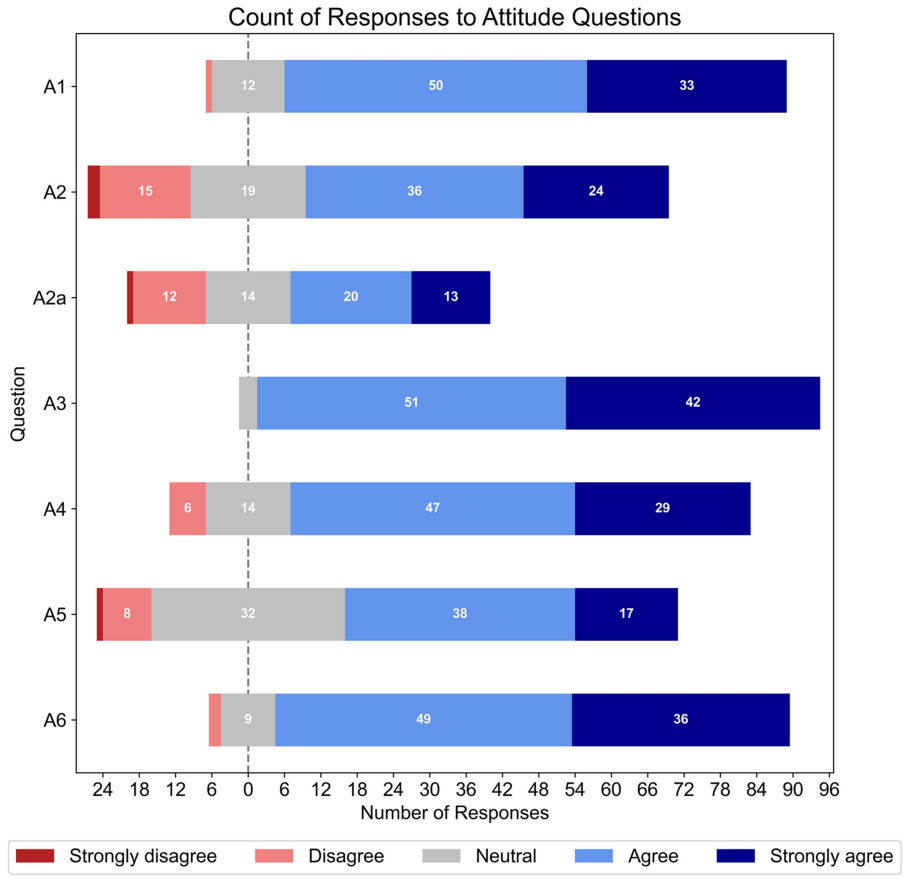


FIGURE 2
Frequencies of responses to each Likert-based item in the attitude section. The total number of responses for each item varied (A1 – A6, $N = 96$; however, Q2a, $n = 60$).

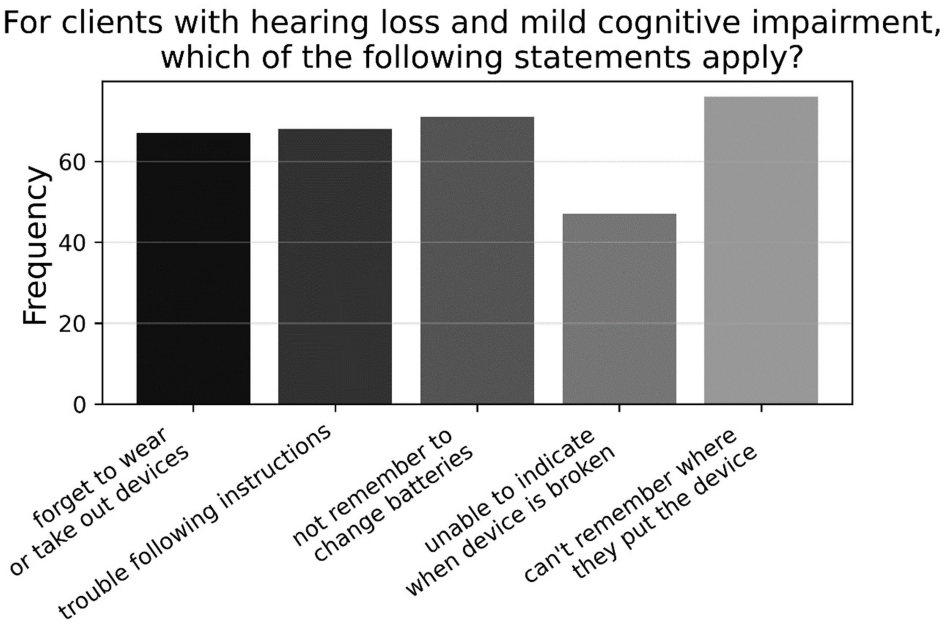


FIGURE 3
Frequencies of responses to multiple-choice-based item A7 in the attitude section ($N = 95$).

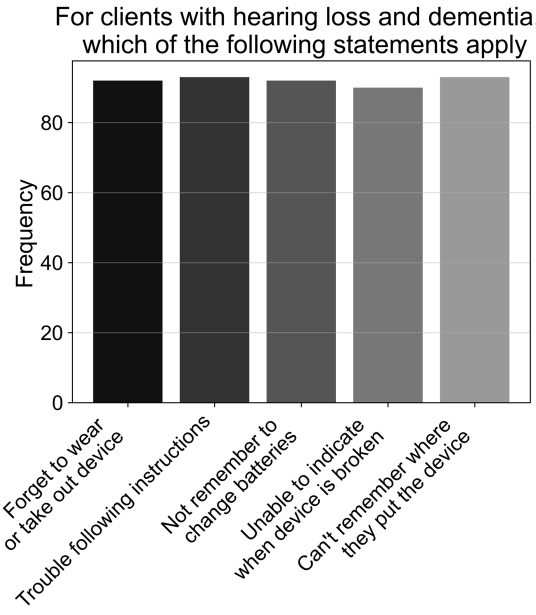


FIGURE 4
Frequencies of responses to multiple-choice-based item A8 in the attitude section ($N = 95$).

impairment could impact their hearing rehabilitation (P6, $N = 95$), and allocated extra time in sessions for patients with suspected comorbidity (P9, $N = 94$). Further, approximately two-thirds of respondents provided instructions for hearing-device use in written or video formats for comorbid patients (P8, $N = 94$). Meanwhile, under half (45.3%) of respondents occasionally asked patients or family/carers about their patient's cognitive functioning (P2, $N = 95$), with 41.2% doing so frequently/very frequently. When asked about having effective tools to help comorbid patients use hearing devices (P7, $N = 94$), 26% strongly disagreed/disagreed, 30.2% were neutral, and 43.7% agreed/strongly agreed. Just over half of respondents also agreed/strongly agreed (59.3%) that their workplace allowed them extra session time to support suspected comorbid patients (P10, $N = 94$), while 23.9% disagreed/strongly disagreed.

Looking at the binary and multiple-choice questions, most respondents had never used a formal cognitive test previously in their practice (77.9%; P5, $N = 95$). As shown in Figure 6, those who had previously used a formal cognitive test had mostly used the MMSE, followed by the (Hi-) MOCA, and GPCOG, with a large proportion using some other task not listed (P5a, $n = 21$). As shown in Figure 7, those who had previously used cognitive screening tests usually did so based on subjective memory complaints from the client or family/carer, or inconsistent hearing-assessment results; less common was the use of cognitive screening tests based on client age, or some unspecified alternative (P4a, $n = 23$).

Further, there was a close split on item P11 ($N = 94$) between respondents who engaged with patients' GPs if they suspected cognitive impairment (57.2%) and those who did not (42.7%). Figure 8 shows that the former preferred to contact GPs by letter, followed by requesting family/carer to contact GP, requesting client to contact GP, email, and phone (P11a, $n = 54$). Finally, as shown in Figure 9, approximately three-quarters of participants (74.5%) indicated that they did not refer any clients to community support services for cognitive impairment (P12, $N = 94$); for those who did refer to such services, Dementia Australia was most popular, followed by Alzheimer's WA and Carers WA, then ESIA Support Groups and Hearing Dogs—eleven respondents referred to some other, unspecified service.

### 3.4.2 Binary logistic regression of practice items and demographic variables

Binary logistic regression with sex as the predictor showed that females were less likely than males (16.2 and 42.8% respectively) to use formal cognitive screening tests as a part of their practice (P5; $OR = 0.26$, 95% $CI$ [0.09, 0.75], $p < 0.014$, $N = 98$, $df = 1$). A further binary logistic regression with qualification as the predictor indicated that participants with a bachelor's degree were less likely (15.3%) than those with a postgraduate degree (47.5%) to ask patients or their families about a patient's cognitive status (P2; $OR = 0.20$, 95% $CI$ [0.04, 0.98], $p < 0.050$, $N = 97$, $df = 1$). All other binary logistic regressions with practice items were non-significant.

## 3.5 Support received and preference for training

Approximately three-quarters of respondents (74.47%; T1, $N = 96$) reported not receiving training to support patients with cognitive impairments. As shown in Figure 10, of those who did receive training, most attended online or in-person workshops, which was followed in popularity by journal articles, unspecified alternative forms of training, and books (T1a, $n = 24$).

When asked to rank their preference for different forms of training aimed at improving care for comorbid patients (T2; $N = 86$; see Figure 11), 85.2% listed online training as either their first or second preference, followed by 60.2% for in-person training in first or second preference. When asked about what contents to include in the training (T3, $N = 85$; see Figure 12), 81.8% of respondents listed "clinical strategies for assessing and rehabilitating hearing-impaired clients with cognitive impairment" as either their first or second preference, while 70.6% of participants listed "how to talk about memory loss with hearing impaired clients" as their first or second preference.

# 4 Discussion

The current study investigated allied hearing-healthcare professionals' (AHHPs) knowledge, attitude, and practice in relation to providing services and care for patients with comorbid hearing loss and suspected cognitive impairment. While our sample size ($N = 101$) was lower than that recommended by our power calculation ($N = 351$), our sample was reasonably reflective of the general AHHP population in Australia—that is, mostly female with postgraduate qualifications (33).

Our findings suggest that AHHPs are highly aware of the established link between hearing loss and cognitive impairment. According to our survey, many AHHPs increased consultation time for clients suspected of having comorbid hearing loss and cognitive impairment, spoke about the effects of cognitive impairment on hearing rehabilitation to their clients, and provided instructions for hearing-aid use in visual formats; these suggest that professional standards for treatment modification in the "Scope of Practice for

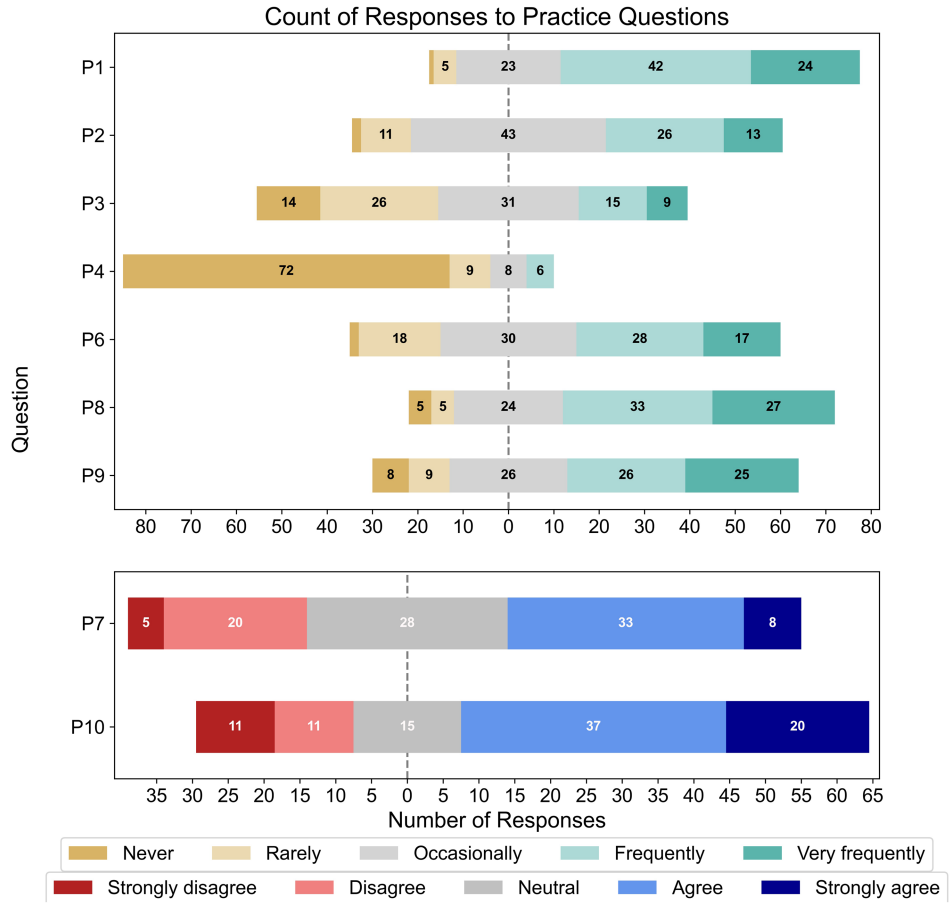


FIGURE 5
Frequencies of responses to each Likert-based item in the practice section; note that the total number of responses for each item varied (P1 – P4, $N = 95$; P6 – P10, $N = 95$).

Audiologists and Audiometrists" (30), namely related to cognitive impairment and hearing loss, are generally being upheld.

However, our results further suggest that AHHPs are not confident in performing cognitive assessments, and have limited training to support comorbid patients with cognitive impairment and hearing loss; both findings are consistent with previous reports (32, 34). Many respondents were also uncertain about the existence of cognitive assessments designed to account for hearing loss [e.g., the Hearing-impaired version of the Montreal Cognitive Assessment (HI-MOCA); (35)].

Furthermore, while our results suggest that AHHPs generally valued asking clients about their cognitive status and being further involved in identifying cognitive impairments, their confidence for performing these tasks was low. This lack of confidence and reduced feeling of responsibility to carry out cognitive testing may have reflected respondents' lack of knowledge and attitudes in other areas of healthcare practice and medical disciplines. For example, there was a relative lack of knowledge about initiating referral pathways for patients requiring further cognitive assessment; further, agreement was lower for the suggestion that AHHPs should be administering cognitive screening tests, which belong to another discipline and may not be generally considered core competency for an AHHP. Another potential contributor to AHHPs' lack of confidence could be related to the negative effects on patient-clinician interaction of a patient having cognitive impairment. [e.g., (36, 37)]. Indeed, discussion of dementia or mild cognitive impairment can be a highly emotional experience for both patient and clinician. To compound this, communication difficulties due to cognitive impairment (38) could contribute to AHHPs apprehension to probe the subject more deeply with a patient or their family. However, as the current study did not assess AHHPs' feelings regarding the emotional aspects of engaging with patients with cognitive impairment, further research is needed on AHHPs' need for training on the emotional aspects of dealing with cognitive impairment.

Moreover, our findings suggest that current practices by AHHPs mainly consist of informal assessment of patients' cognitive status, primarily through direct questioning of patients and/or their family/carers, rather than formal cognitive testing. While this form of assessment has utility to detect subjective memory complaints and cognitive issues, it is markedly less accurate than formal cognitive screening (39); it may also contribute to underdiagnosis of comorbid MCI and hearing loss in audiology clinics. Indeed, while current practices of informal questioning may be sufficient under present professional standards (30), they are likely insufficient to effectively screen for MCI. Thus, adopting assessments like the Dementia Screening Interview, which have been used to assess MCI (40), may allow for minimal changes to current practices that could improve screening outcomes. For further potential improvements to client outcomes, current standards could be modified to require more-robust cognitive screening tools specific to the hearing impaired [e.g., HI-MoCA; (35)], which could be performed by audiologists

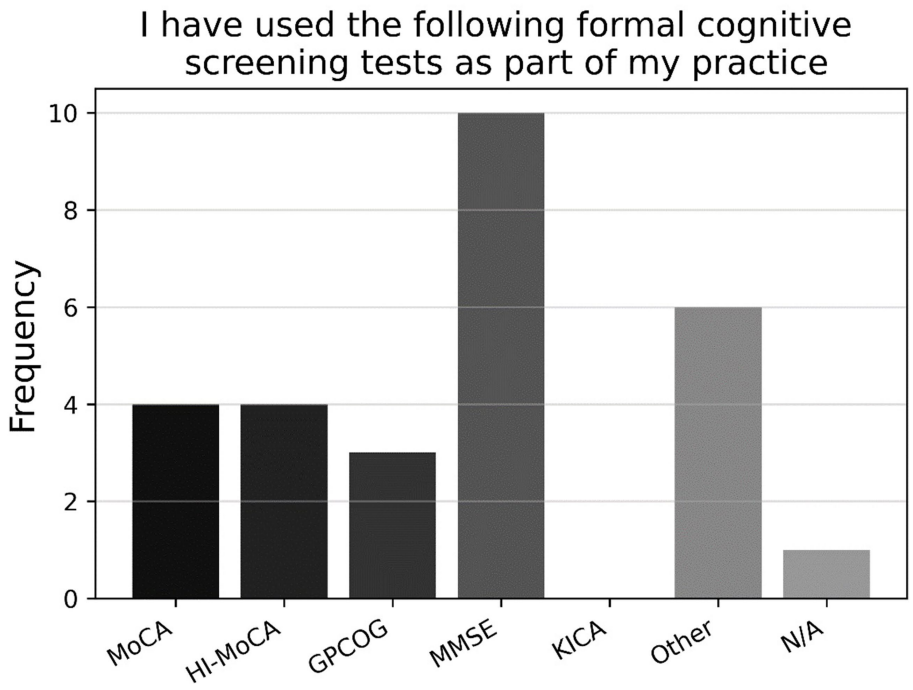


FIGURE 6
Frequencies of responses to multiple-choice-based item P5a in the attitude section ($n = 21$).

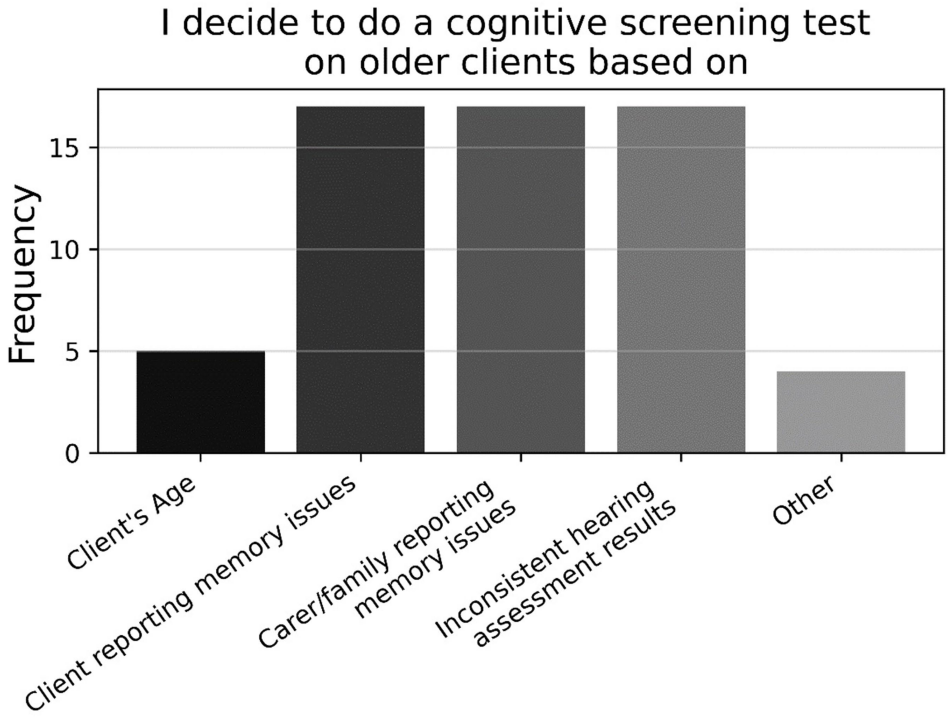


FIGURE 7
Frequencies of responses to multiple-choice-based item P4a in the practice section ($n = 23$).

or through more-formalised referral pathways established in audiological practice. Future work is required to encourage the adoption of formal, objective cognitive tests in audiological practice. Meanwhile, improving interdisciplinary collaboration with other healthcare disciplines and services involved in caring for patients with comorbid hearing loss and cognitive impairment—such as with general practitioners, geriatricians, and memory clinicians—may help to improve AHHPs' knowledge and

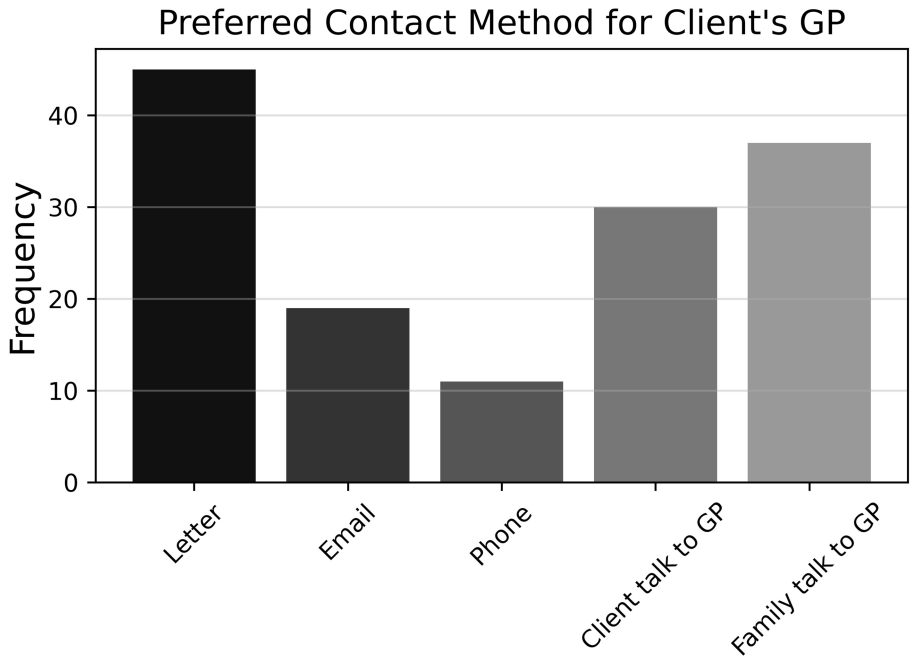


FIGURE 8
Frequencies of responses to multiple-choice-based item P11a in the practice section ($n = 54$).

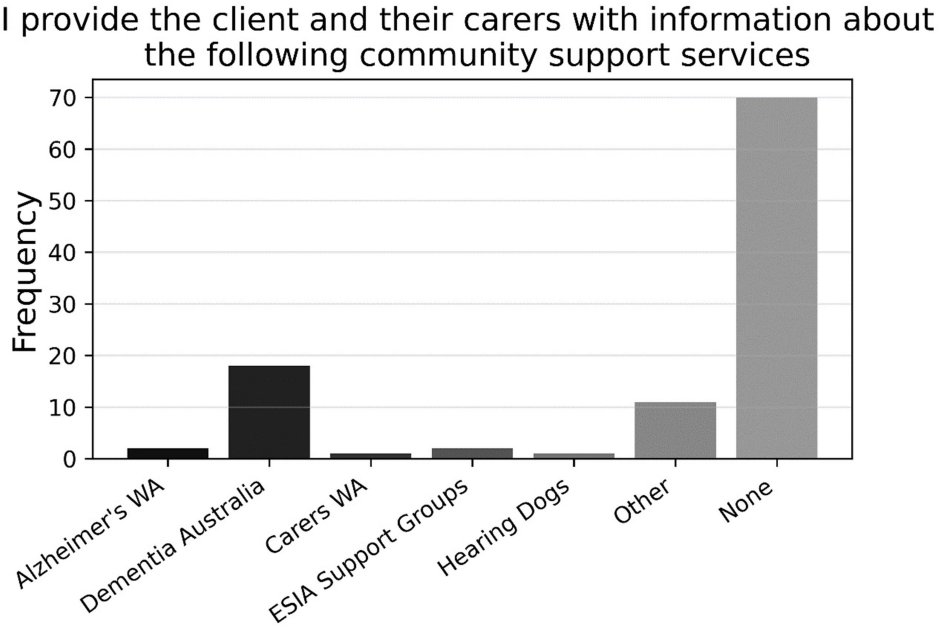


FIGURE 9
Frequencies of responses to multiple-choice-based item P12 in the practice section ($N = 94$).

skills in cognitive assessment. Our study also suggests that some AHHPs tend to adopt informal paths of referral (i.e., asking family and carers to take the client directly to a GP themselves) for patients with comorbid cognitive impairment and hearing loss, namely when further medical and cognitive assessment is needed. This finding further suggests that AHHPs require training to improve their confidence in directly referring clients for further assessment to other health professionals, which would facilitate interdisciplinary communication and collaborative care.

Increased training for AHHPs in cognitive assessment and the management of patients with comorbid hearing loss is also essential. Indeed, approximately 60% of AHHP respondents in our survey had not received formal training for performing cognitive assessments. Of note, there was a general trend for female AHHPs to indicate less

training, experience, and awareness than male AHHPs for cognitive screening and support issues. Furthermore, female AHHPs rated themselves as less confident to ask patients about memory issues, and to administer cognitive screening tests in audiological sessions. However, due to the subjective nature of our primary measure, it is not possible to know whether these observed sex differences were due to objective differences or simply differences in perception of knowledge and skills by female versus male AHHPs. For instance, male AHHPs may have rated their knowledge and experience higher due to overconfidence. Therefore, further investigation is needed to determine whether the observed sex differences are objectively detectable, namely with behavioural measures, or simply subjective due to differences in confidence; this is especially important when considering that females account for the majority of AHHPs in Australia. Moreover, respondents with postgraduate qualifications were more likely than those with bachelor's degrees to value and provide services beneficial to comorbid patients; this may simply reflect the different levels of education and occupational responsibilities that each degree confers. Finally, more years in the hearing-healthcare profession did not coincide with improved knowledge, attitudes, or practices relevant to comorbid hearing loss and cognitive impairment. This finding is perhaps surprising, as one may expect knowledge, attitudes, and practices to improve with greater experience. One possible explanation is that, due to the recent increase in research investigating the link between hearing loss and dementia [for recent reviews, see (5, 41)], audiology courses may be placing greater emphasis on cognitive impairment, thus improving the awareness of newer AHHPs. Conversely, more-experienced audiologists may not have sufficiently focused on the issue of cognitive-impairment. Nevertheless, it is clear that both experienced and inexperienced AHHPs are in equal need of training in the area of comorbid hearing loss and cognitive impairment.

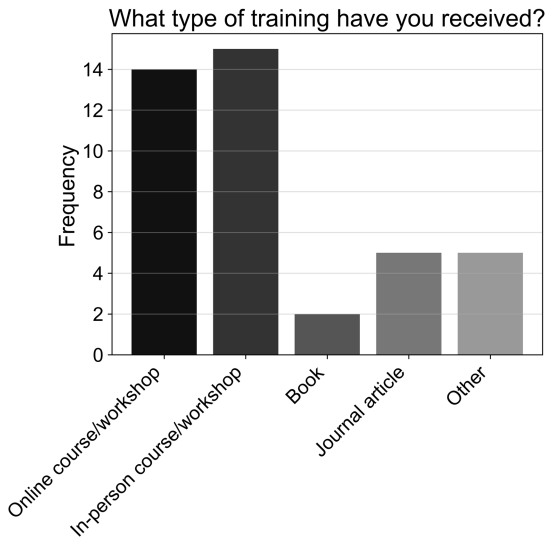


FIGURE 10
Frequencies of responses to multiple-choice-based item T1a in the practice section ($n = 24$).

With respect to types of training, of those who had received cognitive-assessment training, most had done so through online or in-person courses and workshops; these forms of training were also ranked most desirable for future training to improve in this area. AHHPs also reported the most desirable topics for training as being greater information about behavioural issues related to memory problems, and theories and background information about hearing loss and dementia itself. Thus, there is an urgent need for new cognitive-assessment training programs aimed at AHHPs in Australia, with the current findings providing insight into how such programs should be designed and implemented. The aim of such a programme would be to empower AHHPs in Australia to better understand the link between hearing loss and cognitive impairment, gain confidence in caring for comorbid patients at risk, and facilitate improvement of cognitive screening methods in audiology.

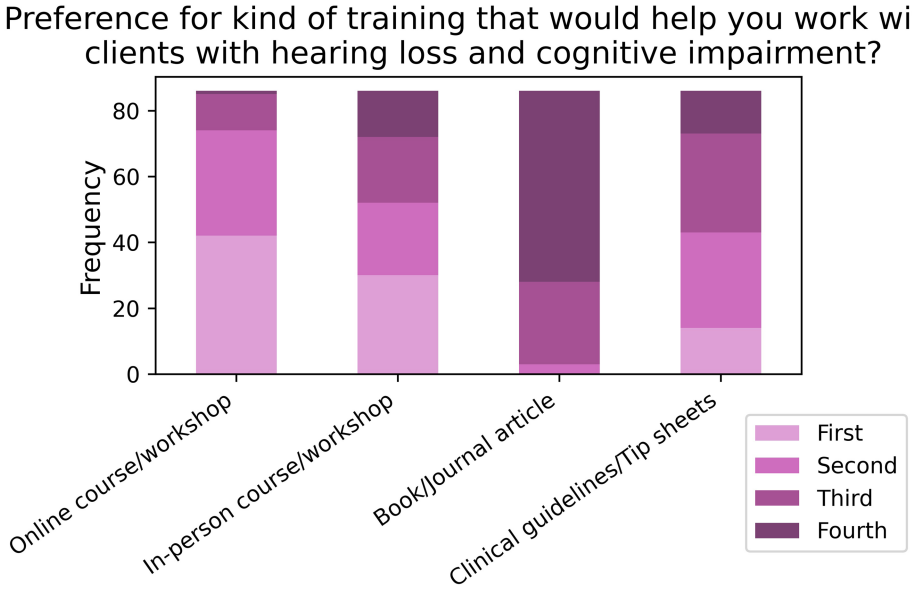


FIGURE 11
Frequencies of responses to rank-based item T2 in the training section ($N = 86$).

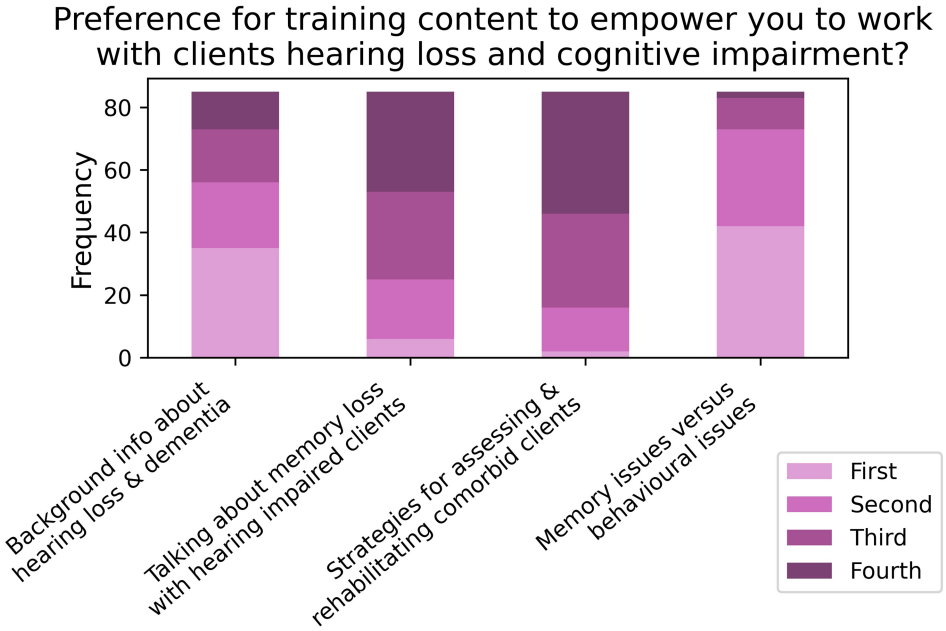


FIGURE 12
Frequencies of responses to rank-based item T3 in the training section ($N = 85$).

## 4.1 Study limitations

Only 117 AHHPs out of 4,000 invited responded to the survey. Indeed, low web-survey response rates among healthcare professionals is a known problem (42), with response rates seeming to vary by specialty (43). For audiology specifically, response rates of 16 and 8% have been shown in an American (44) and Australian KAP studies (45), respectively. While contributing factors have been explored previously (46), it is unclear what contributed to the current study's lower-than-expected response rates (2.9%). Due to this low response rate, it is possible that our sample was biased towards AHHPs with high interest in the survey topic, potentially skewing data towards higher degrees of knowledge, positive attitudes, and current practices. However, a greater number of participants with less interest in the topic would have likely only bolstered the current finding that more training in hearing loss and cognitive impairment comorbidity is needed. Furthermore, the low response rate could reflect the challenges that may be faced when attempting to implement better interdisciplinary clinical practices; that is, it would be more difficult to educate and train a hard-to-reach audience. Future research should therefore seek ways of improving clinician engagement in research within clinics. A further limitation, as mentioned previously, is that only 101 AHHPs data were included after exclusion criteria, meaning we were underpowered based on our power analysis (recommended $N = 351$), so may have failed to detect some genuine effects. Moreover, our analyses had to be done at the item level, as exploratory factor analysis (see Supplementary material) showed that our KAP-survey items did not form knowledge, attitude, and practice factors (i.e., mean scores). This outcome is somewhat unsurprising, as our KAP survey was primarily designed to learn about points of interest in audiological practice, rather than to measure knowledge, attitude, and practice with psychometric precision. However, to simplify future analyses, subsequent research should seek to modify the present KAP survey to better isolate knowledge, attitudes, and practices. Finally, it was noted above that future research could seek to include objective measures of KAPs, as the self-report measures used presently could upwardly bias estimates.

# 5 Conclusion

This study investigated AHHPs' knowledge, attitude, and practices relevant to providing service and care for patients with comorbid hearing loss and cognitive impairment. In summary, AHHPs generally possessed good knowledge of the link between hearing loss and cognitive impairment, and showed generally positive attitudes towards the value and role of AHHPs to support comorbid patients; this was also true of the relevant practices. However, some aspects of knowledge, attitude, and practice demonstrated a need for additional training and support. This finding was bolstered by our observation that training and support aimed at improving service and care for older adult clients with comorbid hearing loss and cognitive impairment has been limited. Consequently, the current findings encourage the development of training and support programs that empower and upskill AHHPs to care for clients with hearing loss and cognitive impairment.

# Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/t2vgh/.

# Ethics statement

The studies involving humans were approved by Human Research Ethics Committee, The University of Western Australia. The studies were conducted in accordance with the local legislation and

institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

DJ: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. EJ: Investigation, Writing – original draft. IL: Methodology, Writing – review & editing. PM: Formal analysis, Writing – review & editing. MT: Formal analysis, Writing – review & editing. DK: Visualization, Writing – review & editing. NM: Conceptualization, Methodology, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1412475/full#supplementary-material

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# Consonant and vowel production in children with cochlear implants: acoustic measures and multiple factor analysis

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**Introduction:** The acoustic limitations of cochlear implants (CIs) can lead to perceptual limitations and consequently to imprecise phonological representations and production difficulties. The aim of the study is to document the phonological and phonetic skills of children with CIs and their typically hearing peers. Phonetically, three types of segments were targeted, each characterized by contrasting acoustic information: nasal/oral vowels, fricative segments, and voiced/voiceless stops.

**Methods:** Forty-seven typically hearing children (TH) and 23 children with CIs performed a picture-naming task. Productions were analyzed to obtain phonological measures (percentages of correct phonemes, types of errors), and various acoustic measures were collected to characterize the productions on the three types of segments investigated. Multiple factor analyses were conducted to study productive profiles on the various acoustic measures, and the dimensions were correlated with phonological measures.

**Results:** The results showed lower performance in lexical (target word retrieval) and phonological (percentages of correct phonemes) skills among children with CIs (CI group), although with better performances among children exposed to CS. Acoustically, children in the CI group exhibited productions significantly different from those of the TH group in terms of the distinction of fricative consonants, marking nasalization through nasal resonance cues, and in the production of voiceless stops. However, the CI group demonstrated compensatory strategies (lengthening of VOT for voiced stops, marking of nasalization through oropharyngeal configuration cues).

**Conclusions:** The results indicate that children with CIs are at risk of experiencing difficulties in both phonetic and phonological domains. However, there are opportunities for compensation through the exploitation of acoustic cues better coded by the CI and/or through perceptual means (utilization of visual cues).

KEYWORDS

**cochlear implant, speech, acoustic, nasal vowels, fricative consonants, stop consonants, multiple factor analysis**

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# 1 Introduction

Cochlear implantation is now commonly provided to people with severe to profound deafness, and has been shown to effectively restore hearing function and promote oral language development in children (Sharma et al., 2020; Tamati et al., 2022). However, numerous studies on speech sound production by children with cochlear implants have shown specificities compared to age-matched peers with typical hearing, as well as significant variability in performance. Difficulties in production can be explained primarily by delayed access to oral language associated with a lack of oral language stimulation during sensitive periods in the development of the auditory areas associated with language. Another explanatory factor is related to perceptual difficulties that may arise from processing speech through a cochlear implant, as productive skills require precise support from acoustically and phonologically specified representations (Stackhouse and Wells, 1993). The cochlear implant degrades the spectral structure of sound before transmitting it to the auditory nerve. This degradation is related to the limited number of electrodes capable of independently coding the frequency information of the original sound without activation diffusion or interactions between adjacent electrodes (channel-to-channel interactions). Furthermore, frequency ranges perceived via the implant may be limited in both high and low frequencies. The coding of low frequencies depends on the shallowness of the array insertion and potential mismatches in frequency mapping (Başkent and Shannon, 2005; Başkent et al., 2016). Frequencies above ~8,000 Hz reach the limits of the processor in current implants (Loizou, 2006; Reidy et al., 2017), meaning that speech sounds with acoustic cues relying on high frequencies are more likely to be perceived and encoded imprecisely by individuals with cochlear implants. The present study aims to investigate how French-speaking children with cochlear implants produce three types of speech segments: nasal and oral vowels, where the distinction is primarily carried by low-frequency information; fricative consonants, where acoustic cues are mainly carried by high-frequency information; and voiced/unvoiced plosive consonants, where the voicing contrast is supported by temporal acoustic cues, presumed to be better encoded by the cochlear implant than spectral cues.

In French, the production of contrastive nasal vowels involves nasal resonance and a specific vowel quality associated with a characteristic oropharyngeal configuration (lip, tongue, and larynx positioning). The acoustic coupling of nasopharyngeal and oropharyngeal cavities results in various acoustic changes compared to oral vowels, including shifts in frequency, intensity, and bandwidth of the first formant (Delattre, 1954; House and Stevens, 1956; Delattre and Monnot, 1968; Maeda, 1993), as well as changes in intensity ratios between the first harmonics and among different formants (Chen, 1995, 1997; Delvaux, 2002; Delvaux et al., 2002). These acoustic differences between vowels contrasting for nasalization necessitate the precise processing of acoustic information with a sufficient degree of frequency selectivity and sensitivity to amplitude variations, particularly among low-frequency harmonics, which may pose challenges for cochlear implant recipients. The study of nasal and oral vowels in CI users has been the subject of a limited number of studies, possibly due to the non-contrastive nature of vowel nasalization in many languages worldwide. However, Bouton et al. (2012) highlighted difficulties in discriminating minimal pairs based on nasal and oral vowels among French-speaking children with cochlear implants, attributing the challenges to insufficient spectral resolution and difficulty in coding low-frequency information. Borel (2015) and Borel et al. (2019) noticed challenges in identifying nasal vowels among adult French speakers with cochlear implants, particularly when these vowels were phonetically similar in oropharyngeal configuration to other oral vowels in the French system. This observation led to the development of a discrimination task involving phonologically contrasting nasal and oral vowels (according to the nasal-oral distinction in the French phonological system: /ã/-/a/, /ɔ̃/-/ɔ/, /ɛ̃/-/ɛ/) as well as phonetically divergent pairs in which the oral and nasal vowels were close in terms of oropharyngeal configuration (/ã/-/ɔ/, /ɔ̃/-/o/, /ɛ̃/-/a/). A recent study (Fagniart et al., 2024) confirmed these findings in children CI recipients, who have greater difficulty discriminating phonetically matched nasal-oral pairs. Intensive exposure to Cued Speech led to a better utilization of temporal acoustic cues, resulting in improved performance in these children. Subsequent analyses of nasal and oral vowel productions from the same children revealed reduced differentiation based on acoustic cues related to nasal resonance, but increased differentiation based on formant frequencies (i.e., oropharyngeal configuration) and segmental length.[1] These results support the hypothesis of increased difficulty in detecting nasal anti-resonances and other acoustic cues related with phonetic nasality, although this can be compensated for by exploiting more accessible cues conveying the oral-nasal contrast such as formant values or temporal differences.

The production of fricative consonants involves a constriction in the vocal tract generating turbulent airflow. The resulting aperiodic signal (noise source) covers a wide frequency range with significant energy in the high frequencies. It is then filtered by the vocal tract, resulting in a concentration of energy in the mid to high frequencies depending on the location of the constriction (place of articulation). Due to limitations in processing high frequencies by the implant processor, these segments are prone to causing perceptual and productive difficulties in CI recipients. Identifying and discriminating the places of articulation is more challenging for children with CIs (Lane et al., 2001; Mildner and Liker, 2008; Bouton et al., 2012), especially for the phonemes /s/ and /ʃ/ (Giezen et al., 2010; Hedrick et al., 2011). On the production side, late and imprecise emergence of fricative consonants has been observed in the phonemic repertoires of children with implants, although performance improves with age and duration of CI use (Warner-Czyz and Davis, 2008). Concerning phonological accuracy, some authors (Kim and Chin, 2008) identified typical error patterns in CI children, which are associated with fortition errors (e.g., cessation of fricatives, devoicing). These errors match those observed in the early stages of phonological development in typically hearing children (Jakobson, 1968), suggesting delayed

1 Fagniart, S., Delvaux, V., Harmegnies, B., Huberlant, A., Huet, K., Piccaluga, M., et al. (under review). Producing nasal vowels without nasalization? Perceptual judgments and acoustic measurements of nasal/oral vowels produced by children with cochlear implants and typically hearing peers. *J. Speech Lang. Hear. Res.*

acquisition patterns that are not unique to CI children. In the same vein, Faes and Gillis (2016) have shown that phonological accuracy in fricative consonants is delayed when comparing CI and typically hearing children based on age, but not when matched in terms of vocabulary size. Several acoustic studies have also documented difficulties related to the production of fricatives segments in children with CI compared to their age-matched typically hearing peers, such as: diminished differentiation in the /s/-/ʃ/ contrast (Mildner and Liker, 2008; Todd et al., 2011; Reidy et al., 2017), specific patterns in implementing the /f/-/s/ contrasts in French (Grandon and Vilain, 2020), and overall lower spectral values (Yang and Xu, 2023).

The production of stop consonants involves the active and complete closure of the vocal tract by movements of the articulators toward each other, followed by a quick opening that releases a burst of acoustic energy. In voiced stops, vocal cord vibration accompanies the closing phase, contributing to the addition of a periodic sound source voiced. Voice Onset Time (VOT) serves as the acoustic marker for the voicing contrast in stop consonants. VOT represents the duration of the period of time between the release of the oral closure and the onset of vocal cord vibration (Lisker and Abramson, 1964). Since the voicing contrast in stop consonants is carried by temporal cues, one could presume that it is appropriately encoded by CI. This was suggested by Bouton et al. (2012), who noted better performance in children with CIs in discriminating minimal pairs opposing stop consonants on the basis of the voicing feature, compared to other distinctive features. However, this finding has not been consistently verified. For instance, Peng et al. (2019) reported lower performance in discriminating minimal pairs involving voiced vs. voiceless stops among young cochlear implant recipients compared to their hearing peers. Studies using categorical perception paradigms have also yielded contradictory results regarding the performance of children with CIs, with some studies showing lower categorical perception (Giezen et al., 2010), while others did not find any difference when compared to typically hearing children (Medina et al., 2004) for the voicing contrast. Few studies have examined VOT measurements to objectively assess how voiced and voiceless stops are distinguished in the speech productions of children with CI. Uchanski and Geers (2003) and Horga and Liker (2006) observed shorter VOT values for voiceless stops, leading to a reduced voiced-voiceless distinction compared to typical-hearing peers. Grandon et al. (2017) observed shorter VOT values for voiceless stops in French-speaking CI children, but only for the velar consonant/k/. Despite the voicing feature of stop consonants being indicated by temporal cues, studies on the perception and production of this distinctive feature show contrasting results, warranting including them in our study of the speech productions of French-speaking children with CI.

As most studies have focused on a single distinguishing feature in isolation, the main purpose of the present study is to document the productive skills of different types of distinction with the same children, to jointly observe their productive profiles based on phonological and phonetic analysis. To this purpose, we focused on three types of segments: nasal/oral vowels, fricative consonants, and stop consonants, to examine whether there are common production profiles across different types of targeted phonetic features. Productions will be collected through a picture-naming task, to study the phonological representations stored in the children's memory. Taking the literature into account, it can be expected that, children with a cochlear implant (CI):

A) May have difficulty finding the precise phonological form of target words considering their perceptual limitations. These difficulties may manifest in lower naming performance (less retrieval of the target word in the first instance) and/or in more phonemic substitution when producing the target word;
B) May distinct nasal and oral vowels relying more on better-encoded cues, like formant frequencies related to oropharyngeal configuration rather than nasal resonance cues (see text footnote 1);
C) May produce fricative consonants with less distinction of place of articulation (Mildner and Liker, 2008; Todd et al., 2011; Reidy et al., 2017; Grandon and Vilain, 2020);
D) May produce voiceless stops with shorter values (Uchanski and Geers, 2003; Horga and Liker, 2006; Grandon et al., 2017).

The originality of the study lies in jointly examining these different segments, aiming to identify distinct profiles of common difficulties and/or compensatory strategies that may be observed among the children. In addition to studying these different hypotheses through comparisons between CI children and typical hearing peers, different variables likely to have an impact on performance will also be studied, namely chronological age as well as hearing age, age of implantation and exposure to Cued Speech among CI children.

# 2 Materials and method

## 2.1 Participants

Two groups of children were recruited: a group of children with typical hearing (TH group) and a group of children with cochlear implants (CI group). The TH group comprises 47 French-speaking children with typical hearing, with an average age of 56 ± 13 months, who do not exhibit any learning delays or auditory disorders. The CI group consisted of 23 French-speaking children (mean age: 67 ± 15 m.) with congenital bilateral profound hearing loss, 22 of whom had bilateral implants, and one child with a unilateral implant. All CI participants received "oralist" auditory rehabilitation, both at their rehabilitation center and in their family environment. This group was divided based on their exposure to Cued Speech: eight of the children were not exposed to CS (CS0), while 15 were exposed to CS during their speech therapy sessions (two at three sessions per week) and/or in their family context (CS1). Implantation age groups were also created, with children who received their first implant before 16 months considered as early implantations (CI/EI, $n = 12$), and those implanted after 16 months considered as late implantations (CI/LI, $n = 11$). The age of 16 months was chosen to be in line with various studies showing a significant benefit from implantation before 18 months (Sharma et al., 2020). Given the distribution of implantation ages, we lowered the threshold to 16 months, enabling us to create equivalent groups. The list of participants and their characteristics are presented in Table 1.

Both groups were divided into three/four chronological age groups: 2;6-3;6 years (only for TH group), 3;7-4;6 years, 4;7-5;6 years, and 5;6-7 years (see Table 2). For children in the CI group,

TABLE 1 Characteristics of the CI children.

| Subject | Sex | Chronological age (years; months) | Chronological age group | Age at first implantation (months) | Implantation age group: early (E)—late (L) | Auditory age group | Implantation type | CS exposure group |
|---|---|---|---|---|---|---|---|---|
| CI1 | M | 4;6 | 3;7-4;6 y. | 9 | E | 2;6-3;6 y. | Bilateral | CS0 |
| CI2 | M | 6;5 | 5;7-7 y. | 39 | L | 2;6-3;6 y. | Bilateral | CS0 |
| CI3 | F | 5;10 | 4;7-5;6 y. | 15 | E | 3;7-4;6 y. | Bilateral | CS0 |
| CI4 | F | 6;7 | 5;7-7 y. | 7 | E | 3;7-4;6 y. | Bilateral | CS0 |
| CI5 | F | 6;6 | 4;7-5;6 y. | 31 | L | 3;7-4;6 y. | Bilateral | CS1 |
| CI6 | F | 4;7 | 4;7-5;6 y. | 7 | E | 3;7-4;6 y. | Unilateral | CS1 |
| CI7 | F | 7;3 | 5;7-7 y. | 13 | E | 4;7-5;6 y. | Bilateral | CS1 |
| CI8 | M | 4;7 | 4;7-5;6 y. | 13 | E | 2;6-3;6 y. | Bilateral | CS1 |
| CI9 | M | 4;9 | 4;7-5;6 y. | 13 | E | 2;6-3;6 y. | Bilateral | CS1 |
| CI10 | M | 4;6 | 3;7-4;6 y. | 12 | E | 2;6-3;6 y. | Bilateral | CS1 |
| CI11 | F | 4;6 | 3;7-4;6 y. | 18 | L | 2;6-3;6 y. | Bilateral | CS1 |
| CI12 | M | 5;6 | 4;7-5;6 y. | 9 | E | 2;6-3;6 y. | Bilateral | CS0 |
| CI13 | F | 7;3 | 5;7-7 y. | 24 | L | 4;7-5;6 y. | Bilateral | CS1 |
| CI14 | G | 7;10 | 5;7-7 y. | 26 | L | 4;7-5;6 y. | Bilateral | CS1 |
| C15 | G | 6;11 | 5;7-7 y. | 23 | L | 4;7-5;6 y. | Bilateral | CS1 |
| C16 | F | 6;9 | 5;7-7 y. | 20 | L | 4;7-5;6 y. | Bilateral | CS1 |
| C17 | M | 6;0 | 5;7-7 y. | 20 | L | 3;7-4;6 y. | Bilateral | CS0 |
| CI18 | F | 3;9 | 3;7-4;6 y. | 23 | L | 3;7-4;6 y. | Bilateral | CS0 |
| CI19 | F | 5;0 | 4;7-5;6 y. | 12 | E | 2;6-3;6 y. | Bilateral | CS1 |
| CI20 | F | 3;8 | 3;7-4;6 y. | 32 | L | 2;6-3;6 y. | Bilateral | CS1 |
| CI21 | M | 4;11 | 4;7-5;6 y. | 11 | E | 2;6-3;6 y. | Bilateral | CS0 |
| CI22 | F | 6;7 | 5;7-7 y. | 17 | L | 2;6-3;6 y. | Bilateral | CS1 |
| CI23 | F | 5;0 | 4;7-5;6 y. | 13 | E | 3;7-4;6 y. | Bilateral | CS1 |





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TABLE 2 Groups and age subgroups distribution.

| Group | Chronological age subgroups years; months (N) | Auditory age subgroups years; months (N) |
|---|---|---|
| CI | 3;7-4;6 y. (5) | 2;6-3;6 y. (11) |
| | 4;7-5;6 y. (9) | 3;7-4;6 y. (7) |
| | 5;7-7 y. (9) | 4;7-5;6 y. (5) |
| TH | 2;6-3;6 y. (9) | N/A (typical hearing) |
| | 3;7-4;6 y. (10) | |
| | 4;7-5;6 y. (17) | |
| | 5;7-7y. (11) | |

auditory age groups were also formed, considering their age from the time of their first implantation.

## 2.2 Data collection and treatment

### 2.2.1 Procedure

Children's speech samples were collected using a picture naming activity (Philippart De Foy et al., 2018). Target words were carefully chosen by the authors to include all French phonemes in initial, medial, or final syllabic position. In addition, these words were selected for their high lexical frequency and early age of acquisition, to facilitate their retrieval by young children. In terms of target segments, the target words contained 25 fricative consonants, 13 nasal vowels and 69 oral vowels, as well as 42 stop consonants.

The target word pictures were presented to the child one at a time via a booklet, and he or she was asked to orally name each picture. Different prompts were provided if the child did not respond or if the produced word did not match the target (semantic paraphasia or random response). First, semantic cues related to the target word were provided (e.g., for example: "you can use it when it rains" for "umbrella"). If the target word was still not produced, a phonological cue was offered by presenting its initial phoneme (e.g., "it starts with/s/" for "/suri/"—mouse). If these two cues were not sufficient for the child to retrieve the target word, the experimenter would produce the target word and ask the child to repeat it. Thus, each target word could be elicited through four types of elicitation: spontaneous naming, naming after semantic prompt, naming after semantic and phonological prompts, or simple repetition. Production based on naming and on repetition can imply different mechanisms: while naming requires retrieval of a phonological form stored in memory, repetition relies on auditory skills while allowing direct imitation of the stimulus. Based on this principle, the effect of the type of elicitation (direct naming or prompt vs. repetition) will also be studied within productions. The children's productions were recorded using a H5 Zoom portable recorder.

### 2.2.2 Phonological analysis

All the audio files were annotated by an initial examiner and subsequently verified by the first author using the Phon 3.1 software (Hedlung and Rose, 2020). By comparing them with the canonical phonological content of the target words, these annotations made it possible to the extraction of the Percentage of Correct Phonemes (PCP), Correct Fricatives (PCF), Correct Nasal vowels (PCN), Correct Stops (PCS), and to identify the various types of production errors made by the children such as substitution based on place or manner of articulation or voicing.

### 2.2.3 Acoustic analysis

The annotations performed in Phon were subsequently exported to Praat (Boersma and Weenink, 2023). Phoneme alignments were manually corrected to enable the use of semi-automated scripts for extracting acoustic measures on the segments of interest.

#### 2.2.3.1 Nasal vowels

The acoustic description of vowels aimed to study the two main aspects of nasal/oral vowel production: the adoption of an articulatory configuration specific to the vowel quality, on one hand, and the resonance with the nasal cavities (only for nasal vowels) on the other hand. To investigate the acoustic characteristics associated with oropharyngeal configuration, formant values were examined. For the study of nasal resonance, Nasalization from Acoustic Features (NAF) values (Carignan et al., 2023) were generated. A total of 6,605 vowels were analyzed.

Formant measurements were obtained using a semi-automated procedure. For F1, F2, and F3, the formant value used is the median value of the series of values obtained every 5 ms in the interval between 25 and 75% of the total vowel duration. Given the sensitivity of formant value detection to spectrogram parameters, particularly in children, several precautions and verifications were implemented to avoid errors in formant detection. Initially, formant detection parameters were adjusted individually for each vowel and child. After extracting the formant values based on these parameters, a visualization of the productions in the F1/F2 space was utilized to identify any aberrant values. Aberrant values were identified by checking if F1, F2, or F3 values fell beyond plus or minus three standard deviations from the mean formant values of the subject. All outliers were manually verified, with spectrograms examined to correct formant values or exclude vowels with unreadable or unclear signals (with a negligible number of occurrences, around 1%).

To assess the degree of nasality in the vowel productions, a procedure largely inspired by the NAF (Nasalization from Acoustic Features) method (Carignan, 2021; Carignan et al., 2023) was employed. First, a large array of measures was collected through semi-automated procedures to extract acoustic indices at 11 time points within the vowels. These measures included overall amplitude, formant bandwidths for F1, F2, and F3, as well as relative amplitude deltas between formants and poles: A1-P0, A1-P1, A3-P0 (measured using the "Nasality Automeasure Praat" script by Styler, 2017) and various indices proposed by Carignan (spectral moments and nasal murmur). Note that some acoustic indices used in Carignan's initial method, such as formant frequency values and Mel-frequency spectral coefficients (MFCC), were not included here since effects pertaining to oropharyngeal configuration alterations were measured separately with formant values. Secondly, a model was built to reduce the various acoustic cues linked to vowel nasality to a value that would characterize the

oral-nasal dimension. Indeed, it is currently complicated to isolate a single acoustic metric to reflect the degree of nasal resonance (Carignan, 2021). Based on this principle, we drew inspiration from the NAF method to build a machine learning model that predicts a metric value quantifying the oral/nasal character of children's productions based on the series of acoustic cues collected. A supervised machine learning technique was employed: the gradient-boosted decision tree model. This technique necessitates training the model on a portion of the data, requiring a training and test sample. For this purpose, part of the time points over which acoustic measurements were collected within each vowel were used for training, the other for testing. To avoid capturing the effects of pre- and post-vocalic phonetic context, we excluded the time points corresponding to the 0, 10, 90, and 100% portions of the vowel, leaving 7 time points. Next, we partitioned the dataset by extracting the time points at 20, 40, 60, and 80% of the duration of each vowel from the children in the TH group to form the training sample. We chose to include these time points because they represent a relatively stable portion of the vowel that is most likely to carry information related to vowel nasality. The training sample was made up of children from the TH group only, so that the model could be trained on supposedly typical productions. Within the training sample, productions were labeled as oral (0) or nasal (1) based on the target vowel to be produced. Subsequently, a gradient-boosting decision tree model (XGBoost R Package, Chen and Guestrin, 2016) was trained on the scaled selected acoustic features with multiple iterations to optimize hyperparameters and minimize cross-validation errors. Finally, the trained model was used to predict nasality responses on the testing sample. The model was defined with minimized linear regression error, to permit the obtention of values on a scale from 0 to 1 on an oral-nasal mapping dimension. The resulting NAF values ranged numerically from 0 to 1, with higher values indicating a higher predicted degree of nasality, and intermediate values corresponding to those that are halfway to the acoustic characteristics of nasal and oral vowels.

To examine strategies employed in the phonetic implementation of the phonological contrast between nasal and oral vowels, paired comparison analyses were conducted, considering the phonetic (/ã/-/ɔ/, /ɔ̃/-/o/, /ɛ̃/-/a/) and phonological (/ã/-/a/, /ɔ̃/-/ɔ/, /ɛ̃/-/ɛ/) proximity (Borel, 2015) of oral-nasal pairs in French. We also included the pairs/ã/-/o/, as the distinction between /o/ and /ɔ/ is sometimes subtle in children's productions, and /ɔ̃/-/u/, as these segments are also very close phonetically (Fagniart et al., 2024). For each child, each produced nasal vowel was paired with all orally produced vowels that were phonetically or phonologically similar, resulting in a listing of all oral/nasal pairs produced. A total of 30,402 pairs were formed, allowing for comparisons of acoustic cues within each nasal-oral pair. Euclidean distances in the F1-F2-F3 (Bark) planes (as described in Calabrino, 2006) and differences between NAF values were examined for each pair.

#### 2.2.3.2 Fricative consonants

The acoustic characterization of fricative consonants was conducted using recently developed measures (Shadle et al., 2023), allowing for the examination of both the place of articulation, i.e., the location of airflow obstruction, and the quality of the frication noise generated by analyzing intensity ratios across low, mid, and high-frequency bands. These measurements were conducted within spectra generated by the Multitaper Method (MTPS; Blacklock, 2004), which averages a series of periodograms obtained through the collection of mutually orthogonal windows (tapers). The MTPS method is renowned for its minimized errors and enhanced temporal precision (Sfakianaki et al., 2024).

A total of 1917 fricatives were analyzed. A R script adapted from the script developed and provided by Reidy et al. (2017)[2] generated a MTPS using eight tapers at the temporal midpoint of the phoneme. Three acoustic measures were then collected from the generated spectra: spectral peak, levelD, and ampDiff for each target sibilant/s,z,ʃ,ʒ/or ampRange for each target non-sibilant/f-v/. The spectral peak was obtained by extracting the frequency of the amplitude peak in the mid frequencies, levelD was obtained by calculating the difference in acoustic power between mid and high frequencies, and ampDiff represented the amplitude difference between low and mid frequencies. It is worth noting that the indices levelD and ampDiff quantify the energy ratios in low, mid, and high frequencies. A good frication noise source should have a significant portion of acoustic energy in mid and, particularly, high frequencies. Therefore, a good noise source should result in high ampDiff values (as mid frequencies are reinforced compared to lows) and low levelD values (indicating a large proportion of energy in high frequencies). These three measures required the definition of ranges for low, mid, and high frequencies within the spectrum. Since there were no references available for young children, these ranges were established through a meticulous analysis of the spectra, employing trial-and-error to identify parameters that most accurately represented our data. Finally, the values proposed by Shadle for adult females (Shadle et al., 2023) with slight modifications were adopted. Notably, the maximum threshold for the mid-frequency range in the detection of spectral peaks for /s, z/ was adjusted to 10,000 Hz instead of 8,000 Hz, and to 8,000 Hz instead of 4,000 Hz for /ʃ, ʒ/.

#### 2.2.3.3 Stop consonants

A total of 3,012 stops were analyzed. To calculate VOT, stop consonants were manually annotated on Praat by identifying the consonant burst, which represents the moment of stop release, and the onset of voicing, which could precede the burst in the case of voiced consonants or follow it in the case of voiceless consonants. Subsequently, a Praat script was used to extract the VOT of all the annotated stops.

## 2.3 Statistical analysis

Linear generalized mixed models, employing the lme4 package (version 1.1-34; Bates et al., 2015) within the R software (R Core Team, 2020), were used to compare groups among the various acoustic measures on the children's speech productions. These models were constructed by including subject and stimulus characteristics (the variables and their levels are specified in Table 3) and the interaction among these variables. It is worth noting that it was the expected segments relative to the target

2 Freely at: https://github.com/MontrealCorpusTools/SPADE/blob/main/jss_sibilant_revised_jm_0618.R.

TABLE 3 Variables related to subject and stimulus characteristics and their levels.

| LGM variables | Variables and their levels |
|---|---|
| Subject characteristics | Auditory status: cochlear implant children (CI) – typical hearing children (TH) |
| | CS exposure: CI/CS0 = no CS exposure - CI/CS1 = CS exposure – TH |
| | Chronological age group: 2;6-3;6/3;7-4;6/4;7-5;6/5;7-7 |
| | Auditory age group: 2;6-3;6/3;7-4;6/4;7-5;6/5;7-7 |
| | Implantation age group: CI/EI = early (<16 m.) – CI/LI = late (>16 m.) – TH |
| Stimulus characteristics | Segment identity:<br>- Nasal/oral pair:/ã/-/a/, /ã/-/ɔ/, /ã/-/o/, /õ/-/ɔ/, /õ/-/o/, /õ/-/u/, /ɛ̃/-/ɛ, /ɛ̃/-/a/<br>- Fricative consonants: /f/-/s/-/ʃ/-/v/-/z/-/ʒ/<br>- Stop consonants: /p/-/t/-/k/-/b/-/d/-/g/ |
| | Voicing type: voiced – voiceless (for fricative and stop consonants) |
| | Elicitation type: naming – repetition |

word that allowed for labeling the identity of the productions. For example, the /ã/ in "pantalon" (/pãtalõ/- "pants") was labeled as/ã/regardless of the actual production of the segment, i.e., even if it was denasalized. To address inter-subject variability, a random intercept effect for the subject was integrated into the model. Significance assessment of fixed effects were examined using Chi-squared tests and corresponding *p*-values, conducted via the ANOVA function of the Car package (Fox and Weisberg, 2018) applied to the model. Additionally, *post-hoc* analysis were conducted using the emmeans package (Lenth et al., 2024).

Multiple factor analyses were conducted using the FactoMineR package (Le et al., 2008), and graphical representations were created using Factoextra (Kassambara and Mundt, 2020). They were performed on a dataset consisting of subject-wise averages of various acoustic measures aggregated as means, namely:

- Euclidean distance values of F1-F2-F3 and NAF for all nasal-oral pairs, where higher average values indicate a greater distinction between nasal and oral configurations in terms of oropharyngeal configuration and nasal resonance.
- Spectral peak values by place of articulation, averaged levelD and ampDiff for fricatives, where one would expect to observe better articulation places marked by higher and well-distinguished spectral peak values, lower values for levelD, and higher values for ampDiff, representing a reinforcement of high-frequency acoustic energy associated with a good frication source (Shadle et al., 2023);
- Mean differences between VOT values of voiceless and voiced stops, where higher values indicate a greater distinction in voicing between voiced and voiceless stops.

The subjects' characteristics (hearing status, age groups, and CS exposure) were added as supplementary variables not actively involved in constructing the dimensions. This addition allows for observing the distribution of different subgroups based on the constructed dimensions. The description of the generated dimensions along with their constituent variables and the additional variables was performed using the dimdesc function (package FactoMineR). Finally, to determine whether a relationship exists between children's phonological performance and their acoustic profiles, we conducted Pearson correlations between the dimensions of the multiple factorial analysis and the various phonological accuracy scores obtained.

# 3 Results

## 3.1 Naming task performance

As explained in Section 2.2.1, children produced all target words of the naming task but may have done so using different types of elicitation: spontaneous naming or after semantic prompt, after semantic and phonological prompts, or through simple repetition. The percentages of the first type of elicitation, spontaneous naming, are significantly higher in the TH group (84.4%) than in the CI group [77.4%; $\chi^2_{(1)} = 4.96$; $p = 0.02$]. No group effect is observed for the second type of elicitation, i.e., naming on semantic cue [TH: 2.79%; CI: 1.96%; $\chi^2_{(1)} = 1.26$; $p = 0.26$], while the third, based on phonological priming, is found significantly more frequently in the TH group [6.22%; CI: 2.03%; $\chi^2_{(1)} = 10.05$; $p = 0.001$]. Production based on repetition of the target word, the fourth type of elicitation, is significantly more common among children in the CI group [18.38%; TH: 5.95%; $\chi^2_{(1)} = 17.06$; $p < 0.001$]. An effect of CS exposure is observed on the percentage of spontaneous naming (elicitation 1): only children in the CI/CS0 group differ significantly from the TH group [70.8%; $t_{(67)} = -13.65$; $p = 0.02$], with the CI/CS1 group showing similar performance [80.3%; $t_{(67)} = -4.15$; $p = 0.47$]. No effect of chronological or auditory age or age of implantation group was observed.

## 3.2 Phonological analysis

The percentages of correct phonemes are analyzed to document phonological accuracy. Children in the CI group have significantly lower percentages of correct total phonemes [CI: 77.5%—TH: 91.1%; $\chi^2_{(1)} = 31.87$; $p < 0.001$], correct nasal vowels [CI: 74%—TH: 91.5%; $\chi^2_{(1)} = 35.43$; $p < 0.001$], correct fricative consonants [CI: 74.3%–TH: 90.4%; $\chi^2_{(1)} = 36.67$; $p < 0.001$] and correct stop consonants [CI: 76.9%–TH: 90.7%; $\chi^2_{(1)} = 29.07$; $p < 0.001$]. Table 4 presents the percentages of different error types on the target segments. The most frequently observed error type is denasalization of nasal vowels with significantly higher rate than TH children [$\chi^2_{(1)} = 27.07$; $p < 0.001$]. Fricativization [$\chi^2_{(1)} = 10.19$; $p = 0.001$] and stopping [$\chi^2_{(1)} = 10.8$; $p = 0.001$] errors are also retrieved at a significantly higher rate in the CI group as well as voicing of voiceless stops [$\chi^2_{(1)} = 25.96$; $p < 0.001$], these errors being negligible in the TH group (<1%). Devoicing errors are retrieved in the two groups, with a marginally higher rate in the CI group [$\chi^2_{(1)} = 3.04$; $p = 0.08$] while nasalization of oral vowels is negligible in the two groups.

CS exposure displays a significant effect on the correct percentages of nasal vowels [$\chi^2_{(2)} = 43.14$; $p < 0.001$], with the

TABLE 4 Percentage correct phonemes among the cochlear implant (CI) and typically hearing (TH) groups.

| Measure | Group performances (%) | | | | Significance of group comparison tests | | | |
|---|---|---|---|---|---|---|---|---|
| | CI | CI/CS0 | CI/CS1 | TH | CI/TH | CI/CS0-CI/CS1 | CI/CS0-TH | CI/CS1-TH |
| % correct phonemes (PCP) | 77.5 | 72.5 | 79.6 | 91.1 | *** | | *** | ** |
| % correct nasal vowel (PCN) | 74.0 | 65.7 | 77.6 | 91.5 | *** | * | *** | *** |
| % correct fricatives (PCF) | 74.3 | 69.4 | 76.5 | 90.4 | *** | | *** | *** |
| % correct stops (PCS) | 76.9 | 71.7 | 79.2 | 90.7 | *** | | *** | *** |
| % vowel nasalization | 0.53 | 1.28 | 0.2 | 0.16 | | ** | *** | |
| % vowel denasalization | 15.25 | 23.23 | 11.76 | 2.65 | *** | * | *** | ** |
| % voicing errors | 2.94 | 3.33 | 2.77 | 0.41 | *** | | ** | *** |
| % devoicing errors | 5.14 | 3.33 | 5.93 | 3.72 | | | | * |
| % stopping errors | 3.37 | 3.33 | 3.38 | 0.56 | ** | | | * |
| % fricativization errors | 1.29 | 2.26 | 0.87 | 0.31 | ** | * | *** | |

ns, *p < 0.05, **p < 0.01, ***p < 0.001.

CI/CS1 group showing significantly higher score than the CI/CS0 group [77.6 vs. 65.7; $t_{(67)} = -11.8$; $p = 0.05$] but lower than the TH group [$t_{(67)} = -13.9$; $p < 0.001$]. As for the different error types, the CS/CS0 group also shows higher percentages of nasalization of oral vowels and of fricativization of stops than the two other groups. For nasal vowels denasalization, the CI/CS1 group show lower error percentages than the CI/CS0 group but the percentage remain higher than the TH group. Devoicing of voiced stops was observed at a higher percentage in the CI/CS1 group compared to the two others. No effect of chronological or auditory age was observed, nor were there any effects of the age group at implantation.

## 3.3 Acoustic analysis

Table 5 presents the means, as well as the significance of the associated group comparison tests, for the various acoustic measurements carried out on the studied segments, grouped according to auditory status (TH vs. CI) and exposure to CS (CS0 vs. CS1).

### 3.3.1 Nasal/oral vowels

This section will focus on the analysis of acoustic differences within pairs of nasal-oral vowels. Formant and NAF values averaged per target phoneme and per child group, as well as the *p*-values associated with group difference tests, are available in the appendices. Considering nasal-oral pairwise comparisons in terms of Euclidean distances in the F1/F2/F3 plane, an auditory group*pair interaction is observed [$\chi^2_{(7)} = 201.6$; $p < 0.001$]. The CI group exhibits higher values for 5 out of 8 pairs, indicating a greater differentiation in terms of oropharyngeal configuration for these pairs, namely/ã/-/o/, /ɔ̃/-/o/, /ɔ̃/-/ɔ/, /ɔ̃/-/u/, and /ɛ̃/-/a/pairs (see Figure 1). An interaction between elicitation type (naming vs. repetition), pair, and group is observed [$\chi^2_{(21)} = 330.6$; $p < 0.001$]. Indeed, the CI group show higher Euclidean distances between oral and nasal vowels in the repetition condition for all pairs except /ã/-/a/ and /ɛ̃/-/a/, while the TH group shows higher values in the repetition condition for /ã/-/a/, /ɔ̃/-/ɔ/, /ɛ̃/-/a/, and /ɛ̃/-/ɛ/. A significant CS exposure group*pair interaction is also found [$\chi^2_{(14)} = 309.55$; $p < 0.001$], with the TH group showing lower values than the CI/CS0 and CI/CS1 groups for /ɔ̃/-/o/ and /ɔ̃/-/u/, while the CI/CS0 group shows the highest values compared to other groups for /ã/-/o/ and the lowest for /ɛ̃/-/ɛ/. An interaction between elicitation type (naming vs. repetition), pair, and CS exposure group is also observed [$\chi^2_{(35)} = 466.1$; $p < 0.001$]. While the CI/CS1 group showed higher values in the repetition condition for all the pairs except/ɛ/-/a/, the CI/CS0 group is characterized by higher values only for /ɔ̃/-/u/ and /ɛ̃/-/a/, with, conversely, lower values in the repetition condition for /ɛ̃/-/ɛ/ and /ã/-/a/. An interaction between chronological/auditory age group, auditory status group, and pair is observed. Indeed, an auditory age group effect is only observed in the /ɔ̃/-/u/pair, with decreasing values for age groups following 3;7-4;6. In the TH group, a chronological age group effect was observed in /ã/-/a/, /ã/-/ɔ/, and /ã/-/o/, with decreasing values in older age groups. When comparing the groups based on age of implantation, there's an observed interaction effect between the age of implantation groups and pair [$\chi^2_{(14)} = 299.1$; $p < 0.001$]. Specifically, the group of children with later implantation (CI/LI) shows significantly higher values than the group of children with early implantation (CI/EI) for the pair /ɔ̃/-/ɔ/.

The statistical analysis of nasal/oral differences in terms of NAF values revealed an interaction between auditory status group and pair [$\chi^2_{(7)} = 201.5$; $p < 0.001$], with significantly higher values in the TH group for the /ã/-/o/, /ɔ̃/-/o/, /ɔ̃/-/ɔ/, /ɔ̃/-/u/ and /ɛ̃/-/a/ pairs. An interaction between elicitation type, group, and pair

TABLE 5 Acoustic analysis according to auditory status and exposure to Cued Speech (CS).

| Segment type | Measure | Target vowel | Group means | | | | Significance of group comparison tests | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CI | CI/CS0 | CI/CS1 | TH | CI—TH | CI/CS0—CI/CS1 | CI/CS0—TH | CI/CS1—TH |
| Vowel | E.D. F1-F2-F3 (brk) | /ã/-/a/ | 4.41 | 4.39 | 4.42 | 4.6 | | | | |
| | | /ã/-/ɔ/ | 3.62 | 3.34 | 3.72 | 3.49 | | | | |
| | | /ã/-/o/ | 3.45 | 3.97 | 3.28 | 3.06 | * | * | ** | |
| | | /õ/-/ɔ/ | 4.01 | 3.5 | 4.19 | 3.68 | * | * | | * |
| | | /õ/-/o/ | 3.42 | 3.47 | 3.42 | 2.74 | *** | | * | ** |
| | | /õ/-/u/ | 3.32 | 3.52 | 3.27 | 2.84 | ** | | * | * |
| | | /ɛ̃/-/ɛ/ | 3.97 | 3.37 | 4.17 | 4.01 | | * | * | |
| | | /ɛ̃/–/a/ | 3.14 | 3.11 | 3.16 | 2.86 | 0.06 | | | |
| | delta NAF | /ã/-/a/ | 0.114 | 0.08 | 0.13 | 0.17 | *** | | ** | * |
| | | /ã/-/ɔ/ | 0.019 | 0.002 | 0.027 | 0.06 | *** | | * | |
| | | /ã/-/o/ | 0.071 | 0.034 | 0.087 | 0.127 | ** | | ** | * |
| | | /õ/-/ɔ/ | 0.052 | 0.05 | 0.05 | 0.11 | *** | | ** | * |
| | | /õ/-/o/ | 0.109 | 0.097 | 0.114 | 0.178 | *** | | | ** |
| | | /õ/-/u/ | 0.051 | 0.062 | 0.045 | 0.08 | * | | | * |
| | | /ɛ̃/-/ɛ/ | 0.076 | 0.05 | 0.08 | 0.113 | * | | | |
| | | /ɛ̃/-/a/ | 0.08 | 0.06 | 0.09 | 0.124 | ** | | * | * |
| Fricatives | Spectral peak (Hz) | /f/ | 6,689 | 6,009 | 6,990 | 7,611 | *** | * | *** | * |
| | | /s/ | 6,085 | 5,749 | 6,232 | 6,702 | ** | | * | |
| | | /ʃ/ | 4,720 | 4,207 | 4,943 | 5,014 | | 0.08 | * | |
| | | /v/ | 6,421 | 5,948 | 6,620 | 6,618 | | | | |
| | | /z/ | 5,775 | 5,284 | 5,981 | 6,925 | *** | | ** | * |
| | | /ʒ/ | 4,921 | 4,302 | 5,198 | 4,587 | | | | |
| | levelD (dB) | /f/ | 6 | 7.81 | 5.21 | 3.93 | * | | ** | |
| | | /s/ | 6.98 | 8.89 | 6.17 | 2.72 | *** | | *** | ** |
| | | /ʃ/ | 8.27 | 10.4 | 7.34 | 7.29 | | 0.07 | * | |
| | | /v/ | 5.19 | 5.13 | 5.17 | 5.26 | | | | |
| | | /z/ | 6.99 | 7.96 | 6.57 | 1.89 | *** | | *** | *** |
| | | /ʒ/ | 8.46 | 10.23 | 7.67 | 9.23 | | | | |

*(Continued)*





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TABLE 5 (Continued)

| Segment type | Measure | Target vowel | Group means | | | Significance of group comparison tests | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | CI | CI/CS0 | CI/CS1 | TH | CI—TH | CI/CS0—CI/CS1 | CI/CS0—TH | CI/CS1—TH |
| | ampDiff (dB) | /f/ | 13.99 | 13.69 | 14.13 | 13.13 | | | | |
| | | /s/ | 19.09 | 22.23 | 17.77 | 16.91 | * | * | ** | |
| | | /ʃ/ | 19.11 | 20.43 | 18.55 | 19.38 | | | | |
| | | /v/ | 12.93 | 14.6 | 12.26 | 11.42 | | | | |
| | | /z/ | 16.16 | 13.15 | 17.34 | 13.21 | ** | 0.08 | | ** |
| | | /ʒ/ | 16.06 | 16.54 | 15.84 | 16.63 | | | | |
| Stops | VOT (ms) | /p/ | 23 | 29.6 | 20.1 | 32.1 | * | | | * |
| | | /t/ | 34 | 33 | 34.4 | 44.6 | * | | | |
| | | /k/ | 38.2 | 34.8 | 39.7 | 45.3 | | | | |
| | | /b/ | −57.3 | −67.5 | −53.4 | −48.9 | 0.07 | | * | |
| | | /d/ | −78.8 | −87 | −75.7 | −57.3 | * | | 0.09 | |
| | | /g/ | −42.6 | −60.2 | −36.7 | −36.6 | | | | |

ns, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

[$\chi^2_{(21)} = 155.9$; $p < 0.001$] was also observed. Indeed, while TH children benefited from repetition which results in an increase in nasal-oral differences in terms of NAF for the pairs /ã/-/a/, /ã/-/ɔ/, /õ/-/ɔ/ and /õ/-/u/, for children in the CI group this is only the case for the pairs /ɛ̃/-/ɛ/ and /ɛ̃/-/a/. On the contrary, children in the CI group showed a decrease in NAF values in the repetition condition for the pairs /ã/-/a/, /ã/-/ɔ/, /õ/-/o/, /õ/-/ɔ/ and /ɔ/-/u/. Considering CS exposure, an interaction between CS exposure and pair is observed [$\chi^2_{(14)} = 131.6$; $p < 0.001$]. Indeed, the CI/CS0 group had lower values compared to the two other groups for the /õ/-/o/ pair and lower compared to the TH group for the /ã/-/ɔ/ pair. The TH group shows the highest values compared to the other groups for the /ɛ̃/-/a/ pair. An interaction between elicitation type and CS exposure group [$\chi^2_{(2)} = 62$; $p < 0.001$], as well as between elicitation type, CS group, and pair [$\chi^2_{(35)} = 280.9$; $p < 0.001$], was observed. Indeed, while children in the TH and CI/CS0 groups benefited from the repetition condition by seeing their nasal/oral difference values in terms of NAF increase, children in the CI/CS1 group see their overall values decrease. The increase in values in the repetition condition was found significant in the TH group for the /ã/-/a/pairs, /ã/-/ɔ/, /õ/-/ɔ/, /õ/-/u/ and in the CS0 group for the pairs /ã/-/ɔ/, /õ/-/u/, /ɛ̃/-/ɛ/ and /ɛ̃/-/a/. In the CS1 group, values were significantly lower in the repetition condition for the pairs /ã/-/ɔ/, /õ/-/ɔ/, /õ/-/u/. Again, an interaction between chronological/auditory age group, auditory status group, and pair is observed [$\chi^2_{(52)} = 323.2$; $p < 0.001$]. Indeed, a chronological age effect was observed for /ã/-o/, /õ/-o/, /ɛ̃/-ɛ/ and /ɛ̃/-/a/ in the TH group with no increasing chronological/auditory age effect on values in the CI group. In comparing the groups formed on the basis of age of implantation, an interaction effect between age of implantation and the pair is observed [$\chi^2_{(14)} = 108.1$; $p < 0.001$]. Specifically, the group of children with early implantation (CI/EI) exhibited significantly higher values than the group of children with later implantation (CI/LI) for the pair /õ/-/ɔ/.

### 3.3.2 Fricative consonants

Concerning spectral peak values, an auditory status group effect is observed, indicating lower values in the CI group [$\chi^2_{(1)} = 9.4$; $p = 0.002$]. A significant interaction effect is observed between group and phoneme type [$\chi^2_{(5)} = 23.9$; $p < 0.001$], with significant group differences noted for the phonemes /f/, /s/, and /z/, suggesting a more posterior place of articulation for these segments in the CI group (see Figure 2). This spectral peak decreased values have an impact on the distinction of the different places of articulation: the CI group shows no significant differences between places of articulation among the voiceless /f/-/s/, /s/-/ʃ/ and the voiced fricatives /v/-/z/ and /z/-/ʒ/, while this phonemes are significantly distinguished in the TH group (/f-s/: $z = 5.8$; $p < 0.001$ -/v-z/: $z = 11.2$; $p < 0.001$ -/z/-/ʒ/: $z = 10.8$; $p < 0.001$]. An elicitation type*auditory status group interaction effect is observed [$\chi^2_{(5)} = 506.6$; $p = 0.05$]. Indeed, while the repetition condition led to increasing spectral peak values in the TH group, it led to decreased values in the CI group. This effect is significant in the TH group for /f/ [naming: 7,566 Hz—repetition: 9,342 Hz; $t_{(1,890)} = -2.5$; $p = 0.01$] and marginal in the CI group for /v/ [naming: 6,538 Hz–repetition: 4,641 Hz; $t_{(1,890)} = 1.8$; $p = 0.07$]. An interaction

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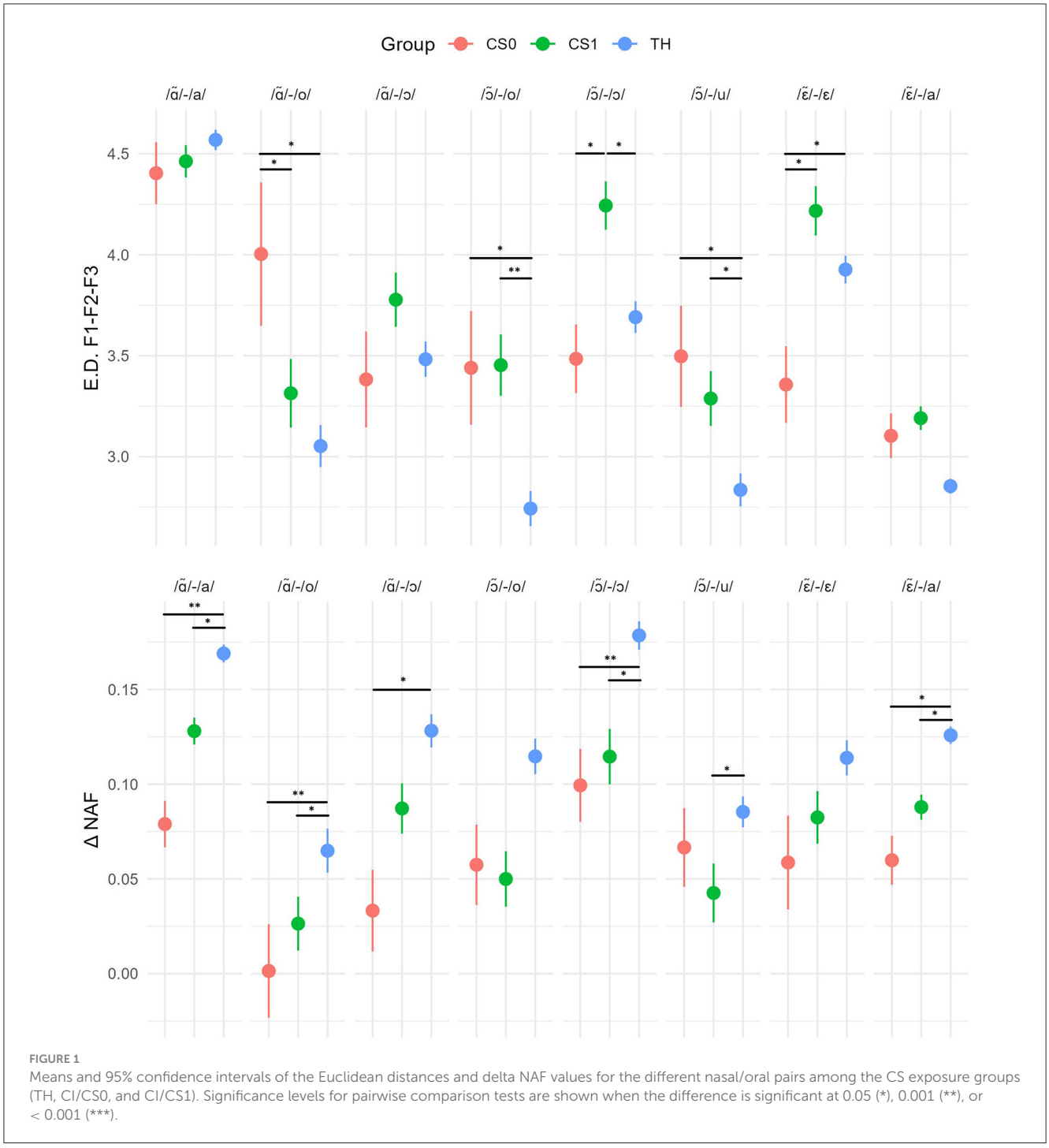


FIGURE 1
Means and 95% confidence intervals of the Euclidean distances and delta NAF values for the different nasal/oral pairs among the CS exposure groups (TH, CI/CS0, and CI/CS1). Significance levels for pairwise comparison tests are shown when the difference is significant at 0.05 (*), 0.001 (**), or < 0.001 (***).

between chronological/auditory age group, auditory status group and phoneme effect is observed [$\chi^2_{(35)} = 66.0$; $p = 0.001$]: while no chronological/auditory group effect appears in the CI group, an effect of chronological age is observed in the TH group, with spectral peak values decreasing with age for /f/ and /s/, resulting in improved distinction of articulation places among voiceless fricatives /f/, /s/, /ʃ/. A CS exposure grouping effect [$\chi^2_{(2)} = 14.7$; $p < 0.001$] as well as an interaction between CS grouping and phoneme [$\chi^2_{(10)} = 28.4$; $p = 0.001$] are obtained: spectral peak values are significantly lower in the CI/CS0 group compared to the TH group ($z = -3.5$; $p = 0.001$) and marginally to the CI/CS1 groups ($z = -2.1$; $p = 0.09$), while the TH and the CI/CS1 group had similar mean values. Regarding phoneme type, CI/CS0 had significantly lower values for /f/ compared to TH ($z = -4.4$; $p < 0.001$) and CI/CS1 group ($z = -2.7$; $p = 0.02$), as well as marginally lower values than TH group for /ʃ/ ($z = -2.1$; $p = 0.08$) and /v/ ($z = -2.2$; $p = 0.08$). For /s/ and /z/, TH group has significantly higher spectral peak values than the other two groups. An effect of age of implantation group [$\chi^2_{(2)} = 10.1$; $p = 0.006$] as well as an interaction between age of implantation group and phoneme type is observed [$\chi^2_{(10)} = 30.5$; $p < 0.001$]. Specifically, values are generally lower in the late implantation group compared to the TH group ($z$

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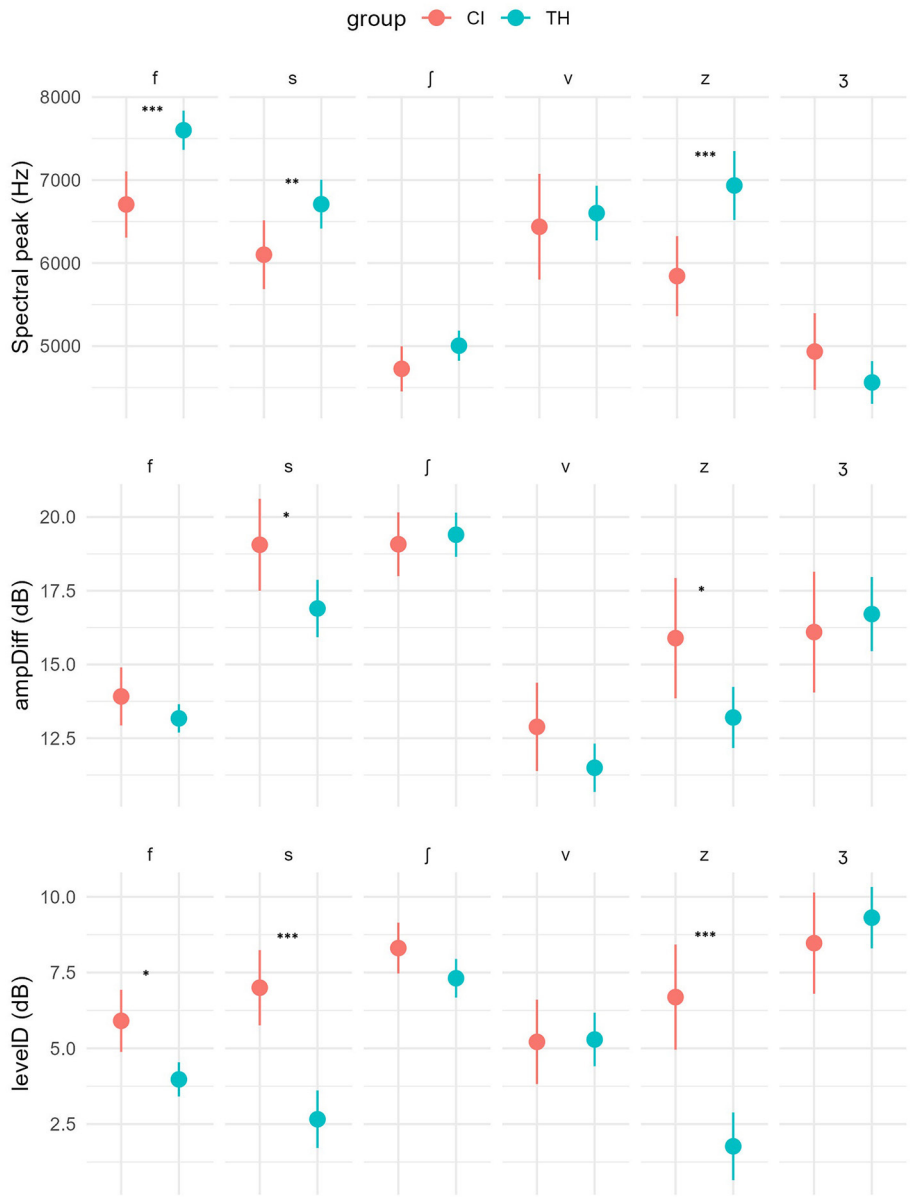


FIGURE 2
Means and 95% confidence intervals of the spectral peak, ampDiff, and levelD values of the different fricative segments of the CI and TH groups. Significance levels for pairwise comparison tests are shown when the difference is significant at 0.05 (*), 0.001 (**), or < 0.001 (***).

$= -2.9$; $p = 0.008$), with this difference being significant for the phoneme/z/ ($z = -3.6$; $p < 0.001$).

AmpDiff values, which reflects amplitude differences between mid- and low-frequency ranges within the fricative spectrum, exhibited an auditory status group effect [$\chi^2_{(1)} = 3.5$; $p = 0.05$], with lower values in the TH group, as well as a group*phoneme interaction effect [$\chi^2_{(5)} = 13.5$; $p = 0.02$] with significantly lower values in the TH group for /s/ ($z = 2.8$; $p = 0.004$) and /z/($z = 2.9$; $p = 0.003$). The higher values observed in the CI group may indicate greater reinforcement of mid-frequency areas compared to TH children. No elicitation type effect was observed. A voicing type effect is observed [$\chi^2_{(1)} = 71.6$; $p < 0.001$], with a significant decrease of the voiced fricatives ampDiff values in the TH ($z = 7.4$; $p < 0.001$) and the CI group ($z = 4.3$; $p < 0.001$), as expected. An interaction between chronological/auditory age group, auditory status group and phoneme are obtained [$\chi^2_{(15)} = 56.7$; $p < 0.001$]: ampDiff values increase with chronological age in the TH group for all phonemes except/f/, while CI group displays a decrease of the values in the older auditory age group for /s/. An interaction between CS exposure and phoneme is observed [$\chi^2_{(10)} = 34.4$; $p < 0.001$], with significantly higher values in the CI/CS1 group compared to the CI/CS0 ($z = -2.3$; $p = 0.06$) and TH groups ($z = 3.5$; $p = 0.001$) whereas the CI/CS0 group had significantly higher AmpDiff values for /s/ compared with the TH group ($z = 2.9$; $p = 0.01$). No effect of implantation group is observed on the ampDiff values.

Regarding the levelD values, which reflects sound level differences between the mid- and high frequency ranges, a

significant group effect was observed, with significantly higher values in the CI group [$\chi^2_{(1)} = 5.6$; $p = 0.01$] as well as a group*phoneme interaction effect [$\chi^2_{(5)} = 98.6$; $p < 0.001$], with values significantly higher for /f/, /s/ and /z/ in the CI group. The higher values of the levelD values in the CI group indicate less reinforcement of high frequencies compared to children in the TH group. An interaction between elicitation type and group was observed [$\chi^2_{(5)} = 47.4$; $p < 0.001$], with repetition condition leading to higher levelID values in the CI group only [naming: 6.7 dB—repetition: 8.9 dB; $t_{(1,891)} = -2.4$; $p = 0.01$]. This trend was significant for /v/ in the CI group [naming: 4.8 dB—repetition: 10.3 dB; $t_{(1,869)} = -1.9$; $p = 0.04$], while in the TH group the repetition condition led to significantly decreased values for /f/ [naming: 3.9 dB—repetition: 0.2 dB; $t_{(1,832)} = 2.1$; $p = 0.03$] and marginally so for /ʃ/ [naming: 7.3 dB—repetition: 3.4 dB; $t_{(1,835)} = 1.9$; $p = 0.06$]. Considering voicing, a marginal group*voicing interaction effect was observed [$\chi^2_{(1)} = 2.7$; $p = 0.09$], with a significant decrease of levelD values for the voiced fricatives only in the TH group ($z = -2.6$; $p = 0.007$). An interaction between chronological/auditory age group, auditory status and phoneme was observed [$\chi^2_{(15)} = 25.4$; $p = 0.04$], with no chronological/auditory age group effect in the CI group, compared to decreased values in older children of the TH group for /f/, /s/, /ʃ/ and /z/. A CS exposure grouping effect [$\chi^2_{(2)} = 7.3$; $p = 0.02$] as well as an interaction between CS grouping and phoneme were observed [$\chi^2_{(10)} = 106.9$; $p < 0.001$]. Indeed, levelD values were significantly lower in general in the CI/CS0 group compared to the TH group, but significantly lower values in the TH group for the phoneme /s/ and /z/, compared to the other two groups. An elicitation type*CS exposure group interaction effect was also retrieved [$\chi^2_{(2)} = 10.1$; $p = 0.006$], with higher values for CI/CS0 group for /f/ compared to CI/CS1 [$\chi^2_{(157)} = 2.3$; $p = 0.06$] and TH group [$\chi^2_{(210)} = 1.9$; $p < 0.001$], with significantly lower values for /z. CI/CS1 had lower values than the CI/CS0 group for /ʃ/ in the repetition condition [$\chi^2_{(231)} = 2.6$; $p = 0.02$]. An effect of age of implantation [$\chi^2_{(2)} = 6.1$; $p = 0.04$] in interaction between group and phoneme type [$\chi^2_{(10)} = 55.7$; $p < 0.001$] was observed. Specifically, the later implanted children showed significantly higher values than the TH children ($z = 2.45$; $p = 0.04$) for the phonemes /f/ and /s/.

### 3.3.3 Stop consonants

An interaction between auditory status group and voicing type (voiced vs. voiceless) was observed on the VOT of the stop consonants [$\chi^2_{(1)} = 30.58$; $p < 0.001$], with higher VOT for voiceless stops and lower for voiced stops in the TH group when compared to the CI group. Phoneme*group pairwise comparisons shown that this group effect was significant for the voiceless stop /t/ and the voiced /b/ and /d/ (see Figure 3).

An elicitation type effect [$\chi^2_{(1)} = 6.4$; $p = 0.01$] as well as an interaction between elicitation type, auditory status group and voicing type [$\chi^2_{(3)} = 39.6$; $p < 0.001$] is observed. Indeed, VOT values are overall higher in the repetition condition, particularly for the voiceless stops, in the TH group (naming: 39.9 ms—repetition: 46.9 ms; $z = 7$–$6.95$; $p = 0.02$), and to a greater extent in the CI group (naming: 33.2 ms—repetition: 43.8 ms; $z = -10.6$; $p = 0.001$), allowing them to reach similar mean values than in the TH group. An interaction between chronological/auditory age group and auditory status group is observed [$\chi^2_{(10)} = 48.4$; $p < 0.001$]. Indeed, in the TH group, an increase of the mean values from younger to older age groups is observed for voiced and voiceless stops, while no (chronological or auditory) age effect is observed in the CI group. A CS exposure grouping*voicing type interaction is observed [$\chi^2_{(2)} = 10.92$; $p = 0.004$], with the CI/CS0 group showing higher VOT values for voiced stops compared to the CI/CS1 [$t_{(68)} = -0.015$; $p = 0.08$] and TH groups [$t_{(68)} = -0.021$; $p = 0.002$], whereas the CI/CS1 group shows the lowest VOT values for the voiceless stops [$t_{(68)} = -0.011$; $p = 0.003$]. Phoneme*CS grouping pairwise analysis reveals that the higher values in the CI/CS0 group is significant for voiced /b/ and /g/ compared to the other groups, while CI/CS1 children shows higher values for /d/ compared to TH children. The CI/CS1 group shows lower values than the TH group for voiceless /t/ and /k/. An interaction between CS exposure grouping, voicing type and elicitation type is also observed [$\chi^2_{(7)} = 40.9$; $p < 0.001$], with a significant increase of the voiceless stops VOT in the repetition condition in the CI/CS1 group (naming: 32 ms—repetition: 42.3 ms; $z = -2.6$; $p = 0.007$), this increase being only marginal in the CI/CS0 group (naming: 36 ms—repetition: 46 ms; $z = -1.7$; $p = 0.08$). An interaction effect is observed between age of implantation and voicing type in plosives [$\chi^2_{(2)} = 34.5$; $p < 0.001$]. Specifically, children in the late implantation group showed significantly longer negative VOT values than children in the TH group ($z = 2.7$; $p = 0.02$). An interaction effect appears between age of implantation and phoneme type [$\chi^2_{(10)} = 47.5$; $p < 0.001$], with the lengthening of negative VOTs in the late implantation group being significant for the phonemes /b/ and /d/.

### 3.3.4 Multiple factor analysis of acoustic measures

A multiple factor analysis was conducted, integrating subject-averaged values of NAF and Euclidean distances in F1-F2-F3 plane between each nasal vowel and the averaged values of the associated oral vowels, the differences between positive and negative VOT values, as well as spectral peak values by location (/f/-/v/-/s/-/z/-/ʃ/-/ʒ/) and ampDiff and levelD mean values. These variables were grouped according to the type of segment characterized (fricative, stop, nasal/oral vowels) but also the production mechanism associated (place vs. frication noise for fricatives, formant vs. NAF values for vowels). Among the 8 dimensions generated, the first three will be analyzed, capturing 61.84% of the explained variance. The first dimension, contributing to explaining 28.5% of the total variance, is more correlated with groups of variables associated with fricative consonants (place = 0.79; frication = 0.62) and with spectral peak variables (SP/s/-/z/= 0.79; SP/f/-/v/= 0.78), while variables associated with frication quality are negatively correlated (levelD = −0.8, ampDiff = −0.44). In other words, positive values on the first dimension indicate high values of spectral peaks as well as lower values of levelD and ampDiff (indicating more reinforcement of high frequencies in the frication), while negative values indicate lower spectral peaks and higher values of levelD and ampDiff (enhancement of mid-range frequencies in the frication). The correlations between additional categorical variables and dimension 1 show

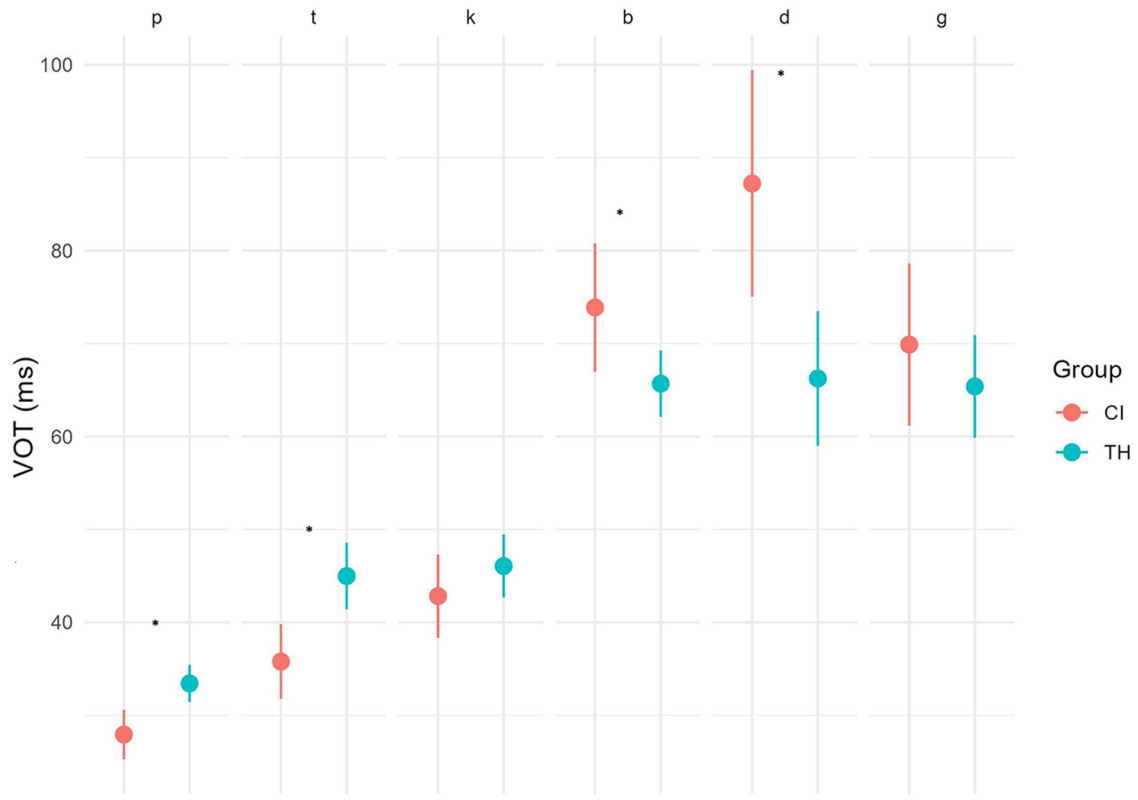


FIGURE 3
Means and 95% confidence intervals of the VOT values of the different voiced/voiceless stops among the CI and TH groups. Significance levels for pairwise comparison tests are shown when the difference is significant at 0.05 (*), 0.001 (**), or < 0.001 (***).

that children in the CI group are negatively associated with the dimension (−0.63), whereas children in the TH group are positively associated with the dimension (0.93). The second dimension, contributing 21.5% of the total variance, is associated with the variable related to nasal/oral differences in terms of NAF values (0.47), with positive correlations associated with the NAF values mean differences (0.69), as well as with the variable associated with VOT values (0.54) and negatively with spectral peak of the posterior fricatives/ʃ/-/ʒ/(−0.63). Positive values are then associated with greater nasal/oral distinction based on NAF values and greater voiced/voiceless VOT values distinction. An association is observed with categorical supplementary variables of chronological/auditory age group, with the older age group positively correlated with the dimension (0.66) and younger negatively correlated (−0.69). The third dimension, contributing 16.8% of the total variance, is associated with the variable related to nasal/oral differences in terms of F1-F2-F3 E.D (0.63) with positive correlations associated with the of the F1-F2-F3 E.D. mean differences (0.79), but negatively with the variable associated with VOT values (−0.54). A link with chronological/auditory age group is observed, with the dimension being negatively correlated with the older chronological/auditory age group (−0.47).

Figure 4 illustrates the distribution of children from the CI and TH groups along dimensions 1 and 2 (left) and 1 and 3 (right), along with ellipses representing 95% confidence intervals around the group means. The ellipses of the two groups are primarily distinguished on dimension 1, with children from the TH group located on the positive side and CI on the negative side. This is consistent with the analyses on fricatives, showing a clear effect of auditory status on productions, with children in the CI group exhibiting lower spectral values, as well as higher levelD values indicating less utilization of high frequencies in their noise frication. On dimension 2, the group mean tends more toward positive values for the TH group and negative values for the CI group, while on dimension 3, both groups are close to 0. It is important to note the large variability around the ellipses. Note the contrasting situation between the two groups in the dimension 1/dimension2 plan: only children from the TH group are situated in the extreme right-hand quadrant (values >1 in dimensions 1 and 2) and only children from the CI group in the extreme left-hand quadrant (values <-1 in dimensions 1 and 2), testifying to contrasting profiles.

Considering the other group variables, different trends between the CI/CS0 and CI/CS1 groups for dimensions 2 and 3 can be observed in Figure 5 (top graphs). Indeed, on dimension 2, the ellipse of CI/CS1 children tends more toward negative values, while the CS0 group leans toward around zero, with more variability. The CI/CS1 group tends to distinguish less nasal/oral vowels based on the NAF values. For dimension 3, the CI/CS1 group has average values toward positive values, showing less nasal/oral distinction based on F1-F2-F3 E.D. values,

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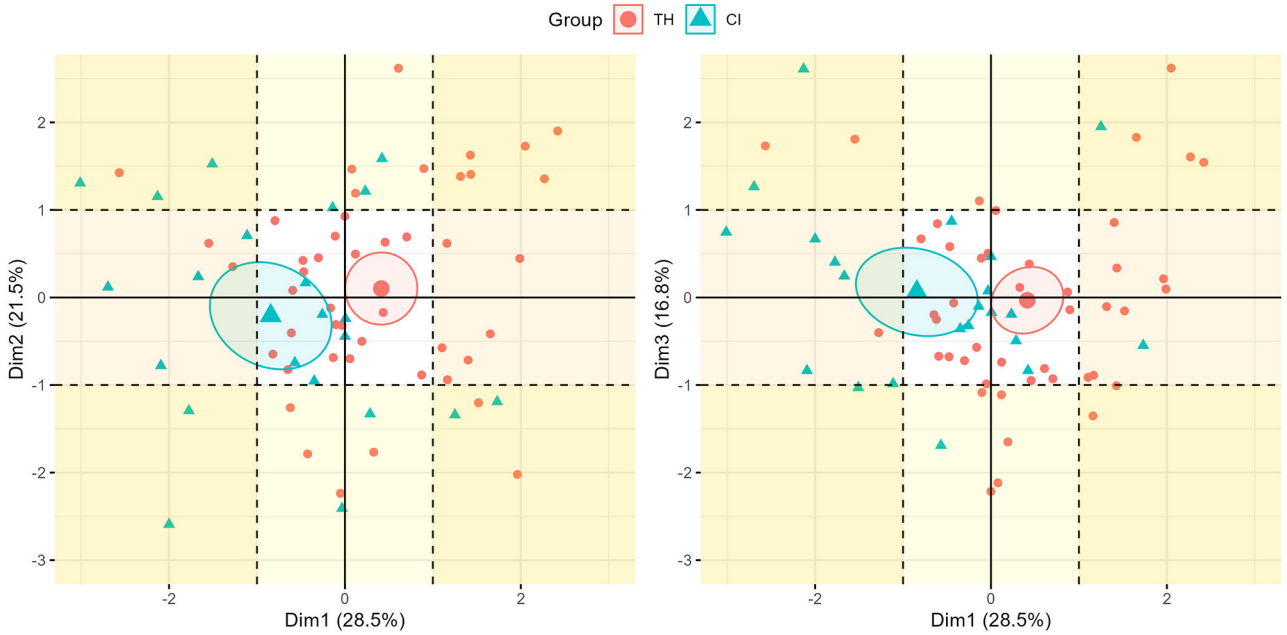


FIGURE 4
Scatter plot of statistical individuals based on dimensions 1 and 2 **(left)** and 1 and 3 **(right)** of the multiple factor analysis. Ellipses represent confidence intervals around the mean points of TH and CI groups.

whereas the CI/CS0 group is situated in negative values with again a large variability. Considering the chronological age groups (middle graphs), we can see a trend for younger children to be positioned more to the right on dimension 1, in negative values on dimension 1, and positive on dimension 2. It seems that younger chronological age group 2;6-3;6 (age group represented only by children from the TH group) produce their fricatives with high spectral peaks with frication noise rich in high frequencies, while they mark the nasal/oral distinction more based on the oropharyngeal configuration (F1-F2-F3 E.D.) and less on nasal resonance. This effect is attenuated when considering auditory age, thus including children from the CI group within the 2;6-3;6 age group. When considering implantation age groups on dimension 1, early implanted children (CI/EI) have their average values intermediate between those of the late implantation group and (CI/LI) the TH group. It can also be seen that the CI/EI group is situated toward negative values on dimension 2, while the group with later implantation seems to be more situated toward positive values for dimension 3.

## 3.4 Link between phonological performance and acoustic dimensions

The study of correlations between various phonological scores and error types with the three dimensions of multiple factor analysis has revealed moderate and significant correlations between dimension 2, related to the marking of nasal/oral distinctions by NAF values, and various phonological scores among the CI and TH groups (see Table 6). In this regard, high values on the dimension, indicating a better nasal/oral distinction in terms of NAF as well as a better marking of the distinction between voiced and voiceless stops, are associated with better phonological performance. Among children in the TH group, it is also observed that dimension 2 is negatively correlated with the occurrence of errors in oral vowel nasalization and nasal vowel denasalization. A negative correlation between dimension 1 values and the number of voiced errors is observed in the CI group, while a positive correlation is observed in the TH group with the number of voiceless errors.

# 4 Discussion

The present study investigates the phonological and phonetic skills of a group of 23 children with cochlear implants (CI) and 47 children with typical hearing (TH) through the analysis of productions obtained with a naming task. Phonological skills are examined by assessing correct phoneme scores, while phonetic skills are studied through acoustic analysis of three types of segments: nasal and oral vowels, fricative consonants, and stop consonants. These segments have been chosen because each is primarily supported by rather contrasting acoustic cues, namely low-frequency cues, high-frequency cues, and temporal information, respectively. The effect of auditory status, as well as the effects of chronological/auditory age, exposure to Cued Speech, and age at implantation, are studied. Factor analyses were conducted on all acoustic variables, and the resulting dimensions were correlated with phonological scores.

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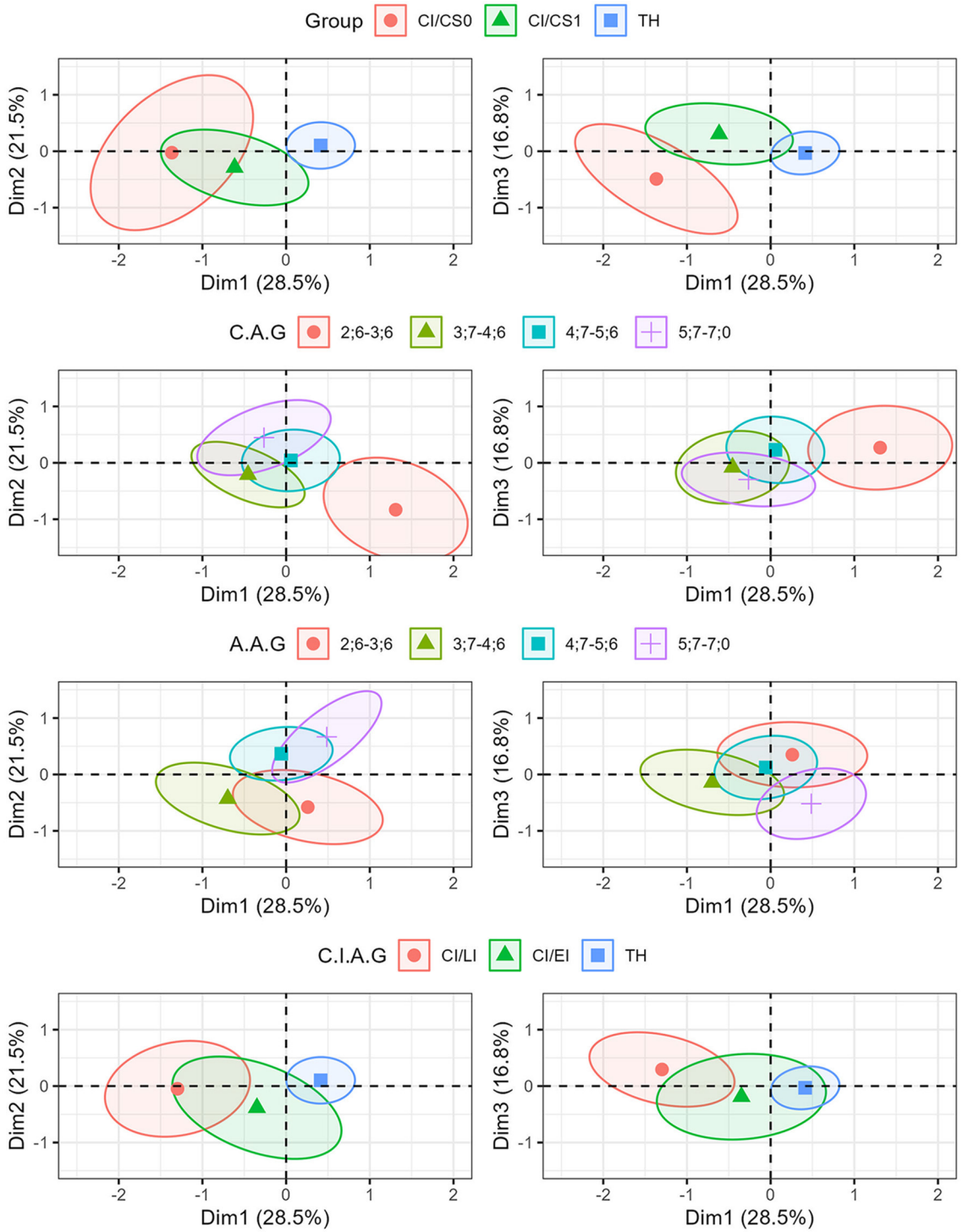


FIGURE 5
Individuals plot representing ellipses around the mean values of the groups based on exposure to CS **(top graphs)**, chronological age **(middle-top graph)**, auditory age **(middle-bottom graphs)**, age of implantation **(bottom graphs)**, according to dimensions 1 and 2 **(left side)**, and dimensions 1 and 3 **(right side)**.

## 4.1 Phonological form retrieval of the target words

It was hypothesized that, given the perceptual limitations of children with CI, their ability to retrieve the phonological form of their target words could be impacted, with repercussions both lexically (target word retrieval) and phonologically (accuracy of the retrieved phonological form). At the lexical level, children in the TH group demonstrated greater ease in retrieving target words, as evidenced by their significantly higher percentage of spontaneous naming (84%), as well as their higher percentage of retrieval based on phonological cueing. Children in the CI

TABLE 6 Correlations between phonology and acoustic analysis.

| Factor analysis dimension | Group | % correct phonemes (PCP) | % correct nasal vowel (PCN) | % correct fricatives (PCF) | % correct stops (PCS) | % vowel nasalization | % vowel denasalization | % voicing errors | % devoicing errors |
|---|---|---|---|---|---|---|---|---|---|
| 1 | CI | 0.19 | 0.11 | 0.23 | 0.19 | −0.006 | −0.03 | −0.44* | 0.01 |
| | TH | −0.07 | −0.23 | −0.17 | −0.05 | −0.02 | 0.21 | 0 | 0.35* |
| 2 | CI | 0.45* | 0.42* | 0.46* | 0.47* | −0.07 | −0.18 | −0.26 | −0.33 |
| | TH | 0.46** | 0.54*** | 0.54*** | 0.45** | −0.31** | −0.38** | 0 | −0.25 |
| 3 | CI | 0.11 | 0.2 | 0.06 | 0.07 | −0.22 | −0.18 | 0.15 | 0.11 |
| | TH | 0.05 | 0.18 | 0.03 | 0.08 | −0.03 | −0.11 | 0.19 | 0.047 |

ns, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

group showed lower percentages in spontaneous naming (77%) and relied more on repetition (18%). Semantic and phonological cueing provided little assistance in target retrieval, suggesting differences in lexical storage rather than access difficulties compared to their typically hearing peers, who benefited to a greater extent from phonological prompts. A considerable number of studies investigating lexical production in children with cochlear implants have shown comparable performances to typically hearing peers of the same chronological age (Caselli et al., 2012; Luckhurst et al., 2013) or when matched for auditory age (Duchesne et al., 2010) or in early implanted children (Manrique et al., 2004; Connor et al., 2006; Maner-Idrissi et al., 2009; Rinaldi et al., 2013). Other studies show more moderate lexical performances (Young and Killen, 2002; Nittrouer et al., 2018) or with clear difficulties identified (Cambra et al., 2021). Our results seem to align more with these studies, with significantly lower performance than those of children with typical hearing, without a positive effect of chronological, auditory age, or age of implantation. However, a beneficial effect of exposure to Cued Speech is observed, with performances among children exposed to Cued Speech reaching those of the TH group. These findings support literature that has highlighted a positive impact of Cued Speech on children with CIs, both for perceptual skills (Leybaert and LaSasso, 2010; Van Bogaert et al., 2023) and productive abilities (Machart et al., 2021). Studies have also shown a positive impact on early lexical development (Moreno-Torres and Torres, 2008; Rees and Bladel, 2013). Cued Speech, providing complete visual access to all distinctive features of speech sounds, may enable the child to develop more precise phonological representations and thus be more efficient in the storage and retrieval of lexical targets.

On the phonological level, lower performances are also observed in children in the CI group for all types of targeted phonemes: fricatives, nasals, and stops. Certain types of errors were predominantly found in children in the CI group, such as voicing errors, denasalization of nasal vowels, stopping, or fricativization. While stopping errors have been previously reported in children with moderate (Teveny and Yamaguchi, 2023) and profound deafness (Baudonck et al., 2010), and can be classified, along with denasalization errors, as typical errors in development according to Jakobson's markedness theory (Jakobson, 1968), voicing and fricativization errors suggest a more atypical developmental profile. Furthermore, we did not find any effects of chronological/auditory age or age of implantation on phonological scores and error patterns, suggesting more an effect of auditory status than developmental delay. These results support the notion of phonological development constrained by the limitations of the CI described previously, which may lead to underspecified phonological representations and consequently result in production errors. Within this study, this proposition is supported by the observation of a positive effect of exposure to Cued Speech on performances, although scores of CS1 group do not reach the levels of typically hearing children. The group exposed to CS also made fewer errors of oral vowels nasalization, which is consistent with previous studies on vowel nasality perception (Fagniart et al., 2024) and production (see text footnote 1), as well as fewer errors of fricativization, indicating greater stability of phonological representations regarding manner of articulation.

## 4.2 Nasal-oral vowels distinction

The acoustic analyses characterizing the distinction between nasal and oral vowels reveal an increased marking of the nasal/oral contrast based on indices related to oropharyngeal configuration (formant values) in the CI group compared to TH group. This result is consistent with previous findings obtained in a pseudo-word repetition task and supports the hypothesis that CI children may be more inclined to employ perceptually salient acoustic cues both in perception and production (Fagniart et al., 2024; see text footnote 1). However, the results showed lower values of NAF, representing the degree of nasalization predicted based on a series of acoustic indices related to nasal resonance, suggesting a lesser exploitation of nasal resonance through velopharyngeal opening to distinguish nasal and oral vowels. As described in Section 1, indices related to nasal resonance, primarily carried by low-frequency information associated with fine spectral resolution, are more likely to be poorly transmitted by the CI. This could explain the difficulties observed in phonological production [percentage of correct nasals and (de)nasalization errors], as already noted in the literature on nasal/oral vowel perception (Bouton et al., 2012; Borel, 2015; Borel et al., 2019; Fagniart et al., 2024). These perceptual difficulties may therefore lead to atypically specified phonological representations (marking related more to visually accessible cues such as information related to oropharyngeal configuration), thus resulting in these atypical productions compared to hearing peers. Children exposed to CS exhibit the lowest values in terms of NAF, suggesting a productive profile even more reliant on a phonological system constructed around the most salient cues to access the distinctive features of their oral language. Specifically, in the case of nasal vowels, this relies more on oropharyngeal configurations at the expense of cues related to nasal resonance. The comparison of productions according to the type of elicitation (spontaneous naming or repetition of the target word) supports these findings. Indeed, while children in the TH group improve the marking of nasal-oral distinction in repetition condition for both types of cues as well as NAF values, children in the CI group see their values increase only for the F1-F2-F3 E.D. cue, and on the contrary, their NAF values decrease. In perception, they thus seem to be able to correctly exploit visually accessible information (lip rounding, mouth opening) but not the information related to velopharyngeal opening.

## 4.3 Fricatives production

Regarding the acoustic study of fricatives, the results confirmed various findings already reported in the literature. Indeed, lower acoustic values had been observed for the center of gravity of fricatives in children with CI (Yang and Xu, 2023), as well as in French-speaking children (Grandon and Vilain, 2020). However, these studies had been limited to the investigation of fricatives /s/-/z/ or all voiceless fricatives in French (/f/, /s/, /ʃ/), and this observation is here extended to voiced segments. The differences between groups were significantly observed for the phonemes /f/, /s/, and /z/, whose spectral peaks are on average higher than those of segments /ʃ/ and /ʒ/, characterized by lower values. This is entirely consistent with the acoustic limitations in high frequencies mentioned previously. These lowered thresholds also result in a lack of distinction among the three places of articulation among children in the CI group, as the peaks of the segments /f, v/, /s, z/, and /ʃ, ʒ/ are not significantly different. An effect of CS is observed to produce /f/ and marginally for /ʃ/, with values for the CI/CS1 group approaching those of the TH group. However, it is noteworthy that the distinction between the three places of articulation is still not significant in this group. Unlike the productive skills of nasal vowels, the contribution of CS is only moderate for the distinct production of the places of articulation of fricatives. The use of manual cues to provide visual support during the perception of fricative segments may not be enough to develop sufficiently specified representations. It is possible that the acoustic limitations for this distinction are too significant to be compensated for using CS, or that these segments, being among the last to be acquired in the development of children with typical hearing, may be even more challenging for children with CIs. To our knowledge, there is no study documenting fricative productions in terms of frication noise among CI users. The results of the present study show a clear tendency in the CI group to express frication by exploiting energy in mid-range frequencies and less in high frequencies, unlike children with typical hearing. This trend could also directly result from the perceptual limitations of the implant, restricting the perception of frequency ranges above ~8,000 Hz. Indeed, the quality of fricative noise can only be perceived auditorily, with no visual/temporal cues supporting this type of production. This is supported by the study of values in the repetition condition: while TH children see improvements in their productions during repetition (increased spectral peaks, increased energy in high frequency resulting in decreased levelD values), children with CIs, on the contrary, experience slight deterioration in their productions (lower spectral peaks, increased levelD values). The perceptual limitations of CIs do not allow them to access the acoustic information related to the characteristics of fricative segments, thus preventing them from benefiting from repetition for these segments. Possible difficulties in adequately perceiving characteristics related to fricative sound could explain the higher occurrence of errors in articulation mode for stopping or fricativization errors observed in the study, and more broadly in the literature among individuals with moderate (Teveny and Yamaguchi, 2023) or severe deafness (Baudonck et al., 2010). However, an effect of the age of implantation on levelD values was observed, with higher values (and thus less reinforcement in high frequencies) in children with late implantation. It is therefore possible that early implantation allows, to some extent, better exploitation of high-frequency information, despite the technical limitations of the implant, due to the stimulation provided during the sensitive periods of the development of auditory cortical areas.

## 4.4 Voiced/voiceless stops production

Regarding the production of the voicing feature of stop consonants, a differentiated group effect is observed depending on the type of segments. Indeed, for voiceless consonants, there is a shortening of VOT values in the CI group compared to the TH

group, which is congruent with the literature (Uchanski and Geers, 2003; Horga and Liker, 2006; Grandon et al., 2017). However, in Grandon et al.'s (2017) study on French-speaking children, only the phoneme/k/showed a significant shortening in the CI group, whereas in the present study, it is precisely the phonemes /p/ and /t/ that are significantly shorter in terms of VOT. Grandon had suggested that obtaining a difference only on the phoneme/k/could be attributed to a difficulty in coordinating the articulatory gesture, as/k/has the longest positive VOT in canonical production. However, it is noteworthy that the children in Grandon's study were in a higher age range (6;6-10;6). This difference may explain why, within the TH group, the productions were not sufficiently differentiated between the places of articulation of the voiceless segments, as the average positive VOT of/k/(45 ms) differed little from/t/(44 ms). As a result, the results did not show differences between the CI and TH groups for this phoneme, but rather for the more anterior phonemes /p/ and /t/, whose values were significantly lower in the CI group. Children in the CI group seem to have difficulty coordinating the articulatory gestures associated with the production of voiced stops in a picture naming task. However, when these segments are to be produced in repetition, children in the CI group produce the segments with elongation, allowing them to reach values similar to those of children in the TH group: thus, they are capable of effectively exploiting the acoustic information related to VOT to adjust their productions. On the other hand, for voiced segments, it is the TH group that exhibits a shortening of VOT values, for the phonemes /b/ and /d/. The study of the effects of exposure to CS showed that it mainly involves an elongation of VOT values found among children in the CI/CS1 group. It is possible that relying on temporal cues is a more prevalent strategy in the CI/CS0 group.

### 4.5 Acoustic profiles

The factorial analyses revealed two distinct trends in the productive profiles of the three investigated segments. Firstly, Dimension 1, which discriminates children well according to their auditory status, consisted of variables related to the quality of fricative production, both in terms of spectral peak and in terms of the utilization of high-frequency energy in frication. It was observed that children in the TH group were predominantly situated on the positive values on the dimension 1, indicating fricatives with high average spectral peak values, and frication noise containing a higher concentration of high frequencies. Dimension 2, on the other hand, was mainly associated with marking the nasal/oral distinction in terms of NAF values, but also, to a lesser extent, with the distinction between voiced and voiceless stop consonants. It is quite interesting to note that among children in both groups, positive correlations are observed between the values on this dimension and various phonological scores. Better marking of the nasal/oral distinction in terms of nasal resonance thus seems to be associated with better phonological performances, both among TH and CI children. Therefore, despite significantly lower NAF values among CI children, there seems to be some variability in the exploitation of nasal resonance cues, which may contribute to part of the variability in linguistic outcomes. In this regard, it is more surprising to see that Dimension 3, more associated with marking vowel nasality through cues related to oropharyngeal configuration (E.D. F1-F2-F3), is not positively correlated with phonological scores in the CI group. One might have expected that this marking strategy, reflecting a greater reliance on information assumed to be better coded by the CI, would be beneficial phonologically overall. In the study by Fagniart et al. (see text footnote 1) the use of this strategy was associated with better intelligibility of nasal and oral segments. This study seems to indicate that this improvement in segment production is not necessarily associated with better phonological performances overall. These findings support the notion that while the perception-production of fricatives remains critical among the CI population, despite aids such as CS, the perception/production of nasal/oral vowels and stops entails significant variability, which may indicate possible compensations of the perceptual system in children with CIs. These findings are important to consider in the management and evaluation of language skills in children with CIs, to refine auditory stimulation techniques more based on perceptual skills accessible through the CI for critical segments, such as nasal vowels, and to quickly diagnose difficulties that may manifest subclinically.

The various findings of this study must be viewed considering certain limitations. Indeed, it is challenging to assemble a sizable sample with homogeneous characteristics among children with CIs, which complicates the generalization of results. Nevertheless, the results presented here are largely supported by existing literature and can therefore be taken seriously. Regarding the acoustic analyses, it should be noted that the target words were selected to create a list with frequent words, easily imaginable, and with low age of acquisition. These constraints did not allow for controlling various elements, such as phonemic neighborhood or overall syllabic context. Protocols targeting specific segments, with better control over parameters influencing the acoustic characteristics of productions, could be developed to address this bias in future investigations.

## 5 Conclusion

This study aimed to investigate and correlate phonological and phonetic skills through the analysis of picture naming tasks among children with CIs and their hearing peers. The following observations can be highlighted:

1) Children in the CI group exhibit more difficulties in lexical and phonological domains, which may be compensated for by exposure to Cued Speech.
2) CI users can exploit visually accessible information (such as oropharyngeal configuration) or information better coded by the CI to compensate for their perceptual difficulties, as noted in the production of nasal/oral vowels or voiced/voiceless stops, particularly among children using CS.
3) Distinctive features relying on information not accessible through the implant and less compensable visually and/or temporally, such as the distinction of fricative consonants, are critical among CI children.

4) Adequate exploitation of nasal resonance in distinguishing nasal/oral vowels is associated with better phonological performances.

These findings emphasize the perceptual system's ability to adapt and compensate for the limitations of CIs, a phenomenon that should be prioritized in children's management. Segments most at risk, such as fricative consonants, warrant particular attention to avoid significant phonological underspecification and associated linguistic delays.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

Ethical approval was not required for the study involving human samples in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

SF: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. BC: Writing – review & editing, Resources, Methodology, Conceptualization. VD: Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. AH: Writing – review & editing, Resources, Methodology, Conceptualization. BH: Writing – review & editing, Supervision, Methodology, Conceptualization. MP: Writing – review & editing, Supervision, Methodology, Conceptualization. KH: Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# The development of the Questionnaire of (Central) Auditory Processing: a screening tool of auditory processing

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**Objective:** The aim of this study was to develop a screening questionnaire for auditory processing disorder (APD) targeted for the Maltese pediatric population.

**Method:** The questionnaire consisted of 25 close-ended questions in which parents rated their child's listening skills. The data was collected from 101 typically developing Maltese bilingual children and 30 children forming a clinical group, aged between 7;00 and 9;11 years.

**Results:** The tool was found to be highly reliable with an internal consistency of 0.92 and test-retest reliability of 0.94. Significant differences emerged between normal and clinical groups ($p = <0.001$). Correlational analysis demonstrated a significant correlation between the Questionnaire of (Central) Auditory Processing (QCAP) and the speech-in-noise test, Duration Patterns Test and tests of dichotic listening.

**Conclusion:** The QCAP is potentially an effective screening tool for highlighting listening difficulties in Maltese children at risk of having APD.

KEYWORDS

**auditory processing disorder, listening difficulties, screening tool, questionnaire, children**

## 1 Introduction

Auditory processing is the proficiency of the central nervous system to perceptually process information coming from the auditory channels, and incorporates the mechanism of electrophysiological auditory potentials arising from the neurobiological activity responsible for processing this information (Yalçinkaya et al., 2009). The conscious perception of auditory signals occurs in the auditory cortex, with the primary sensory cortical areas being the region where initial perception occurs. This also has been found to be the site where bottom-up and top-down processing come together (Moore and Hunter, 2013).

Auditory processing disorder (APD) has been described as a mixture of unrefined listening skills causing poor speech perception, especially in noisy environments (Rosen et al., 2010). These difficulties are typically evident in the presence of normal hearing (de Wit et al., 2016). Prevalence studies on APD have reported differing results, ranging between 0.2% (Nagao et al., 2016) and 10% (Bamiou et al., 2001) in the pediatric population. When combined with other developmental disorders, the prevalence has been found to increase to between 30 and 50% (King et al., 2002; Ramus, 2003). The most recent definition of APD offered by the British Society of Audiology (2018) provides a broad approach, suggesting that the symptoms occur as a result of impaired neural function

within the afferent and efferent pathways of the central auditory nervous system, along with its related top-down modulation (including vision, cognitive functions of speech and language, attention, executive function, fluid reasoning, memory, and emotion). This definition implies that APD frequently occurs in conjunction with (and could be a contributing factor of) the primary disorders of those systems. The British Society of Audiology (2018) suggest that "APD may thus include both auditory and cognitive elements" (p. 6).

Questionnaires are valuable tools that enable the extrapolation of information using an array of specific questions. It is a useful way of collecting quantitative primary data (Malhotra, 2006), while exploring respondents' preferences and drawing out trends in perspectives. Auditory screening questionnaires have the advantage of highlighting auditory behavioral concerns (O'Hara and Mealings, 2018), which could in turn warrant the necessity of further assessment. They are also easy to administer, cost effective, and gather details that can be provided by different people such as parents and teachers. Their disadvantage, on the other hand, stems from possible biases of the individuals filling out the questionnaire (Schow et al., 2007). They could also be misleading or unclear at times; and if too long, could result in fatigue or lack of interest, which could in turn produce inaccurate information (Wilson et al., 2011). In addition, one cannot exclude the fact that the behavioral characteristics of children with APD overlap with those of children having language and learning difficulties (American Speech-Language-Hearing Association Working Group on Auditory Processing Disorders, 2005).

Various screening questionnaires have been used over the years. Initially, the three most commonly used questionnaires were the Children's Auditory Processing Performance Scale (CHAPPS), the Screening Instrument for Targeting Educational Risk (SIFTER; Anderson, 1989), and Fisher's Auditory Problems Checklist (FAPC; Fisher, 1976; Emanuel, 2002). Studies have examined the relationship between the screening tools and APD assessments: Wilson et al. (2011) found weak to moderate correlations between the CHAPPS, SIFTER and the Test of Auditory Perceptual Skills—Revised (TAPS–R; Gardner, 1997) screening tools and diagnostic APD assessments, even when the tools were expected to assess similar auditory skills. The authors also found weak correlations between two screening tests (CHAPPS and SIFTER) indicating that these two tests are screening different sets of skills to a certain extent. These results were consistent with those obtained from previous studies such as Drake et al. (2006) and Lam and Sanchez (2007) who both reported no relationship between screening questionnaires and the diagnosis of APD. Fisher's checklist has been criticized, on the grounds that it includes a wide range of characteristics with only a small amount linked to listening (Smoski et al., 1992). Likewise, the SIFTER has been criticized for not being developed specifically to detect the possibility of APD, but rather more general learning difficulties (Wilson et al., 2011). Despite the pitfalls reported in these auditory screening questionnaires, the CHAPPS seems to be a widely used screening questionnaire of auditory processing. The CHAPPS consists of 36 items all related to a child's listening skills. The individual filling in this questionnaire scores each item through a seven-point Likert scale and is required to compare the child's listening behavior with other children of the same age in relation to quiet, noisy, and ideal situations, auditory memory and attention span, and multiple input situations. In a survey carried out by Emanuel (2002) and Emanuel et al. (2011) it was found that 75% of audiologists use questionnaires as an initial screening of auditory processing skills, out of which a high percentage tend to use the CHAPPS [43% reported by Emanuel (2002) and 51% reported by Emanuel et al. (2011)]. This questionnaire may be effective in detecting the behavioral characteristics salient to APD. Significant differences were reported between clinical and non-clinical APD groups on all CHAPPS subscales (Iliadou and Bamiou, 2012).

More recently, other questionnaires have been developed which could potentially detect the behavioral characteristics salient to APD. One such questionnaire is the Scale of Auditory Behaviors (SAB; Schow et al., 2007), which was reported to exhibit strong and significant correlations with tests of speech in noise as well as tests of temporal processing (Nunes et al., 2013). The Auditory Processing Domains Questionnaire (APDQ; O'Hara and Mealings, 2018) attempted to bring out differences between the listening difficulties specific to APD when compared with other developmental disorders of attention and language by dividing the questions posed into auditory processing, attention, and language sections. Their results showed contrasting types of auditory difficulties amongst groups.

The goal of this study was to develop a parent screening questionnaire, named the Questionnaire of (Central) Auditory Processing (QCAP), related to how they perceive the listening skills of their children. The aim was to bring out any salient behavioral characteristics which would highlight the need for further assessment of auditory processing skills. The article explains the procedure of the QCAP construction, data collection, results and analysis.

# 2 Methods

## 2.1 Questionnaire development

The *Questionnaire of (Central) Auditory Processing* (QCAP; Tabone, 2018) was designed and provided in both Maltese and English. The main objective of running this questionnaire was to obtain information regarding the behaviors that may be present in individuals with auditory processing disorder. The aim of developing the QCAP was for use as an informational tool by clinicians, to acquire an understanding of parents' views about their child's difficulty with auditory tasks. The information obtained in this questionnaire was valuable in obtaining a behavioral profile of children's auditory skills, as well as correlating the parents' perspectives of their child's auditory skills with the other behavioral tests in the auditory processing assessment battery.

The first draft of this questionnaire was developed by Causon (2010) to target the adult Maltese population. Causon (2010) had based his questions on Rosenberg's (1998) list of characteristics observed by parents and teachers in children with reported listening difficulties. This study further developed Causon's (2010) questionnaire to target the pediatric population. While its structure, in terms of five open-ended questions followed by 20 statements

TABLE 1 Auditory skills highlighted in the QCAP.

| Auditory skill | Question numbers |
|---|---|
| 1: Auditory attention and memory | 6, 13, 14, 15,18, 20, 22, 24, 25 |
| 2: Following conversations | 9, 16, 19, 23 |
| 3: Listening in noisy situations | 7, 8 |
| 4: Sensory stimulation | 10, 12 |
| 5: Social aspects | 17, 21 |

using a 5-point Likert scale was retained, the instructions were modified to target parents and the statements were linked to typical pediatric situations such as the school environment. An extensive literature search was carried out to strengthen its content validity (Iliadou and Bamiou, 2012; Moore et al., 2010; Rosen et al., 2010; Scheich et al., 2011; Umat et al., 2011). Two experts on child language vetted the adapted questionnaire and their feedback was noted. It was also given to the parents of five children for their feedback on its readability and presentation. A complete revision of the previous literature was conducted and published in 2018 (Tabone, 2018).

## 2.2 Questions

This research opted to use a structured, close-ended questionnaire, with the intention of analyzing responses quantitatively. The QCAP consists of a total of 25 close-ended questions. The first five questions were created to obtain parental report of their child's developmental history concerning ear infections, hearing loss, and related neurodevelopmental disorders that have been found to cause similar behavioral characteristics as those observed in individuals with auditory processing difficulties, such as Attention Deficit Hyperativity Disorder (ADHD), characterized by poor attention, impulsivity, and hyperactivity (Kim et al., 2024), and Developmental Language Disorder (DLD; Tabone et al., 2020), an impairment affecting primarily the development of language in children (Lai et al., 2024). In these five questions carers were required to reply by simply indicating "yes" or "no" below the statement. The following 20 questions targeted various auditory skills. An exploratory factor analysis, as reported in Tabone et al. (2016) was carried out to determine the number of underlying dimensions that make up the tool. The outcome indicated that there was one strong component which alone accounted for 42.28% of the variance, but a total of five components above the eigenvalue of 1. Hence, the questions were grouped in accordance with the five components as shown in Table 1.

Throughout this part of the questionnaire, carers were required to answer each statement by choosing a score between 1 and 5, according to the level of agreement with it. A score of 1 indicated that the statement was not relevant to their child, whilst a score of 5 indicated the highest level of relevance. The questions and scoring were posed in a way that the lower the score of each question, and in turn the lower the overall score, the less difficulties were perceived.

## 2.3 Data collection

Research ethics approval was obtained in 2011 from the University Research Ethics Committee (UREC) at the University of Malta (reference number 023/2011). The questionnaire was completed by the parents of 101 typically developing Maltese bilingual children, 42 male and 59 female, and 30 children forming a clinical group, holding a diagnosis of DLD, ADHD, or a combination of both. In contrast to the TD sample there were more males in the clinical group (60%). All participants underwent pure tone audiometry and tympanometry. They exhibited normal hearing thresholds and middle ear function. The Maltese educational system comprises three school-types, being state, church and independent schools. Overall, most children attended mainly state or church schools, with the amount attending state schools being slightly more than church schools. Fewer children were reported to attend independent schools. The primary language was found to vary between schools. In state schools more children spoke Maltese. Similarly, most children attending church schools used Maltese as their primary language. However, this was less than in state schools. The language use of children who attended independent schools portrayed a different picture, with the vast majority using English as their primary language.

## 2.4 Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) software, version 22. The tool was assessed for reliability and validity using the Cronbach alpha and Spearman correlations. The data was found to be of a non-normal distribution, hence to evaluate the differences between groups on the questionnaire responses the Mann-Whitney test was used. Correlation analysis using all the participants in this study was carried out between the QCAP and various APD subtests to determine the extent with which they agree.

# 3 Results

## 3.1 Reliability and validity measures

The Cronbach's alpha was used to measure how closely related the items in the QCAP are as an evaluation of auditory processing skills. The internal consistency was found to be highly reliable (Cronbach alpha = 0.92).

The parents 10% of the sample were asked to complete the QCAP at the initial assessment date and again following a 2 week interval in order to assess the test-retest reliability of the questionnaire. Spearman's rank correlation of the total scores obtained on the two occasions revealed a positive and high correlation, $r_s = 0.94$, $p = 0.000$, indicating that the questionnaire outcomes should not change significantly over a specific amount of time between administrations.

In order to examine equivalence reliability, the parents of 30 children (20 TD and 10 clinical group) were requested to complete both the QCAP and an already established and widely used questionnaire developed to assess auditory processing skills:

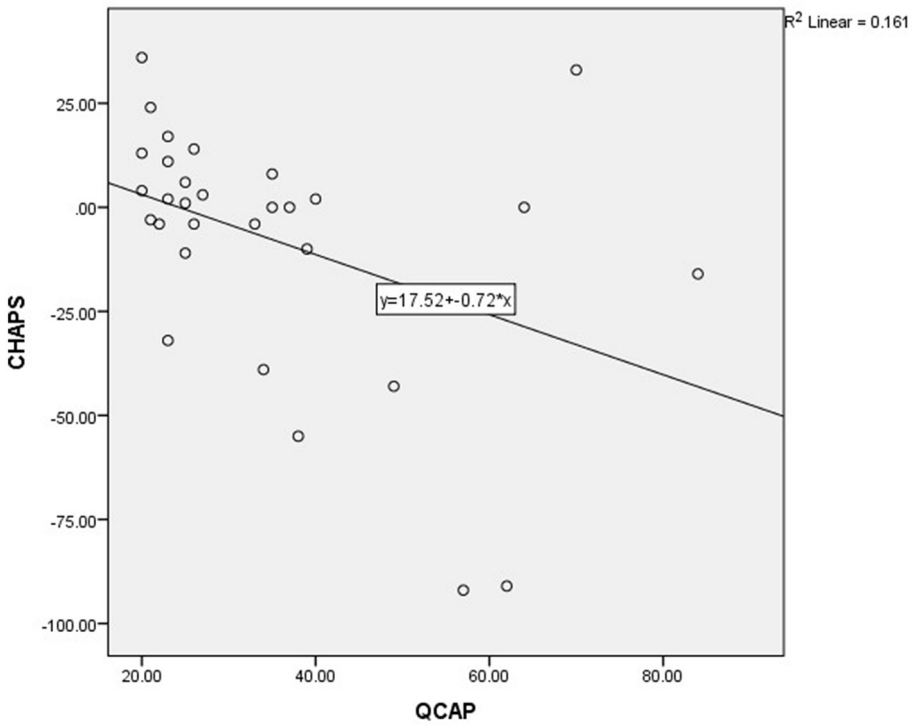


FIGURE 1
Correlation between the QCAP and the CHAPPS.

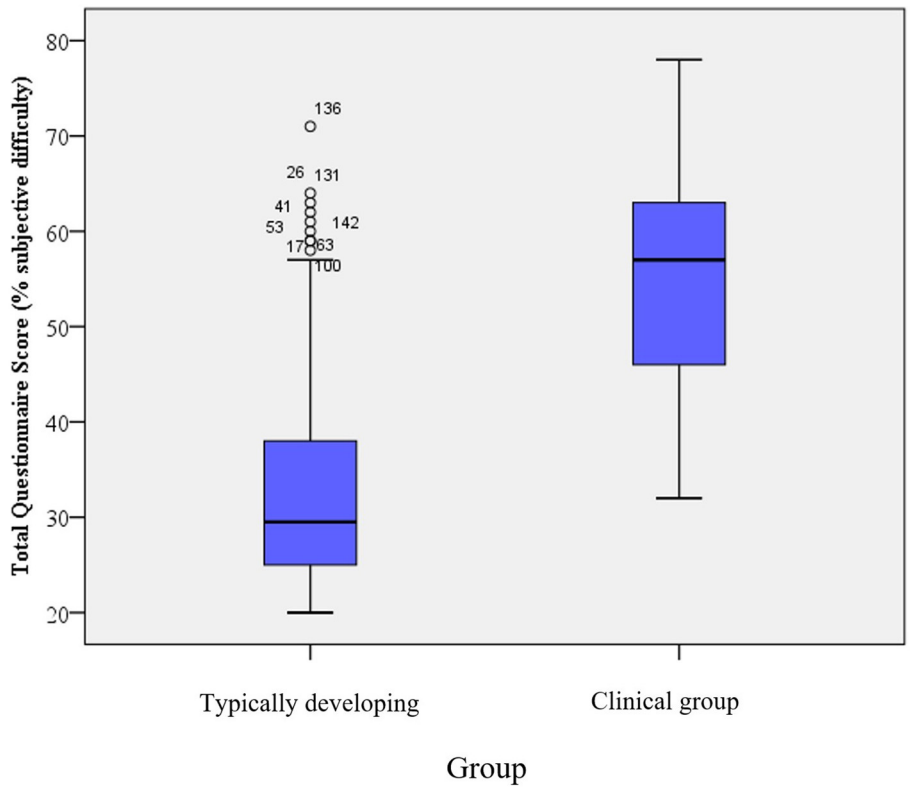


FIGURE 2
Graphical illustration of the median QCAP scores.

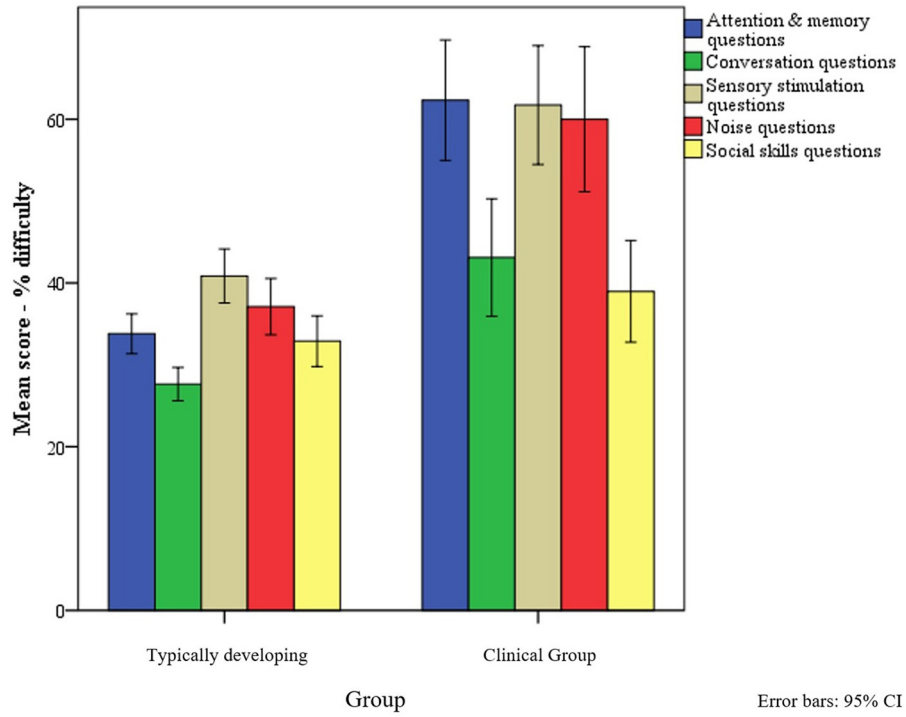


FIGURE 3
Graphical illustration of the mean QCAP scores in each of the emerged factors.

the CHAPPS (Smoski et al., 1998). The Spearman correlation was administered to investigate relations between the total scores in the QCAP and the CHAPPS. It was expected that a negative correlation would emerge since the scoring methods of the two questionnaires were inverse to each other.

A moderate and (as expected) negative correlation (Figure 1) was obtained, which was statistically significant at the 0.05 level ($r_s = -0.401$, $p = 0.028$). This result was satisfactory, considering the limitation in obtaining equivalence reliability through parallel forms due to the difficulty in finding two assessments to investigate the same behavior (Miller, 2008).

Internal validity was assessed through a principal component analysis with Oblimin rotation and Kaiser Normalization. The results revealed a Kaiser-Meyer-Olkin score above 0.7 and low probability value. The Barlett's test of Sphericity was significant ($p = 0.000$), therefore supporting the use of factor analysis. The reader is referred to Tabone et al. (2016) and Tabone (2018) for an in-depth explanation of this analysis.

## 3.2 Performance of the TD and clinical group on the QCAP

Figure 2 illustrates the scores obtained by the two groups on the QCAP. It clearly indicates a substantial difference between the questionnaire scores of the two groups. While the TD subjects obtained a mean score of 32.95 (SD = 11.36), the clinical group presented with a mean score of 54.45 (SD = 12.81) indicating parental perceptions of greater listening difficulties.

The Mann-Whitney test was used to analyze the difference between groups since data did not fit a normal distribution curve. A statistically significant difference was found between the two groups: $U = 431.5$, $p = <0.001$ between the TD (Mdn = 29.5) and the clinical (Mdn = 57.0) groups.

Further analysis was carried out to investigate whether the difference between the groups is evident in all the emerged factors (Table 1). Figure 3 reveals a substantial difference in scores between groups related to "attention and memory," "conversation skills," "sensory stimulation," and "noise," indicating that the children forming the clinical group were reported to exhibit greater difficulties in these areas. A difference, but to a lesser extent, was also evident in the questions related to "social skills." These results are further explained in Table 2.

Through the Mann-Whitney test, it emerged that the differences between groups in all subtests was statistically significant (Table 3).

## 3.3 Correlational analysis

The Spearman's rho correlating the QCAP with subtests investigating the different auditory processing skills, including speech-in-noise tests (Maltese and English Nonword repetition tests in noise; Tabone, 2018), the Duration Patterns Test (Musiek, 1994), the Frequency Patterns Test (Musiek and Pinheiro, 1987), the Dichotic Digits Tests (Musiek, 1983), and the Gaps in Noise Test (Musiek, 2003) are presented in Table 4. A statistically significant correlation emerged between the QCAP and the Maltese

speech-in-noise test, Duration Patterns Test (DPT) and tests of dichotic listening. In these tests there was a statistically significant difference between the TD and clinical groups, where the latter performed significantly poorer as detailed below:

- QCAP: $U = 431.5$, $p = <0.001$ between the TD (Mdn = 29.5) and the clinical (Mdn = 57.0) groups.
- Speech in noise (Maltese; mNWRTn): TD group (M = 9.47, SD = 3.31) and clinical group (M = 14.19, SD = 6.72) groups: $t_{(121)} = -4.674$, $p = <0.001$.
- DPT, right: $U = 835.5$, $p = 0.002$ between the TD (Mdn = 66.67) and the clinical (Mdn = 46.67) groups.
- DPT, left: $U = 757.5$, $p = < 0.001$ between the "TD group" (Mdn = 66.67) and the "clinical group" (Mdn = 46.67) groups.
- Dichotic Digits test, right: $U = 1{,}013$, $p = 0.005$ between the TD (Mdn = 95.0) and the clinical (Mdn = 95.0) groups; Dichotic Digits test, left: $U = 710.5$, $p < 0.001$ between the TD (Mdn = 95.0) and the clinical (Mdn = 95.0) groups.

## 4 Discussion

The main aim of this research was to devise a questionnaire that identifies listening difficulties in children at risk of APD, warranting the need for further assessment. With only 20 5-point Likert scale items forming the test, the QCAP could be a quick and attractive tool to quantify the perceived listening difficulties across different situations.

Perhaps the greatest challenge in determining the reliability and validity of this tool stems from the great variability across audiology centers in the assessment of auditory processing disorders. If one were to follow Ferguson and Moore (2014) suggestions in establishing a strong test, then the tool is to have good construct validity and test-retest reliability, as well as a high sensitivity and specificity in a specific population. However, achieving high sensitivity and specificity in a tool could be problematic when one is to consider the reported high comorbidity of children reported to present with a profile of APD as well as having a diagnosis of some other developmental disorder. For this reason it might make more sense take an approach of examining the reliability and validity of tools assessing the different skills that have been reported to underlie auditory processing disorders, such as understanding speech in noise, temporal processing and dichotic listening.

The inter-item (0.92) and split-half (0.86) reliability outcomes indicate very good homogeneity (internal consistency) of the tool, suggesting that all the items on a scale seem to measure one construct (Heale and Twycross, 2015); that of listening difficulties across an array of situations, and the possible consequences of these difficulties. The stability of the QCAP was tested through test-retest and equivalence reliability. Through test-retest, there was a positive and high correlation between the results obtained on the two occasions, indicating that the questionnaire outcomes should not change over a specific amount of time between administrations. Test-retest reliability of the QCAP has already been previously investigated. Cassar (2014) reported a very good test-retest reliability with a Cronbach's Alpha score of 0.997. Equivalence reliability for the QCAP was attempted as a means of analyzing the reliability of the new questionnaire with an already established questionnaire found to conceptualize behavioral findings related to APD. In light of the previous findings related to screening questionnaires, the researcher has opted to devise this questionnaire as an aid to highlight auditory behavioral concerns in Maltese children rather than as a screening tool of APD. The moderate and significant correlation between the two questionnaires suggests that the QCAP might measure the same behavioral characteristics reported in the CHAPPS. However, this result needs to be interpreted with caution due to the differences evident between the two tools.

A validated questionnaire would be useful in picking up the listening difficulties widely reported in children diagnosed with, or suspected of having APD (Moore et al., 2012). Attempting to extract validity measures for this questionnaire was of importance to this study, especially in light of reports that many questionnaires used to screen APD in general have not been validated (American Academy of Audiology, 2010; Moore, 2012; Moore et al., 2012). On the other hand, the validation of a questionnaire investigating behaviors commonly linked with auditory processing is also complicated due to the lack of consensus about the construct to be investigated (de Wit et al., 2016). The QCAP results compared with the CHAPPS gave rise to a significant moderate correlation in this sample. Although there seems to be little known validity data on the CHAPPS, studies have shown poorer scores from children with

TABLE 3 Comparison of means between the two groups categorized by "group."

| % difficulty | Mann-Whitney test | | | |
|---|---|---|---|---|
| | *U* | *W* | *z* | *p* |
| Auditory attention and memory | 480.5 | 10,633.5 | −6.512 | <0.001 |
| Following conversations | 943.5 | 11,096.5 | −4.826 | <0.001 |
| Listening in noisy situations | 887.0 | 11,040 | −4.891 | <0.001 |
| Sensory stimulation | 921.5 | 11,074.5 | −4.843 | <0.001 |
| Social skills | 1,470 | 11,623 | −2.572 | 0.010 |

TABLE 2 Group score means and standard deviations for the TD and clinical groups.

| Group | Score mean (and SD) | | | | |
|---|---|---|---|---|---|
| | Auditory attention and memory | Following conversations | Listening in noisy situations | Sensory stimulation | Social aspects |
| TD | 33.8 (14.7) | 27.6 (12.3) | 37.1 (20.8) | 40.1 (19.8) | 32.9 (18.6) |
| Clinical | 62.3 (19.3) | 43.1 (19.7) | 60.0 (23.3) | 61.7 (19.1) | 39.0 (16.3) |

TABLE 4 Spearman's correlations between subtests.

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | QCAP Score | 1 | 0.239** | 0.178 | −0.315** | −0.254** | 0.117 | 0.115 | −0.248** | −0.361** | −0.113 | −0.294** | 0.043 | −0.013 | 0.087 | −0.083 |
| 2 | mNWRT(n) | | | | | | | | | | | | | | | |
| 3 | eNWRT(n) | | | | | | | | | | | | | | | |
| 4 | DPT (right) | | | | | | | | | | | | | | | |
| 5 | DPT (left) | | | | | | | | | | | | | | | |
| 6 | FPT (right) | | | | | | | | | | | | | | | |
| 7 | FPT (left) | | | | | | | | | | | | | | | |
| 8 | DD(FA) (right) | | | | | | | | | | | | | | | |
| 9 | DD(FA) (left) | | | | | | | | | | | | | | | |
| 10 | DD(FR) (right) | | | | | | | | | | | | | | | |
| 11 | DD(FR) (left) | | | | | | | | | | | | | | | |
| 12 | GIN Ath (right) | | | | | | | | | | | | | | | |
| 13 | GIN % (right) | | | | | | | | | | | | | | | |
| 14 | GIN Ath (left) | | | | | | | | | | | | | | | |
| 15 | GIN % (left) | | | | | | | | | | | | | | | |

**Correlation is significant at the 0.01 level (2-tailed).





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APD in this questionnaire (Ferguson et al., 2011; Iliadou and Bamiou, 2012). This demonstrates the possibility of the QCAP extracting similar findings to the CHAPPS. One area that warrants further investigation for the QCAP is the influence or relation with cognitive factors. For example, Barry et al. (2015) examined four questionnaires used in the assessment of auditory processing, and their ability at detecting the presence of listening difficulties. While the authors reported all questionnaires to be sensitive to listening difficulties, they also correlated with measures of cognition used in the study. The effect of cognition has also been examined in relation to the CHAPPS (Moore et al., 2010), with similar outcomes to the Barry et al. (2015) study. Moore et al. (2010) found that in 1,469 mainstream school children aged between 6 and 11 years, the variance in the CHAPPS was primarily accounted for by factors of cognition and attention. These findings thus elicit queries as to which construct the questionnaires are tapping into listening, cognition, or perhaps an amalgamation of the two.

There were significant correlations between the QCAP and tests of dichotic listening. Dichotic listening requires working memory in order to execute them as a task. Working memory has been described as a multifaceted system. It is linked to the execution of complex tasks such as those involving attentional control to suppress less important information, or tasks that involve storage and processing (Engle, 2002; Riches, 2012). Accordingly, a good working memory capacity is linked to better ability to use attention to avert distraction (Engle, 2002). This correlation result was expected since, on examination of the rotated component matrix for the QCAP, the largest component is made up of questions related to auditory attention and memory. So if a child is to score poorly in the questionnaire, there is an increased chance that a high proportion of the weak scores fall within "component 1." In this case the child may also score poorly on the tests of dichotic listening.

Temporal processing skills are essential for the perception of speech in noise, since they are reported to support auditory stream segmentation (Anderson et al., 2010). The DPT also poses a cognitive load, in which an individual must pay attention to, and store the sequence of tones in short-term auditory memory (Iliadou and Bamiou, 2012). With components of "auditory memory and attention" and "listening in noisy environments," this may explain the significant correlations that emerged between the QCAP and both tests of speech in noise as well as tests of temporal processing.

When the questionnaire scores between the two groups were analyzed, a statistically significant difference emerged overall and across all components. The aim of the QCAP development and use was to extract any listening difficulties that the children might have, warranting the need for further assessment of auditory processing skills. This corroborates with other research findings of greater reported listening difficulties in children with DLD (Azzopardi, 2015; Ferguson et al., 2011; Tabone et al., 2016), literacy difficulties and ADHD (Tabone et al., 2016). The clinical group in this study also performed significantly worse than the TD cohort on tests of dichotic listening and speech in noise (Tabone, 2018), suggesting that the listening difficulties which emerged in the QCAP also surfaced in these subtests. This might not be surprising when considering that several questions in the QCAP targeted difficulties with understanding longer and more complex sentences, and speech in noisy environments.

## 5 Conclusion

In this study, the Questionnaire of (Central) Auditory Processing (QCAP) was developed as a screening tool for APD in the Maltese population. It aimed to bring out the listening difficulties, as perceived by parents, in children aged between 7 and 9 years. The QCAP shows evidence of strong reliability and validity, giving it the potential to be an effective screening tool for highlighting listening difficulties in Maltese children at risk of having APD, in turn warranting the need for further assessment.

## Data availability statement

The datasets presented in this article are not readily available because the data is available only to the primary author. The co-authors may have access to the anonymized data. Requests to access the datasets should be directed to: nadine.tabone@um.edu.mt.

## Ethics statement

The studies involving humans were approved by Faculty of Health Sciences Research Ethics Committee (FREC), University of Malta. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

## Author contributions

NT: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. HG: Writing – review & editing, Supervision. D-EB: Writing – review & editing, Supervision.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Over the counter hearing aids self-fitting using the Gaussian Process Classification

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**Introduction:** To provide better access to hearing aids and lower the devices' costs for patients with mild to moderate hearing loss, the Food and Drug Administration (FDA) changed its rules for hearing aid distribution, making them available to consumers over-the-counter without the supervision, involvement, or prescription of a licensed health care professional. While this regulation provides some patients direct access to hearing aids, the hearing aid fitting creates challenges for the patients and the hearing aid providers. OTC hearing aids should be programmable outside of a clinical setting. This study demonstrates that the self-fitting of hearing aids does not differ significantly from and is non-inferior to the fitting of the device by a licensed audiologist.

**Method:** Hearing aid and patient performance after fitting the device by the patient (self-fitting) and a certified audiologist (clinical fitting) were compared in a laboratory setting and a field trial. The laboratory session used a repeated-measures design to assess the reliability and validity of the self-fitting method. A 7–14 days of wear time was used for the field study. The outcome measures for the laboratory session were the differences in acoustical real-ear aided response (REAR). For the wear-time trial, the outcome was the clinical self-report measure of benefit (Abbreviated Profile of Hearing Aid Benefit, APHAB). The benefit of the hearing aid was tested after the self-fitting and the clinical fitting of the hearing aid with a speech-in-noise test (QucikSIN).

**Results:** The test outcomes showed no statistically significant differences between repeated self-fitting and clinical fitting of the hearing aids. The hearing aid self-fitting was non-inferior to the clinical fitting.

**Discussion:** It is important to emphasize that the results and conclusion obtained in this study strictly relate to the specific self-fitting process using the Gaussian Process. Many other potential methods for fitting hearing aids exist and future field studies are required to compare the efficacy of the self-fitting methods.

KEYWORDS

**over-the-counter, hearing aid, Gaussian Process, self-fitting, hearing loss**

## 1 Introduction

Hearing loss is a global health crisis. According to the World Health Organization (WHO), over 1.5 billion people globally suffer from hearing loss, 466 million of them disabling (Olusanya et al., 2019; WHO, 2021). The same reports suggest that the numbers will almost double by 2050 (Olusanya et al., 2019; WHO, 2021). Unaddressed hearing loss costs the global economy ~US$ 980 billion annually (WHO, 2021). Furthermore, a recent meta-analysis suggested that hearing loss is a modifiable factor for dementia (Lin and Black, 2017; Loughrey, 2022). Untreated hearing loss correlates with accelerated cognitive decline,

anxiety, and depression (Lin et al., 2011; Gallacher et al., 2012; Mener et al., 2013; Chung, 2015; Hopper et al., 2016; Keidser and Convery, 2016; Livingston et al., 2017, 2020). It has been suggested that treating hearing loss will decrease the risk of long-term cognitive decline by 19% (Yeo et al., 2023).

To provide better access to hearing aids and lower the devices' costs for patients with perceived mild to moderate hearing loss, on August 16, 2022, the Food and Drug Administration (FDA) established new rules for the distribution of hearing aids. They can now be distributed to adults "over the counter" (OTC) without the written statement signed by a licensed physician that the patient's hearing has been medically evaluated and the identified hearing loss makes the patient eligible for a hearing aid. While this regulatory change provides some patients direct access to hearing aids, the hearing aid fitting creates challenges for both the patient and the hearing aid providers. OTC hearing aids should be programmable outside of a clinical setting because patients are no longer required to visit or consult an audiologist or physician. In other words, it must be possible to "self-fit" the devices.

Hearing aid fitting typically starts by assessing the patient's audiogram (Hughson and Westlake, 1944; ANSI, 1978; ASHA, 1978; Ravn and Preves, 2015), which provides the base for the hearing aid amplification settings. The settings are assigned using well-known prescriptive standards such as National Acoustic Laboratories (NAL), Desired Sensation Level (DSL), or others using the patient's audiogram (Byrne et al., 2001; Keidser and Convery, 2018). In other words, the audiogram is the starting point for the fitting process. In the following steps, each patient optimizes the hearing aid's settings. Since the fitting is an iterative process that requires the patient's feedback, it is not crucial how well the starting point matches in a hearing aid self-fitting or clinical fitting procedure. The alignment between the audiogram obtained by the audiologist or obtained by the self-fitting procedure is primarily to satisfy the need for documentation. Following this logic, no audiogram would be required for the fitting process. The fitting could start with an arbitrary audiogram, aligning somewhat with the patient's hearing ability. Using such an approach, the fitting will likely take more iterations. We suggest that a good alignment of the results from the self-fitting will optimize the fitting procedure.

Self-fitting of hearing aids is not a novel concept and has been explored under clinical supervision (Convery et al., 2015; Keidser and Convery, 2016, 2018). In this context, a fitting procedure using the Gaussian Process Classification has been proposed to obtain continuous pure-tone threshold curves (Yang et al., 2016; Cox and De Vries, 2021; Boven et al., 2023). The procedure differs from the established hearing aid fitting in a clinical setting, where the hearing aid is adjusted step-by-step, following well-described procedures based on the audiogram. The new procedure combines *in-situ* pure-tone audiometry with Bayesian statistical inference. Our recent study verified that differences in hearing obtained with pure tone audiometry and the Gaussian Process implemented on a hearing aid are within 3 dB of the standard audiogram (Boven et al., 2023). In this study, the pure tone audiometry that was used as a reference for the self-administered hearing test was given by a licensed audiologist.

This clinical study built on and expanded our previously published results (Boven et al., 2023). It was an effort to validate our method for patients to fit their hearing aids outside of a clinical setting using their hearing aids. The study had an in-lab session and a wear-time trial. The in-lab session used a repeated-measures design to assess the reliability and validity of the self-fitting method. The gold-standard measure for the acoustical function of hearing aids was used to assess the reliability of the method; differences in acoustical real-ear aided response (REAR) between two replications of self-fitting the hearing aids (SF) for the robustness and the differences between the SF and the outcomes after fitting the hearing aids by a licensed clinician (CF) to validate the self-fitting of the hearing aid. Differences were tested for significance and the non-inferiority of the self-fitting. The field trial included 7–14 days of wear time. For the wear-time trial, the primary outcome measure is a widely used clinical self-report measure of benefit (Abbreviated Profile of Hearing Aid Benefit, APHAB). For both the laboratory testing and the field trial, patient performance was quantified by the QuickSIN test, a standardized measure of speech communication in noise.

# 2 Methods

This study tested the hypothesis that a self-fitting procedure of hearing aids, based on the GP, is non-inferior to the hearing aid fitting by a licensed audiologist. The performance was tested in an over-the-counter hearing aid (Sontro OTC Hearing Aid) in adults with mild to moderate sensorineural hearing loss. The reliability and validity of the self-fitting method were examined in an in-lab session. A single-blinded, counter-balanced wear-time field trial evaluated the validity of the self-fitting method.

## 2.1 Study participants

### 2.1.1 Subject number justification and target group

The number of test subjects was estimated before starting the study with G*Power using the median values and the variability obtained from published results. The primary outcome measure of the wear-time field trial, the APHAB, powered the sample size. It is the most variable of the outcome measures across all components of this study. Enrollment targets were set to include an equal number of male and female subjects, a representative balance of race and ethnicity, an age group of 18-75 years (primarily 50–70 years, with an average age of ~60 years), and a mix of prior hearing-aid use (aiming for 70–80% persons with no prior hearing aid use). Reading and comprehending English and providing informed written consent was another inclusion criterion.

### 2.1.2 Subject recruitment and inclusion criteria

An initial telephone or internet screening of interested persons took place. During this remote screening, prospective subjects provided their age (subject to verification at Visit 1) and answered a Yes/No question about whether they have difficulties in hearing

in noise. Those who responded with "No" were not considered for enrollment. Those who answered with "Yes" were asked to describe their perceived hearing loss on a 4-point scale (no difficulties, little difficulties, a lot of difficulties, and they cannot hear). Prospects who answered at the two extremes were not considered for this study. Those who responded with "little difficulties" or "a lot of difficulties" were invited to the in-person screen that immediately preceded the hearing aid fittings during visit 1. A licensed audiologist assessed the hearing threshold for each participant before the study to determine whether to include a prospect. The testing equipment was a standard audiometer at the clinic. The study inclusion criterion was mild-to-moderate bilateral sensorineural hearing loss, with hearing threshold elevations >20 dB at least at one frequency ranging from 250 to 8,000 Hz. Hearing thresholds at 500, 1,000, 2,000, and 4,000 Hz must be ≤65 dB hearing level (HL), respectively.

### 2.1.3 Exclusion criteria

Vulnerable patients were not enrolled in this study. Other exclusion criteria included hearing outside of the limits noted above. Subjects were excluded upon self-reported ear-related pathology, including previous middle ear surgery, head trauma/injury, a family history of non-age-related hearing loss, sudden hearing loss, fluctuating hearing loss, active discharge from the ear, pain, fullness, and history of Ménière's disease. Patients were also excluded during the otoscopy evaluation if excessive ear wax completely covered the tympanic membrane, drainage, tympanic membrane perforation, presence of a foreign body, and infections.

### 2.1.4 Compensation

For participating in the study, the individuals either received a $500 gift card or could keep the pair of hearing aids used during the study.

## 2.2 Sequence of study events and data acquisition

### 2.2.1 Procedures during visit 1 (session 1)

After the patients arrived at the clinic following the telephone or internet screening and invitation to the study, they completed a nine-step study protocol.

**Step 1:** The inclusion criteria were validated by taking the case history, the ability to read and comprehend English, the patients' willingness to provide written informed consent, and were 18 years old or older.

**Step 2:** The study and its procedures were explained to the patient, questions by the patient were answered, and written informed consent was obtained. The subjects' payment forms were completed, and relevant demographic information, such as age and gender, was collected.

**Step 3:** The best receiver in canal (RIC) and open ear dome size were selected by the patient under the guidance of the audiologist to comfortably fit the Sontro® Hearing Aid to the subjects' ears.

**Step 4:** All subjects completed an unaided (no hearing aids) Abbreviated Profile of Hearing Aid Benefit (APHAB) test using the Harlmemphis.org APHAB program on a tablet.

**Step 5:** In a sound-reduced enclosure, the AVANT (Stealth) Audiometer (MedRx, Inc., Largo, FL) was used to assess the patients' hearing and to confirm their eligibility for the study. The audiogram also served the audiologist to fit the hearing aids (CF). Thresholds at 3 and 6 kHz were included for the fitting by the audiologist.

**Step 6:** All subjects completed two practice lists of the QuickSIN test (unaided; lists 1 and 2) using the QuickSIN module of the audiometer, followed by two lists in the unaided condition.

**Step 7:** All subjects placed the first set of Sontro® Hearing Aids into their ears, connected them to the app on the phone provided, and repeated the hearing test with the hearing aids. The resulting audiogram was stored and used to complete the self-fit prescription called SFA. The procedure was repeated with the second set of Sontro® Hearing Aids. The audiogram was stored and used to complete the self-fit prescription called SFB. The clinician entered the data from each audiogram into the audiometer's Real Ear measurement module to generate upper gain targets at 90 dB HL and lower gain targets at 50 dB HL for all three fitting conditions. These target gains were generated using the second-generation prescription procedures from the National Acoustics Laboratories (NAL) for fitting hearing aids (NAL/NL2).

**Step 8:** After completion of each fitting condition, the aided QuickSIN scores were determined in the sound-reduced enclosure using two lists, out of all available lists, as directed in a randomization spreadsheet. Half of the subjects wore the devices fitted with the settings obtained by the SFA procedure, and half of the subjects after the device was fitted with the SFB procedure. The other subjects wear the pair of hearing aids fitted by the clinician, the CF procedure. Subjects were blinded to the setting for the field trial. The field trial setting was specified in a randomization spreadsheet.

**Step 9:** After Visit 1, each subject was provided with one set of hearing aids, a pack of 312 batteries, and a copy of the hearing aid's Quick Start Guide ("QSG"). Questions regarding the QSG were addressed before the patient left for the field trial. Furthermore, each subject demonstrated that they could insert and remove the battery, adjust the volume with the rocker switch on the device, and power on and off the device. Subjects could only fine-tune the adjustments to the hearing aid during the field trial for volume. Upon returning to the clinic for visit two, the hearing aid settings were recorded as "after trial fit". For the wear-time field trial, subjects were asked to wear the devices a minimum of 2 h per day in a variety of listening situations during the trial, including (1) while listening to music, (2) while watching TV, (3) while using the telephone, (4) while visiting noisy environments such as a restaurant, (5) while talking with a group of people of two or more.

### 2.2.2 Procedures during visit 2 (session 2)

After the one to two-week wear-time trial, the subjects returned to measure the REAR, completed the aided APHAB, and aided QuickSIN tests.

## 2.3 Study procedures

### 2.3.1 Real-ear aided response (REAR)

#### 2.3.1.1 Description of the test

The real-ear-aided response (REAR) is a method to verify the hearing aid's output within 5 mm of the tympanic membrane (Mueller, 2001; Sinclair et al., 2001). During the real-ear measurements, a thin probe microphone was inserted into the ear canal alongside the hearing aid to measure the sound pressure level SPL in dB (re 20 μPa), as a function of frequency, at the specified measurement point in the ear canal, for a specified sound field, with the hearing aid (and its acoustic coupling) in place and turned on. The audiologist recorded the sound levels the user received from the hearing aid. In the clinical setting, the audiologist adjusted the sound levels to match target amplification levels based on the hearing aid user's hearing loss across the speech frequencies.

#### 2.3.1.2 Implementation of the REAR in the study, data analysis, and statistical testing

In this study, probe-tube microphone measures of the REAR were obtained for @65 dB SPL speech input using the real-ear measurement module of the audiometer. Pure-tone levels at 500, 1,000, 2,000, and 4,000 Hz were averaged, and averages were compared between the different experimental groups. To determine the robustness of the self-fitting procedures, REAR values were measured twice after self-fitting the hearing aid, trial A (SFA) and trial B (SFB). Differences between REAR values after the self-fitting ($REAR_{SFA}$-$REAR_{SFB}$) were averaged, and the corresponding standard deviations, standard errors, and 95%-confidence intervals were calculated. The results were tested for normal distribution using the Jarque-Bera test, [h,p] = jbtest(x) (MATLAB, R2022b). The test provides a decision [h, with h = 1, indicating that the data (x) are not normally distributed] and the corresponding probability (p). The significance level was 0.05. The Mann-Whitney U Test (Wilcoxon rank sum test), [p,h] = ranksum(x,y), (MATLAB, R2022b), was used to test the null hypothesis that data in x and y are samples from continuous distributions with equal medians, against the alternative that they are not. Again, the test provided a decision [h, with h = 1 rejecting the null hypothesis] and the corresponding probability (p) for the decision. For the self-fitting procedure's non-inferiority (NI) testing, the NI margins (M) were $M_1 = -5$ dB and $M_2 = 5$ dB. Non-inferiority was established for $M_1 \leq$ 95% CI lower bound and 95% CI upper bound $\leq M_2$. Significance levels for the 95% CI calculations were adjusted for multiple tests on the dependent variable by applying the Bonferroni method.

The REAR values were also determined after a licensed audiologist (CF) fitted the hearing aid. The average of the differences and corresponding standard deviations, standard errors, and 95%-confidence intervals between the clinical and self-fitting procedures in session 1 ($REAR_{CF}$-($REAR_{SFA}$+$REAR_{SFB}$)/2). For the wear-time field study, the REAR values obtained in session 1 (S1) during visit 1 were compared with the REAR values in session 2 (S2) during visit 2. Since not every participant had the same procedure, the differences in the averages, mean ($REAR_{SF}$) – mean ($REAR_{CF}$), and the corresponding pooled standard deviations, standard errors, and 95%-confidence intervals were calculated. Results were tested for normal distribution using the Jarque-Bera test with a significance level of 0.05. The Mann-Whitney U Test (Wilcoxon rank sum test) was used to compare differences between the groups with a significance level of 0.05. For the self-fitting procedure's non-inferiority (NI) testing, the NI margins (M) were $M_1 = -5$ dB and $M_2 = 5$ dB. Non-inferiority was established for $M_1 \leq$ 95% CI lower bound and 95% CI upper bound $\leq M_2$. The significance levels for the 95% CI calculations were adjusted for multiple tests on the dependent variable by applying the Bonferroni method.

The sequence of the hearing aid fitting was randomized for the patients: (1) SFA, SFB, CF; (2) SFA, CF, SFB; and (3) CF, SFA, SFB. An equal number of subjects received each sequence at each site.

### 2.3.2 Abbreviated profile of hearing aid benefit (APHAB)

#### 2.3.2.1 Description of the test

The APHAB is a 24-item self-assessment inventory. Patients report their difficulties with communication or noises in various everyday situations. The benefit is calculated for each patient by comparing the reported difficulty in the unaided (no hearing aid) with the difficulty in the aided condition (using amplification). The APHAB produces scores for the Ease of Communication (EC), Reverberation (RV), Background Noise (BN), and Aversiveness (AV). The APHAB-global score (GLB), based on all 24 items, increases the reliability of the test.

#### 2.3.2.2 Implementation in the study, data analysis, and statistical testing

Although it is possible to collect unaided and aided scores at the same time by asking the subject to reflect on unaided listening, we obtained unaided APHAB scores during Visit 1 before the initiation of the wear-time trial and determination of the aided APHAB scores during (Visit 2).

The differences in the APHAB scores, aided vs. unaided, provided the benefit ($APHAB_{benefit}$) of using the hearing aid. They were determined by a licensed audiologist during visit 2 after the field trial that followed the fitting of the hearing aid with the self-fitting procedures SFA and SFB and clinical fitting procedure CF. The differences between average $APHAB_{benefit}$ scores, the corresponding pooled standard deviation, pooled standard errors, and 95%-confidence intervals after the clinical-fitting and self-fitting [mean ($APHAB_{benefit\_CF}$) – mean ($APHAB_{benefit\_SF}$)] served to test for equivalence and non-inferiority of the self-fitting procedure. The NI margin for the differences between the benefits was ≤8.4. Results were tested for normal distribution using the Jarque-Bera test with a significance level of 0.05. The Mann-Whitney U Test (Wilcoxon rank sum test) was used to compare differences between the groups with a significance level of 0.05. For the self-fitting procedure's non-inferiority (NI) testing, the NI-margin (M) was M = 8.4. Non-inferiority was established for the 95% CI upper bound ≤ 8.4. Note that significance levels for the 95% CI calculations were adjusted for multiple testing on the dependent variable by applying the Bonferroni method.

TABLE 1 Study participants enrolled in the study.

| | Total | Enrolled | Age_min | Age_max | Age_avg | Age_std |
|---|---|---|---|---|---|---|
| Female | 24 | 16 | 31 | 75 | 60.5 | 11.6 |
| Male | 22 | 13 | 36 | 70 | 56.3 | 11.9 |
| Female + male | 46 | 29 | 31 | 75 | 58.4 | 11.7 |
| By ethnicity | | | | | N | (%) |
| White/Caucasian | | | | | 23 | 79.3 |
| Hispanic | | | | | 0 | 0.0 |
| Hispanic/Black | | | | | 0 | 0.0 |
| Black/African American | | | | | 3 | 10.3 |
| Asian | | | | | 3 | 10.3 |
| Total enrolled | | | | | 29 | 100 |

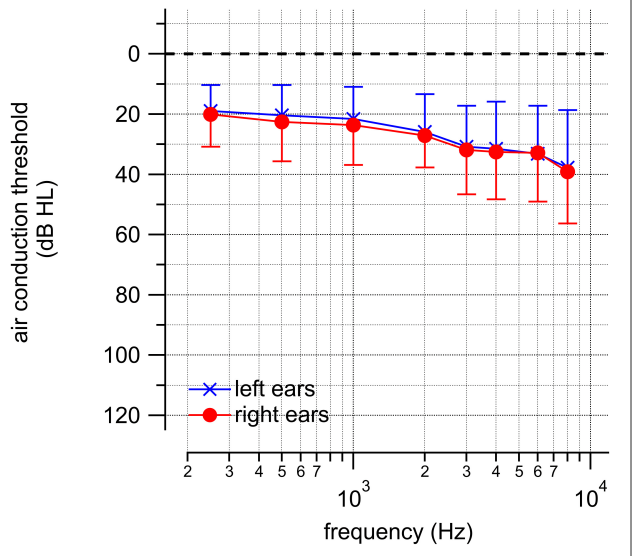


FIGURE 1
The audiograms obtained from the included participants' left and right ears. The averages ± one standard deviation are shown.

## 2.3.3 QuickSIN

### 2.3.3.1 Description of the test

The QuickSIN speech-in-noise test provides 12 lists of six sentences to test the ability to understand speech in background noise at six signal-to-noise ratios (SNRs), 25, 20, 15, 10, 5, and 0 dB. Performance is scored using 5 keywords per sentence, resulting in 30 keywords scored per list. The signal-to-noise ratio (SNR) for which 50% of the presented words are intelligible is calculated by subtracting the number of correct words (out of 30) for a given list from 25.5 (Killion et al., 2004). The test is time efficient; administering a single list takes ~1 min. The standard deviation for an SNR estimate using a single list is 1.4 dB. Averaging multiple lists results in a lower standard deviation (Killion et al., 2004).

### 2.3.3.2 Implementation in the study, data analysis, and statistical testing

At the end of the initial screening during patient visit 1, the SNR loss was determined using two lists presented as practice lists (lists 1 and 2). Out of the remaining 8 lists (lists 3–10), two were randomly assigned to each of the following conditions: unaided (during initial screen; to permit measures of relative benefit), in-lab final SFA, in-lab final SFB, in-lab final CF, and at the end, the one-to-two-week field-trial wear period (Visit 2; either SF or CF). The condition, order, and list pair assigned for each condition were randomized for each subject. Each QuickSIN score was based on two lists, 60 keywords. No list was repeated for a given subject.

All QuickSIN measures, unaided and aided, were binaural. The patients were sitting in a chair in the center of the sound-reduced enclosure facing the speaker, from which the test materials were played (0 degrees azimuth, 1-meter distance). The level was chosen to approximate a typical conversational level (60–65 dB SPL) and match the speech input level used for the REAR measures (65 dB SPL). The level of the co-located background four-talker babble increased across the six sentences for signal-to-noise ratios (SNRs) ranging from +25 to 0 dB SNR (in steps of 5 dB). The subjects were asked to repeat each sentence. The audiologist scored whether the subjects correctly repeated the predetermined keywords in each sentence. The resulting scores were interpreted as an SNR loss where a value near 0 indicates better hearing and larger values indicate more difficulty listening in noise.

The QuickSIN test was given for four conditions: unaided, with the aid of the self-fitted hearing, $QSIN_{SFA}$, and $QSIN_{SFB}$, and after the hearing aid fitting by an audiologist, $QSIN_{CF}$. The results were tested for normal distribution using the Jarque-Bera test with a significance level of 0.05. The Mann-Whitney U Test (Wilcoxon rank sum test) was used to compare differences between the groups with a significance level of 0.05. Non-inferiority of the self-fitting (SFA or SFB) vs. the clinical fitting (CF) procedure was tested after the field trial ($QSIN_{CF}$-$QSIN_{SF}$). For the self-fitting procedure's non-inferiority (NI) testing, the NI-margin (M) was $M = -1.5$. Non-inferiority was established for the 95% CI lower bound $\geq -1.5$. The significance levels for the 95% CI calculations were adjusted for multiple tests on the dependent variable by applying the Bonferroni method.

## 2.4 Study endpoints

The two primary endpoints to test for non-inferiority of the self-fitting procedure vs. the clinical fitting were the outcomes of the REAR measurements and the APHAB score. The three

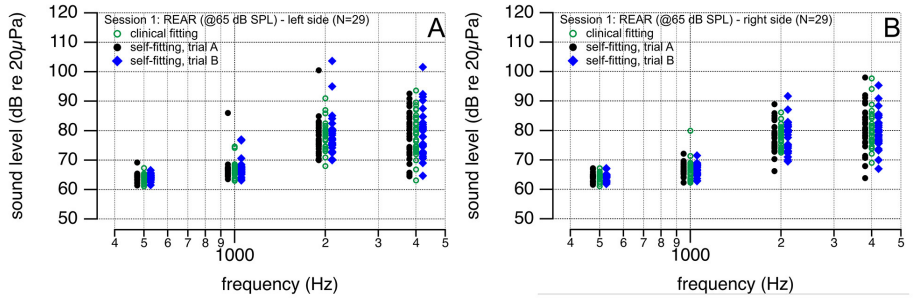


FIGURE 2
**(A,B)** REAR (@65 dB SPL) after the hearing aid was self-fitted by the participant (black circles and blue diamonds) and fitted by a licensed audiologist (green circles). Outcomes are similar.

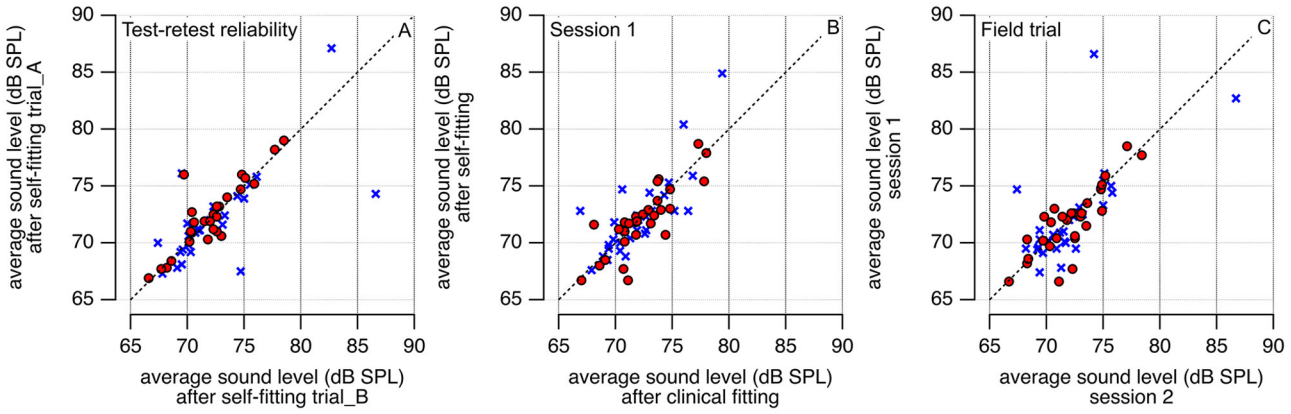


FIGURE 3
REAR measurement results (@65 dB SPL) after the hearing aid was self-fitted by the participant and fitted by a licensed audiologist. Sound levels at 500, 1,000, 2,000, and 4,000 Hz are averaged. In **(A)** the participants' test-retest reliability is shown; in **(B)** the averaged participants' REAR levels after the self-fitting procedure are compared with the results after the clinical fitting. **(C)** Compares the results from session 1 (S1) with those obtained in session 2 (S2). Red circles are data from the right and blue crosses from the left ear.

secondary endpoints were the performance on the QuickSIN test. The robustness of the self-fitting procedure was tested using the results from the REAR measurements, the APHAB, and QuickSIN tests.

## 2.5 The hearing aid

Sontro® Hearing Aids have been used for the clinical study. The device has been designed for users 18 years and older to treat their perceived mild to moderate hearing loss through sound amplification. To meet their hearing needs, hearing aid users can adjust the device's settings without the aid of a hearing care professional. The fitting of the hearing aids is done with an app called otoTune®, installed on the patient's smartphone. The app instructs installing the batteries into the hearing aid battery door. Closing the door activates the Hearing Aid. After the left and the right Hearing Aids were placed into the user's ear canals, the user paired them with the smartphone. If the Hearing Aids were powered on for the first time, they started with basic settings and a small linear gain of <15 dB. User controls were limited until the self-fitting process with the dedicated fitting feature on the otoTune® app was completed.

During the fitting procedure, the hearing aid presented the users with a series of tones. The user taped the app on the smartphone screen to indicate when or if a tone was heard. Based on the user's responses to these tones, initial gain settings were applied according to the NAL/NL2 fitting algorithm. This self-assessment of hearing loss, described in detail in a previous publication (Boven et al., 2023), does *not* provide the user with feedback about the accuracy of their responses, nor does it give the user a diagnosis or information about their hearing loss. The information obtained during this process is used internally to fit the device to the NAL/NL2 prescribed gain by frequency in each ear. An important element of the Sontro® Hearing Aid is the possibility of fine-tuning the devices for volume via the rocker switches after the initial fitting. During the self-fitting, the Hearing Aids monitor the broadband background noise level. If the noise level was too

TABLE 2 Outcome measures from the REAR test.

| | $REAR_{CF} - (REAR_{SFA} + REAR_{SFB})/2$ | $REAR_{SFA} - REAR_{SFB}$ | $REAR_{CF(S1)} - REAR_{CF(S2)}$ | $REAR_{SF(S1)} - REAR_{SF(S2)}$ |
|---|---|---|---|---|
| **Number of sets** | 58 | 58 | 22 | 36 |
| Both ears | | | | |
| avg_all | 0.2 | −0.1 | −0.5 | −0.2 |
| std_all | 1.9 | 2.5 | 1.9 | 1.5 |
| serr_all | 0.2 | 0.3 | 0.4 | 0.3 |
| 95% CI_upper bound_all | 0.8 | 0.7 | 0.6 | 0.4 |
| 95% CI_lower bound_all | −0.4 | −0.9 | −1.5 | −0.9 |
| **Number of sets** | 29 | 29 | 11 | 18 |
| Left ears | | | | |
| avg_left | 0.0 | −0.4 | −0.6 | −0.2 |
| std_left | 2.1 | 3.2 | 1.3 | 1.2 |
| serr_left | 0.4 | 0.6 | 0.4 | 0.3 |
| 95% CI_upper bound_left | 0.9 | 1.0 | 0.4 | 0.5 |
| 95% CI_lower bound_left | −0.9 | −1.8 | −1.6 | −0.9 |
| Right ears | | | | |
| avg_right | 0.3 | 0.3 | −0.3 | −0.3 |
| std_right | 1.7 | 1.5 | 2.3 | 1.9 |
| serr_right | 0.3 | 0.3 | 0.7 | 0.4 |
| 95% CI_upper bound_right | 1.1 | 0.9 | 1.5 | 0.8 |
| 95% CI_lower bound_right | −0.4 | −0.4 | −2.2 | −1.3 |

loud during the hearing assessment and self-fitting, the user was instructed to repeat the self-fitting in a quieter environment.

## 2.6 Ethics declaration

All experimental procedures with human subjects followed ethical standards and the 1964 Helsinki Declaration and its later amendments. The study was submitted and approved by BRANY IRB (*BRANY File # 22-02-771-1327*). Each subject gave informed written consent before participating in this study.

# 3 Results

## 3.1 Test subjects

Forty-six potential patients were screened. Twenty-nine, 13 men and 16 women fulfilled the inclusion criteria and enrolled in the study. By ethnicity, 79.3% ($N = 23$) were White/Caucasian, 10.3% ($N = 3$) Black/African American, and 10.3% ($N = 3$) Asian (Table 1). All patients who were enrolled completed the study. The age of the patients ranged from 31 to 75 years, on average 58.9 ± 11.7.

The educational level was a different demographic obtained during enrollment. Participants had a Doctoral degree ($N = 1$, 3%), a Master's degree ($N = 5$, 17%), a Bachelor's degree ($N = 12$, 41%), an Associate degree ($N = 2$, 7%), and some college education ($N = 9$, 31%).

The inclusion criterion required at least one hearing threshold >20 dB HL. This selection criterion bears the possibility that for the frequency range between 250 and 8,000 Hz, many individuals may have normal hearing at most or nearly all audiometric frequencies. The audiograms of the left and right ears are shown in Figure 1. With an evident hearing loss of more than 20 dB for frequencies above 1,000 Hz, the device must provide amplification, and the setting of the hearing aid gain through self- vs. clinical fitting is crucial.

## 3.2 Real-ear-aided response (REAR)

The sound pressure level in dB relative to 20 μPa (SPL) was determined as a function of frequency at a specific point in the ear canal with the hearing aid in place and turned on. Measurements were completed after the hearing aids were fitted using the SFA, SFB, and CF procedures. They are shown in Figure 2. The results demonstrate that little amplification is required at 500 and 1,000 Hz. Different for 2,000 and 4,000 Hz. REAR outcomes following the self-fitting procedure, trial A and trial B, and the fitting by a licensed audiologist are similar at the selected frequencies. The confidence intervals of the REAR differences after self- and clinical fitting of

TABLE 3 Results from the two-sided Wilcoxon rank sum test to test the null hypothesis that data are samples from continuous distributions with equal medians, against the alternative that they are not.

| Criterion tested | *P* | decision (0 = not significant) |
|---|---|---|
| Left ear: $REAR_{SFA}$-$RAER_{SFB}$ | 0.85 | 0 |
| Right ear: $REAR_{SFA}$-$RAER_{SFB}$ | 0.77 | 0 |
| Both ears: $REAR_{SFA}$-$RAER_{SFB}$ | 0.91 | 0 |
| Left ear: $REAR_{CF(S1)}$-$REAR_{SF(S1)}$ | 0.70 | 0 |
| Right ear: $REAR_{CF(S1)}$-$REAR_{SF(S1)}$ | 0.60 | 0 |
| Both ears: $REAR_{CF(S1)}$-$REAR_{SF(S1)}$ | 0.51 | 0 |
| Left ear: $REAR_{CF(S2)}$-$REAR_{SF(S2)}$ | 0.22 | 0 |
| Right ear: $REAR_{CF(S2)}$-$REAR_{SF(S2)}$ | 0.26 | 0 |
| Both ears: $REAR_{CF(S2)}$-$REAR_{SF(S2)}$ | 0.11 | 0 |
| $APHAB\text{-}benefit_{GLB\_CF}$-$APHAB\text{-}benefit_{GLB\_SF}$ | 0.57 | 0 |
| $APHAB\text{-}benefit_{EC\_CF}$-$APHAB\text{-}benefit_{EC\_SF}$ | 0.56 | 0 |
| $APHAB\text{-}benefit_{RV\_CF}$-$APHAB\text{-}benefit_{RV\_SF}$ | 0.22 | 0 |
| $APHAB\text{-}benefit_{BN\_CF}$-$APHAB\text{-}benefit_{BN\_SF}$ | 0.17 | 0 |
| $APHAB\text{-}benefit_{AV\_CF}$-$APHAB\text{-}benefit_{AV\_SF}$ | 0.74 | 0 |
| $QSIN_{SFA}$ – $QSIN_{SFB}$ | 0.60 | 0 |
| $QSIN_{CF(S1)}$ – $QSIN_{SF(S1)}$ | 0.41 | 0 |
| $QSIN_{CF(S2)}$ – $QSIN_{SF(S2)}$ | 0.79 | 0 |

All results showed that differences are not statistically different.

the hearing aids were within −5 and 5 dB SPL in each frequency band.

In addition to sound levels at individual frequencies, the average sound levels were then calculated using the results at 500, 1,000, 2,000, and 4,000 Hz. In Figure 3A, the outcomes after fitting the hearing aid using the self-fitting procedures SFA and SFB were compared to document the robustness of the procedure. Figure 3B shows the results following the self-fitting, SF (SF = (SFA + SFB)/2), and the clinical fitting CF procedures. Figure 3C shows the REAR levels after the self- and clinical fitting of the hearing aid during session 1 and the clinic fitting in session 2. The REAR values are comparable for all three conditions after the self- and clinical fitting and for the left and right sides (Figure 3).

Table 2 shows the averages in sound levels for those frequencies, the differences between the average sound levels following SFA and SFB ($REAR_{SFA}$-$REAR_{SFB}$), and the difference in average sound levels after the SF and the CF in session 1 ($REAR_{CF}$-($REAR_{SFA}$+$REAR_{SFB}$)/2), and the SF and CF procedure after the field trial (before-after). The 95% confidence intervals (CI) were calculated for both ears and the right and left ears separately.

The Jarque-Bera test showed that all REAR values from the left ear and the combined left and right ear data are not normally distributed. The two-sided Wilcoxon rank sum test was used to test the null hypothesis that data are samples from continuous distributions with equal medians against the alternative that they are not. Results for the different conditions tested are shown in Table 3.

A non-inferiority analysis was conducted to further compare the outcomes of the self-fitting and clinical fitting procedures. The REAR results showed that the self-fitting procedure was non-inferior to the clinical-fitting procedure (Figure 4). For the calculations of the confidence intervals, the significance level was adjusted for the number of analyses on the dependent variable, two primary endpoints, using the Bonferroni method (Table 4).

S1–S2 shows the difference between the average performance on the QuickSIN test after the clinical fitting and the clinical fitting. Bars show the confidence interval, 95% CI [−1.3, 1.5]. SFA-SFB shows the difference between the average performance on the QuickSIN test after the clinical-fitting trial A (SFA) and the self-fit trial B (SFB). Bars show the confidence interval, 95% CI [−1.1, 1.3]. CF-SF shows the difference between the average performance on the QuickSIN test for the field study. One group had the clinical fitting, and the other had the self-fitting procedure for the hearing aids. Bars show the confidence interval, 95% CI [−1.5, 0.8].

## 3.3 Abbreviated profile of hearing aid benefit (APHAB)

The APHAB is a self-assessment inventory for patients to rate their challenges with communication or noises in various everyday situations. The scores and benefits of the hearing aid for the two approaches, clinical-fitting and self-fitting, are shown and quantified (Figure 5). Both approaches show an improvement in the APHAB scores for the global (GLB), ease of communication (EC), reverberation (RV), and background noise (BN). The aversion (AV) increases after using the hearing aid for the clinical fitting and the self-fit group. Scores during session 2 (S2) were lower than during session 1 (S1), demonstrating a perceived benefit of the hearing aid use. Scores between the self-fitting and the clinical fitting groups compare, being higher in the clinical-fitting group. Session 2 reflects the self-assessment after 1 week of hearing aid use.

A graphic representation of the data is given in Figures 5, 6. Green markers indicate the data obtained from the patients using the clinical fitting, and the red circles show the data from the patients with the self-fitting procedure. All hearing aid fitting procedures show an improvement of the APHAB scores for the global (GLB), ease of communication (EC), reverberation (RV), and background noise (BN). The aversion (AV) increases after using the hearing aid for the clinical-fitting and the clinical-fitting groups. The raw data, averages, and standard deviations are shown in Figure 6. The red markers show the data for the clinical fitting,

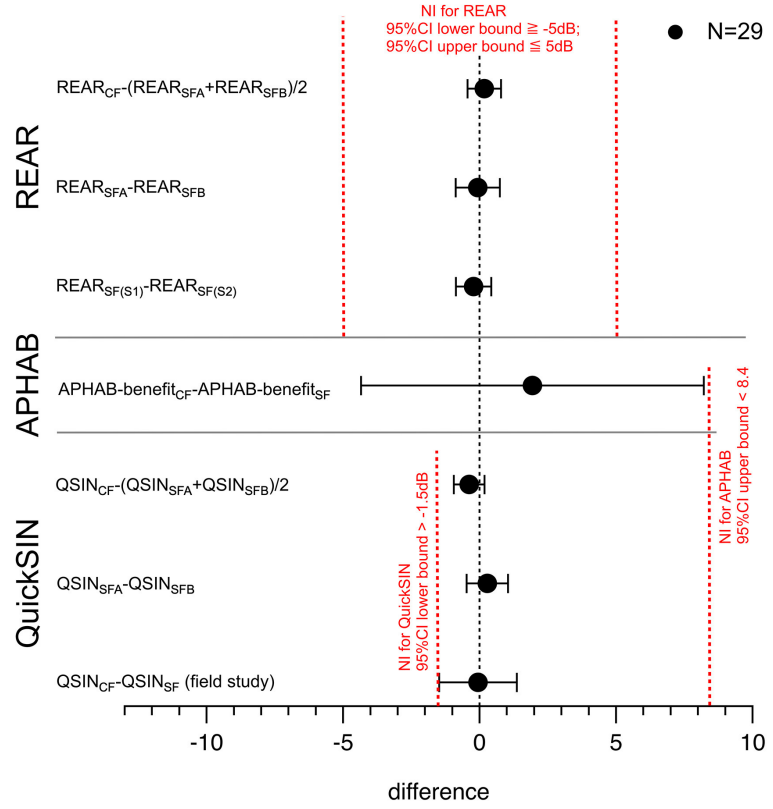


FIGURE 4
The point estimate of the REAR values (both ears) for the self-fitting procedure is 1.9%, favoring the clinical fit. The figure shows the difference between the means, lower, and upper bound of the 95%-confidence interval. The point estimate of the REAR measurements $REAR_{CF}$-($REAR_{SFA}$+$REAR_{SFB}$)/2 demonstrates non-inferiority. The upper bound of the 95% CI for clinical-fitting benefit—clinical-fitting benefit is <M, and the lower bound is <0, demonstrating non-inferiority.

circles for the raw data, circles with black lines for averages ± one standard deviation, the green markers show the data for the clinical fitting, circles for the raw data, and circles with black lines for averages ± one standard deviation. The cyan diamonds indicate the differences in benefits of using a hearing aid for clinical fitting and self-fitting procedures. Differences >0 favor the clinical fitting, and differences <0 favor the self-fitting; for differences =0, none of the conditions is favored.

To test for non-inferiority in hearing aid benefits using the self-fitting and the clinical-fitting procedures, we calculated the averages ± one standard deviation of the benefits determined by the APHAB for the two conditions (Figure 4). The average differences of befit for the hearing aid use are 1.9 ± 6.9, 2.0 ± 11.7, −6.0 ± 15.6, 7.0 ± 11.2, and 0.2 ± 16.1 for GLB, EC, RV, BN, and AV, respectively. Note that the standard deviations reflect the pooled standard deviations for the two groups. For the non-inferiority testing, the confidence intervals are calculated; the upper and lower bounds are shown in Figure 4. Since the sample size in any of the groups is below 30, the value for t-critical was taken from the t-distribution table of critical values with a degree of freedom of 27 (n1 + n2 − 2), with n1 the number of patients in the clinical-fitting group, and n2 the number of patients in the CF group.

The GLB was one of the primary endpoints for our study, with a non-inferiority margin of 8.4%. The average difference for the hearing aid benefits (clinical-fitting minus self-fitting) determined by the global results of the APHAB is 1.9%, with a 95% CI [−4.35, 8.21]. The point estimate of the clinical-fitting benefit—clinical-fitting benefit is 1.9%, favoring the clinical fit. The lower bound, −4.35%, is below 0, and the upper bound of the 95% CI for clinical-fitting benefit–clinical-fitting benefit is 8.21% < M, demonstrating non-inferiority (Figure 4).

## 3.4 Quick speech-in-noise (QuickSIN) test

The SNR losses in dB for the subjects participating in the study are shown in Figure 7. For all patients, the performance on the QuickSIN test was first obtained without a hearing aid ($QSIN_{unaided}$). It was then repeated with a hearing aid after fitting it with the self-fitting ($QSIN_{SFA}$ and $QSIN_{SFB}$) and the clinical fitting ($QSIN_{CF}$) procedure. The plots in Figure 7A show that hearing aids improve performance for participants with hearing loss. Figure 7B shows the results after the two trials of self-fitting the hearing aids; red circles show the values obtained after SFA, and the blue circles after SFB. Figure 7C compares the performance after using the clinical fitting and self-fitting procedure following the one-week field trial. The results for the three secondary endpoints (SE1 to SE3) are tabulated in Table 4.

TABLE 4 Averaged results from the QickSIN tests.

| N | ID | Raw data | | | | | | | | SE 1 | SE 2 | SE 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Session 1 (S1) | | | | Session 2 (S2) | | | | S1 | | S2 | |
| | | $QSIN_{unaided}$ | $QSIN_{SFA}$ | $QSIN_{SFB}$ | $QSIN_{CF}$ | $QSIN_{SFA}$ | $QSIN_{SFB}$ | $QSIN_{CF}$ | $(QSIN_{SFA} + QSIN_{SFB})/2$ | $QSIN_{CF} - (QSIN_{SFA} + QSIN_{SFB})/2$ | $QSIN_{SFA} - QSIN_{SFB}$ | $QSIN_{SFA}$ or $QSIN_{SFB}$ | $QSIN_{CF}$ |
| Number of sets | | 29 | 29 | 29 | 29 | 10 | 8 | 11 | 29 | 29 | 29 | 18 | 11 |
| Avg | | 2.84 | 2.07 | 1.79 | 1.55 | 1.60 | 1.81 | 1.64 | 1.93 | −0.38 | 0.28 | 1.69 | 1.64 |
| Std | | 2.52 | 1.82 | 1.26 | 1.44 | 1.56 | 1.44 | 1.70 | 1.31 | 1.28 | 1.72 | 1.47 | 1.70 |
| Serr | | 0.47 | 0.34 | 0.23 | 0.27 | 0.49 | 0.51 | 0.51 | 0.24 | 0.24 | 0.32 | 0.35 | 0.51 |
| Avg ($QSIN_{CF}$) – Avg ($QSIN_{SF}$) | | | | | | | | | | | | −0.06 | |
| std_p | | | | | | | | | | | | 1.56 | |
| serr_p | | | | | | | | | | | | 0.60 | |
| 95% CI_upper bound = [avg($QSIN_{CF}$) – avg($QSIN_{SF}$)] + tc*s_error | | | | | | | | | | 0.183 | 1.032 | 1.36 | |
| 95% CI_lower bound = [avg($QSIN_{CF}$) – avg($QSIN_{SF}$)] – tc*s_error | | | | | | | | | | −0.94 | −0.48 | −1.47 | |





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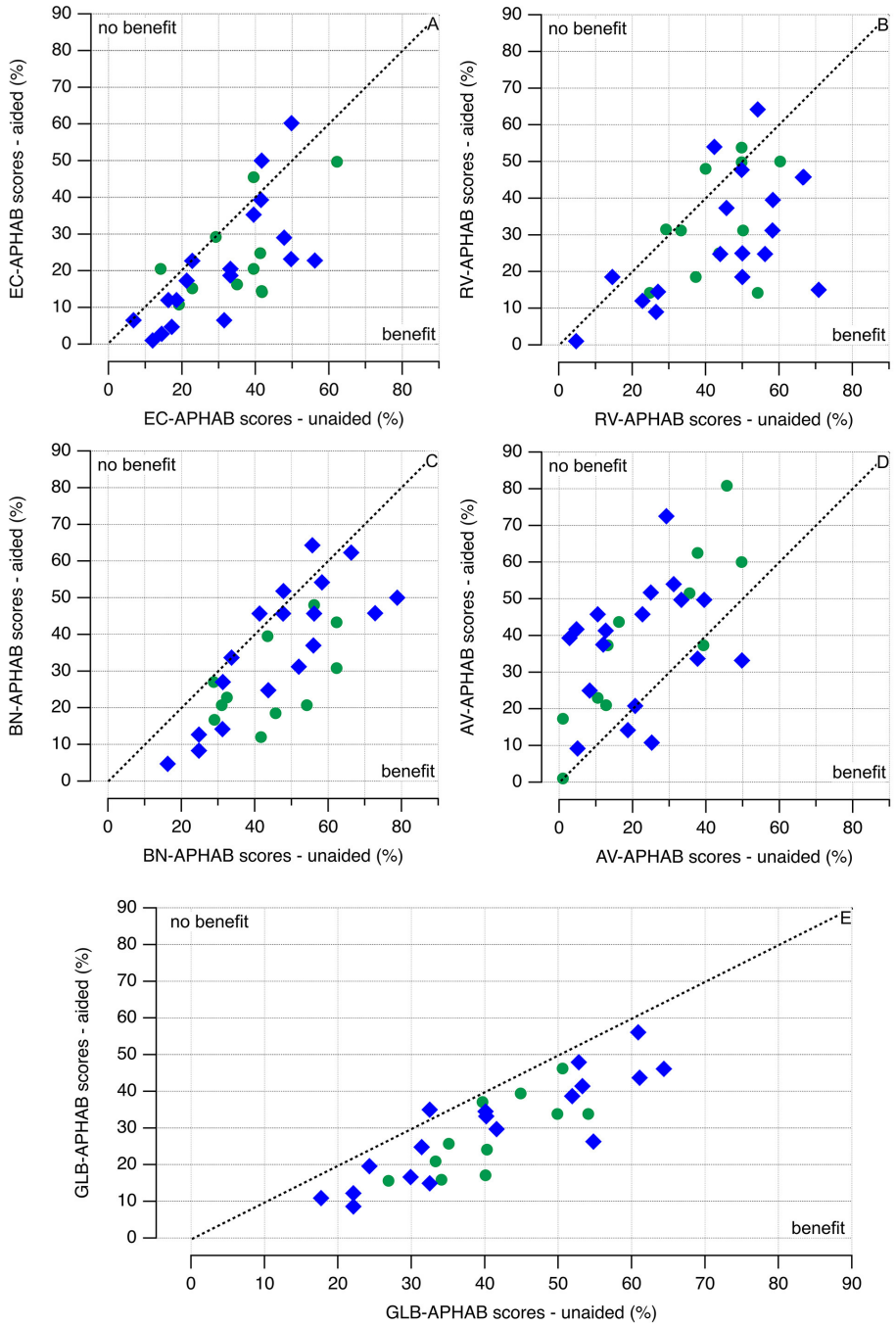


FIGURE 5
**(A–E)** APHAB test scores. Blue diamonds indicate that the hearing aid was self-fitted, and green circles indicate the outcomes of a healthcare professional fitting the hearing aid. The APHAB benefit is calculated by subtracting the patient's reported scores (difficulty) in the aided condition from their scores (difficulty) in the unaided condition. The hearing aids benefit if the data points are below the broken line (APHAB scores unaided > APHAB scores aided). While the data are variable, no clear difference between clinical fitting and self-fitting of the hearing aids can be seen from the plots.

While S2-S1(CF) provides the difference between the performance on the QuickSIN test in session 1 and session 2 after the field trial with the clinical fit of the hearing aid, S2-S1(SF) provides the difference after the field trial with a clinical fitting of the hearing aid. The columns with the header SFA-SFB provide the performance in session 1 on the QuickSIN test after the clinical-fitting trials, $QSIN_{SFA}$, and $QSIN_{SFB}$. The columns with the header CF-SF provide the performance in session 1 on the QuickSIN test after the self-fitting ($QSIN_{SF}$) and the clinical fitting ($QSIN_{CF}$) procedure.

The QuickSIN SNR losses in Figure 7A appear considerably lower and more homogeneous than those previously reported in other extensive studies (Fitzgerald et al., 2023; Smith et al., 2024).

This may indicate that most of the patients had normal or near-normal hearing. Figure 8 shows QuickSIN SNR losses in our study. They are in agreement with the reported values in the literature. For example, Fitzgerald et al. (2023) demonstrated the relation between the high-frequency pure tone average (HFA), an average of the audiogram at 1,000, 2,000, and 4,000 Hz, and the SNR loss. An HFA <15 dB HL (normal hearing) has a mean QuickSIN SNR loss of 2.16 dB (range: −3.5 to 13.5 dB), an HFA of 16–25 dB HL (normal hearing) has a mean QuickSIN SNR loss of 3.14 dB (range: −3.5 to 16.5 dB), an HFA of 26–40 dB HL (mild hearing loss) has a mean QuickSIN SNR loss of 5.09 dB (range: −3 to 25.5 dB), and an HFA of 41–55 dB HL (moderate hearing loss) has a mean QuickSIN SNR loss of 8.21 dB (range: −3.5 to 23.5 dB). For the right ears, in our study, the QuickSIN SNR loss was 2.5 dB (HFA: <15 dB HL), 1.86 dB (HFA: 16–15 dB HL), 3 dB (HFA: 26–40 dB HL), and 7.5 (HFA: 41–55 dB HL); For the left ears it was 2.0 dB (HFA: <15 dB HL), 1.79 dB (HFA: 16–15 dB HL), 3.14 dB (HFA: 26–40 dB HL), and 6.83 (HFA: 41–55 dB HL).

To test the non-inferiority of the clinical fitting procedure, the difference in performance on the QuickSIN test was compared with the results after the clinical fitting. The difference in the averages on the QuickSIN was calculated to compare the two methods, including the corresponding pooled standard deviations and confidence intervals (Table 4). The data showed non-inferiority for the clinical-fitting procedure compared to the clinical-fitting procedure (Figure 4).

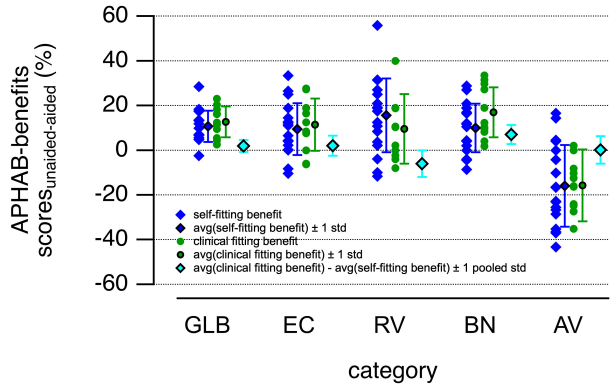


FIGURE 6
The figure shows the hearing aid benefits obtained by subtracting the APHAB scores for the aided from the unaided condition. The benefits for the clinical-fitting group (green circles) and the self-fitting group (blue diamonds) in sessions 1 and 2 are shown. The averaged benefits for the clinical-fitting group (green circles with black lines) and the self-fitting group (blue diamonds with black lines) in sessions 1 and 2 are plotted next to the raw data. Error bars equal ± one standard deviation. The differences in hearing aid benefits for the self- and clinical fitting procedures were calculated by subtracting the average of the APHAB scores after self-fitting the hearing aids from those obtained after the clinical fitting procedure (cyan diamonds with black lines). The error bars show the pooled standard deviations for the differences. Abbreviations for the sub-categories of the APHAB are global (GLB), ease of communication (EC), reverberation (RV), background noise (BN), and aversion (AV). Averages and standard deviations were calculated.

## 4 Discussion

The study aimed to validate that the self-fitting of hearing aids is non-inferior to the clinical fitting of the devices. The study results include the REAR values, outcomes from the APHAB test, and the results from the QuickSIN test. All primary and secondary endpoints were reached. The results showed good test-retest reliability and that the self-fitting of the OTC hearing aids is non-inferior to fitting the same hearing aids by a licensed audiologist. OTC hearing aids constitute a viable option in treating mild-to-moderate hearing loss in adults, with the added benefit of lower costs to the patients and the ability to treat in locations

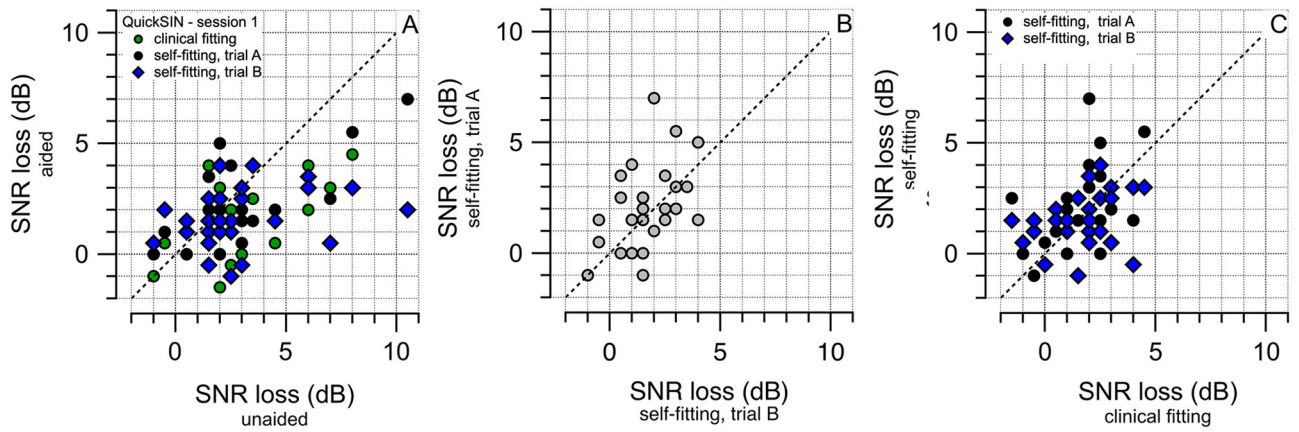


FIGURE 7
The results of the QuickSIN test after the hearing aid fitting during session 1 are shown. The fitting procedures are the self-fitting, SFA and SFB, and the clinical fitting (CF). **(A)** Shows the changes before or after the fitting of the hearing aids. The color of the circles indicates the fitting method, SFA (first trial) by the black circles, SFB (second trial) by the blue diamonds, and clinical fitting shown by the green circles. For participants, changes in the aided condition appear favorable over the unaided. **(B)** Shows the outcomes of the QuickSIN test after the two SF procedures, SFA and SFB. Outcomes are comparable, confirming the test-retest reliability. **(C)** Shows the outcomes of the QuickSIN test for the field trial (one week of use of the fitted hearing aid). Outcomes between the self-fitting and the clinical fitting are comparable.

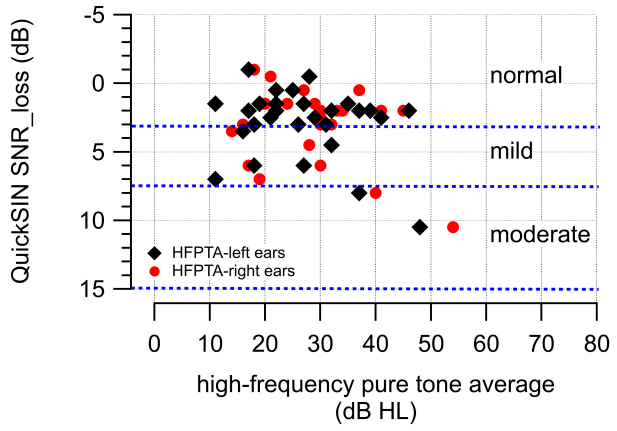


FIGURE 8
The figure shows the high-frequency pure tone averages obtained for the left and right ears of the participants and the corresponding QuickSIN SNR losses in dB.

with limited access to health care providers. Noteworthy is that the patient's audiogram, which serves as the starting point for the fitting process, was obtained with the hearing aids and the Gaussian Process as described before (Boven et al., 2023).

Hearing aid fitting by a certified health professional starts with establishing a starting condition, typically a patient's behavioral hearing threshold (audiogram). From this initial information, amplification parameters for the hearing aid are deduced. The patient's hearing experience is then adjusted through fine-tuning. For over-the-counter hearing aids, the device fitting process needs the patient, who will accomplish the fitting process. Hereby, the level of the participants' education is a factor that can affect the outcomes of the self-fitting procedure. This study has a significant number of participants with some college education ($N = 9$, 31%) and a Bachelor's degree ($N = 12$, 41%). The distribution of the level of education and the relatively small number of study subjects do not allow a decision on how much education affects the outcomes of the self-fitting procedure.

The idea of self-fitting hearing aids is not novel (Köpke et al., 1984). However, barriers to the first concepts included missing sound sources, training algorithms, and additional user controls to further fine-tune the device (Dillion et al., 2006). Hearing aid self-fitting procedures include steps like those of an audiologist. The procedures enable users to perform threshold measurements, leading to a prescribed hearing aid setting and fine-tuning. No audiological support or access to other equipment is required for this procedure (Köpke et al., 1984; Convery et al., 2011a,b,c; Keidser and Convery, 2016, 2018). While self-fitting hearing aids have been commercially available for some time, the challenge for the devices is the simplicity and robustness of the fitting process. Previously published results demonstrated that under controlled conditions, in a sound-reduced environment, the Gaussian process constitutes a fast and robust method to determine a patient's audiogram (Cox and De Vries, 2016, 2021). The audiogram is converted into amplification settings of the hearing aid and serves as the starting point for fine-tuning the hearing aid fitting. We expanded on the concept and have shown that similar results can be achieved in a "field setting" with a patient's hearing aid (Boven et al., 2023).

This study confirmed that self-fitting the hearing aid is non-inferior to an audiologist's fitting of the devices. While the results are reassuring, one must be aware of the limitations of purchasing hearing aids without the involvement of a physician or audiologist. The devices are for treating perceived mild to moderate hearing loss. The patient makes this decision without direct feedback or reports from a professional healthcare provider. Therefore, patients with normal hearing thresholds may use a hearing aid. The device fitting under those conditions, when little to no amplification is required, is difficult, and the benefit of a hearing aid can be limited. Our REAR measurements and the APHAB results demonstrate that the hearing aid can be self-fitted and benefit the patient.

According to large-scale studies, high-frequency pure tone averages (HFPTA) and the performance on a speech-in-noise test (QuickSIN) or word recognition test correlate (Fitzgerald et al., 2023; Smith et al., 2024). While the correlation is obvious, the variability of the results is still large. For example, patients with close to normal HFPTA can have a range of QuickSIN SNR losses found in normal hearing patients and SNR losses in patients with moderate hearing loss. In both scenarios, the patient may decide to use a hearing aid. Even if the patient has normal hearing, it is important that the self-fitting procedure does not overamplify the sound. In this study we tested, by measuring the REAR, the acoustic output of the hearing aid after self-fitting and fitting by an audiologist. We also verified that the results obtained by each patient are repeatable.

An important question is whether a selection bias in the testing procedures and materials exist and might have affected the study outcomes. The QuickSIN test includes 18 lists. The equivalency of the lists was determined by the mean recognition performance of normal hearing- and hearing-impaired listeners (McArdle and Wilson, 2006). Their data showed that nine lists provide homogenous results for normal and hearing-impaired listeners. The performance by normal-hearing listeners was 2.8–4.3 dB SNR and 10–14.3 dB SNR by hearing-impaired listeners. Individual performance for lists 4, 5, 13, and 16 showed high-performance variability for the hearing impaired but not for normal hearing listeners. Consequently, listeners with hearing loss require a more favorable SNR to obtain equal performance. In response to McArdle and Wilson (2006) and Killion et al. (2006), argued that including the non-homogenous lists should not influence the results. For our study, we did not distinguish between homogenous and non-homogenous lists during the testing.

Whether a subjective description of the patient's hearing abilities is sufficient for the hearing aid fitting or if the assessment of the patient's hearing is essential remains to be discussed. Important remains the fine-tuning, where the patients adjust the amplification parameters of the hearing aids for user satisfaction (Dillion et al., 2006).

In summary, it is important to emphasize that the results and conclusion obtained in this study strictly relate to the specific self-fitting process using the Gaussian Process. This method was implemented in the Sontro® Hearing Aids. Since many other potential methods for fitting hearing aids exist, the proposed method should not be extended to a general class called self-fitting or OTC hearing aids. Future field studies are required to compare the efficacy of the self-fitting methods.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were submitted and approved by BRANY IRB (BRANY File # 22-02-771-1327). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

CB: Resources, Project administration, Funding acquisition, Writing – review & editing, Supervision, Software, Methodology, Investigation, Conceptualization. JT: Validation, Resources, Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. KD: Writing – review & editing, Investigation. C-PR: Conceptualization, Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation.

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## Conflict of interest

CB and JT are members of the Soundwave Hearing technical team. KD is employed at Evanston Audiology, PLLC. C-PR is employed at Northwestern University and served as a consultant to Soundwave Hearing.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



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# Real-world assessment of listener preference for hearing aid technology levels in socially involved situations

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**Introduction:** Current hearing aids have an abundance of feature options and technologies. It is important to understand the clinical impact of hearing aid technology selection and how to individualize fittings to optimize hearing aid performance according to listening environment. To probe the naturalistic listening experiences researchers can use *in-situ* outcome measures. Survey-based real-world assessments can increase knowledge of hearing aid users' everyday scenarios, beyond the limits of lab-based scenarios. This study aimed to assess the relationship between subjective preference ratings of adult listeners and hearing aid technology level using Ecological Momentary Assessment (EMA). A secondary research question explored survey completion as a function of real-world participation in socially involved situations.

**Methods:** This study aimed to capture and assess in-the-moment listening situations and participant preference for hearing aid technology levels, using EMA through an app-based survey. Surveying was completed indoors (at home), indoors (away from home); and outdoors, and while in a listening situation with at least one communication partner. Fourteen older adults, aged 61–82 years, who were experienced bilateral hearing aids users were included in this study. Participants completed a 2-week acclimatization period wearing study-provided hearing aids, and a 2-week data collection period. *In-situ* surveying was used to evaluate technology-level preference in real-world listening situations with at least one communication partner. Survey data captured in-the-moment details surrounding environment, activity, and listening preference. Mixed methods were used to analyze the data, including Bayesian analyses for preference data and content analysis for text-based survey responses, including the use of the International Classification of Functioning, Disability and Health to guide activity categorization.

**Results:** Across a wide variety of categorized activities, participants demonstrated a preference for mid- to high-level hearing aid technologies when compared to the lowest level. Technology preference also varied according to reported activity location.

**Discussion:** The use of *in-situ* surveying provided a broader understanding of hearing aid users' listening environments when conversing with one or more communication partners and related technology preferences. EMA was found

to be a feasible method of data collection for this cohort and may help guide clinical, person-centered selection of technology level.

KEYWORDS

**Ecological Momentary Assessment, hearing aids, listening effort, loudness perception, self-report, patient preference**

# 1 Introduction

Hearing aid technologies are traditionally evaluated using in-lab measures involving pre-recorded stimuli and sound treated rooms. These methods are effective in establishing performance benchmarks using standardized materials; however, resulting outcomes may not generalize to performance in real-world listening situations. When looking at the correlates of hearing aid use, research suggests that adult hearing aid users are likely to be involved in more social activities than nonusers (Sawyer et al., 2019). Furthermore, participation in socially involved listening situations (defined as a listening environment where the hearing aid user is involved in conversing with one or more people) is one of the most important use cases for hearing impaired listeners wearing hearing aids (Sawyer et al., 2019; Holman et al., 2021). Hearing aid users often report difficulties in challenging socially involved listening situations, including effects on social isolation and emotional wellbeing (Yadav et al., 2023). Social interactions generally involve one or more communication partners, with increased communication effort in the presence of background noise (Pasta et al., 2022). Recognizing situation-specific challenges can help address technology needs.

To better probe the naturalistic listening experiences from the user's perspective, researchers often incorporate outcome measurement options, such as real-world assessments involving the use of surveys, questionnaires, or interview-style follow-up. This allows for the exploration of everyday scenarios encountered by users of hearing aids in real life. With the abundance of feature options and technology levels available in current hearing aids, it is important to learn how to best individualize fittings, to optimize hearing aid performance for each listening environment, and to utilize hearing aid technology to the fullest.

Experience Sampling Methods (ESM) can be used to collect data surrounding unique real-world listening environments. One type of ESM that captures repeated sampling of participants' behaviors and experiences in real-world natural environments is known as Ecological Momentary Assessment (EMA; Schinkel-Bielefeld et al., 2020; Shiffman et al., 2008). EMA data can be collected in-the-moment via questionnaires delivered through paper-and-pencil survey formats or through electronic surveys, during or shortly after an activity of interest (often referred to as real-time sampling, or near-real-time sampling). Studies that use traditional survey methods are often subject to systematic errors in self-reporting resulting from memory decay, also known as recall-bias (Khare and Vedel, 2019). This memory decay occurs when participants are required to retroactively complete surveys that are not simultaneously occurring with the activity of interest. This bias is reduced by using EMA, which allows for the assessment of individual experiences in day-to-day life and in real-time, when using mobile devices to administer (Shiffman et al., 2008). In a recent study, *in-situ* self-reports collected through EMA methods were found to be more sensitive to measures of outcomes between different hearing aid listening conditions than retrospectively collected data (Wu et al., 2020). EMA is described as a feasible and valid research methodology to assess hearing aid users' individualized hearing experiences and can inform more responsive, personalized, and family-centered hearing care (Galvez et al., 2012; Glista et al., 2021; Timmer et al., 2017; Wu et al., 2015; Xu et al., 2020; Christensen et al., 2024a; Vercammen et al., 2023). While EMA can be used to collect information at certain times or upon detection of specific environmental parameters (e.g., through hearing-aid integrated applications), it is also commonly self-initiated, allowing listeners to decide when an event of interest takes place as the trigger to report on their experiences by manually accessing a survey (Holube et al., 2020). Additionally, EMA can provide the opportunity to describe experiences or environments using an open-text field.

Mobile device-based EMA methods have been used more recently to capture daily life listening experiences from individuals wearing hearing aids (Wu et al., 2020, 2015, 2023). One common type of evaluation completed using EMA is a preference assessment, which can be used to help assess an individual's understanding and provide clarity of their personal values, health care situations, treatment options, and likely outcomes through an iterative, cognitive process (Brennan and Strombom, 1998). Preference ratings are highly valued by clinicians as one of the most important factors in decision-making processes, especially when considering patient-centered care (Boisvert et al., 2017; Bridges et al., 2012). Additionally, being able to infer preference in real-world settings using EMA, may make clinical decision-making about hearing aid technology levels more relevant and contextualized for the hearing aid users. Outside of EMA methods and over the past decade, studies have begun to focus on end-user preferences for different technology levels, including a comparison of basic and premium hearing aids, evaluations with new hearing aid users, evaluations of audiological parameters such as noise reduction, brightness,

Abbreviations: 4PTA, Four frequency pure-tone average; CI, Credible interval; Db HL, Decibels Hearing Level; DB SPL, Decibels Sound pressure level; EMA, Ecological Momentary Assessment; ELPD, Expected log predictive density; ESM, Experience Sampling Methods; ICF, International Classification of Functioning, Disability and Health; MCMC, Markov chain Monte Carlo; P, Program; PSIS-LOO, Pareto smoothed importance sampling leave-one-out cross-validation; RECD, Real ear to coupler difference; RIC, Receiver-in-the-canal; SE, Standard error.

and soft gain, and in field trial or lab-based environments (Pasta et al., 2022; Christensen et al., 2024a; Cox et al., 2016; Hausladen et al., 2022; Plyler et al., 2021; Saleh et al., 2022; Houmøller et al., 2023; von Gablenz et al., 2023). Several of these field trial studies used recall-based assessments, identifying that participants indicated varying levels of preference for premium hearing aids, from just over half, to a strong majority (Hausladen et al., 2022; Plyler et al., 2021; Saleh et al., 2022; Christensen et al., 2024b). In contrast, Cox et al. (2016) found no significant differences between hearing aid technology level preferences across four pairs of hearing aids from various brands. While there are studies evaluating technology levels and user preference, there remains a gap in the literature surrounding knowledge of users' in-the-moment preference for real-world scenarios, rather than retrospective evaluation or simulated environments, and evaluations of hearing aid technology levels beyond basic and premium. Additionally, no studies were found to capture the complexity of a listening situation through the use of pre-established categorization frameworks.

Hearing aid manufacturers spend considerable research and development resources creating new and updated iterations of their technology (referred to as platforms). These platforms are offered at different price points (often associated with technology level) that are differentiated by varying degrees of device performance. Typically, the latest product at the highest price point will include the newest features and offer the best performance. Products at a lower price point may not offer the newest features or will offer features with reduced performance capability. For example, the highest price point may include an automatic program that can characterize the listening situation based on acoustic classification and adjust the performance according to the demands of the situation. Such a product may have a fine resolution in acoustic classification (e.g., number of classes) and included the latest signal processing features. At lower price points the device may still include an automatic program, but with fewer situations that can be detected and may not include the most advanced signal processing features or reduced performance of the features that are available. Portfolios of hearing aid technology levels are often marketed to the consumer as successive "sophistication levels", ranging from entry-level devices to premium, each of which provide a prescribed set of features or feature capabilities. More channel numbers or levels (i.e., feature potential) have been found to relate to more technologically advanced devices, with the potential to be fitted with a higher level of sophistication (Lansbergen and Dreschler, 2020). Innovations such as environmental adaptation and binaural data streaming may be embedded in higher-end devices, whereas more simplified technologies would be incorporated into basic-level devices, such as limited environmental classifications, fixed microphone directionality, and fewer compression channels (Hausladen et al., 2022; Plyler et al., 2021; Johnson et al., 2016). Although cost often plays a large contributing role in device-level selection, there may be perceptible differences in sound quality, listening difficulty/effort, and program options that may influence end-user decisions (Johnson et al., 2016). It is important to note that perceptual differences may be viewed as a benefit to some hearing aid users and as a barrier to use for others (Searchfield et al., 2024; Windle et al., 2023). As part of a holistic aural rehabilitation and fitting process, these functional differences may have a greater contribution than device cost in influencing the listener's overall experience with their hearing aids, including how they perceive daily life activities.

To better understand the activities that hearing aid users engage in as a function of real-world hearing aid use, we can use classification frameworks, such as the International Classification of Functioning, Disability, and Health (ICF) (World Health Organization, 2004) or the common sound scenarios (CoSS) (Wolters et al., 2016). These frameworks offer further information a common language for describing health-related states. For example, the ICF domain *activities and participation* offers classification information including (1) learning and applying knowledge; (2) general tasks and demands; (3) communication; (4) mobility; (5) self-care; (6) domestic life; (7) interpersonal interactions and relationships; (8) major life areas; and (9) community, social, and civic life. The CoSS can be used to categorize a listening environment into (1) main intention categories (speech communication, focused listening, and non-specific), (2) task categories (number of people, live or media device sounds, or monitoring surroundings and passive listening), and (3) the sound scenario (conversation at home, conversation on metro, meeting in office, car ride with family, phone call at home, mobile call in the street, lecture, at a concert, watching tv, listening to car radio, vacuum cleaning, city walk, relaxing with a book, relaxing on train). The ICF framework was selected to categorize the execution of a task of action, related to participation in conversation with listening partner(s), without overlapping with additional survey questions or evaluating listeners' intent. The use of the ICF classification framework for the purpose of collecting and distilling important details linking hearing aid users' technology preference with associated daily activities is a novel addition to field trial literature. The current study is part of a larger project investigating objective and subjective metrics of hearing aid technology level in socially involved situations. The primary objective of this study was to assess the correlation between subjective preference ratings of adult listeners and hearing aid technology level using in-the-moment EMA methods. Specifically, this study explored technology level (or maximum reported device performance by product price point) separate from automatic configuration depending on device classification of listening situation. Device-level preferences were evaluated in the context of participant location at the time of EMA surveys, as well as participant-reported background noise exposure. The secondary objective of this study was to investigate the open-text responses of the EMA survey using content analyses to guide systematic categorization of activities reported.

# 2 Methods

## 2.1 Participant characteristics

This study was approved by the Western University Research Ethics Board. All participants received details of the study in the form of an electronic letter of information and provided electronic written consent prior to participation. Fourteen participants, with an equal split of males and females between the ages of 61 and

82 years ($M = 71.9$; $SD = 6.3$), were recruited to participate in this study. One additional participant withdrew during the trial period of the study, prior to initiating data collection, due to health-related reasons, two participants were deemed ineligible to participate due to their hearing loss falling outside the fitting range of the devices used for the study. This study took place following the onset of the COVID-19 pandemic, with participant enrollment beginning in December 2021 through to September 2022. Study delays and participant recruitment challenges related primarily to public health restrictions and/or participant illnesses. Participants were recruited from a database held at the National Center for Audiology and using snowball sampling methods.

Participants were included in the study if they fulfilled the following criteria: (a) adult listeners (minimum 18 years of age); (b) those with self-reported frequent social interactions with one or more friends, family members, or acquaintances; (c) those who presented with symmetrical mild to severe hearing loss thresholds [with a four frequency pure-tone average (4PTA), calculated using 500, 1,000, 2,000, and 4,000 Hz values, not exceeding 70 dB HL, bilaterally; symmetry not exceeding 15 dB HL using the 4PTA], and (d) with at least 12 months' experience of hearing aid use (American Speech-Language-Hearing Association, 2020; Dawes and Munro, 2017; Yamada et al., 2017). Participant self-reported frequency of social interactions suggested that participants would be able to fulfill the required social interaction component of the study, reducing barriers to participate for those who may be more prone to social isolations. Air conduction audiometric assessment included pure-tone threshold measurement at octave and inter-octave frequencies between 250 and 8,000 Hz, in addition to otoscopy and middle ear analyses. Participants were also required to be able to use the technologies involved in the study on their own with a pre-trial demonstration, the hearing aids (including the program and volume toggle and the charging unit), and the Bluetooth functionality of the tablet. These capabilities were assessed by a member of the research team at the initial appointment.

## 2.2 Hearing aid fitting

Participants attended 2–3 appointments during this study, depending on whether the participant required additional hearing aid adjustments. During the first study appointment, participants underwent audiometric threshold measurements and real ear to coupler difference (RECD) measures. In the case that a recent clinical audiogram was available (i.e., within 6 months), the recent audiogram was then used as the basis for the hearing aid fitting. Participants were loaned Unitron Discover Next (DX) Moxi Move rechargeable hearing aids, fitted with medium power (M) receivers. Participants were fit with vented domes ($n = 10$), power domes ($n = 2$), or open domes ($n = 1$), and one participant was fit with a vented dome in one ear and an open dome in the other; dome selection (herein referred to as acoustic coupling) depended on (1) evidence-based best fit for their hearing loss, (2) previous experience, or (3) participant preference. On-ear hearing aid fitting included the application of the DSL v5.0 adult prescriptive method (Scollie et al., 2005), incorporating foam-tip RECD values and real-ear probe tube measurements using the Audioscan Verifit 2 (Version 4.24.4). Fine-tuning was completed using the Verifit 2 standard speech signal at input levels of 55, 65, and 75 dB SPL, and for tone bursts at 90 dB SPL to assess the maximum power output. Further adjustments were made to the hearing aids to address participant subjective reports. Fit-to-target deviations were within 5 dB root mean square error using 500, 1,000, 2,000, 4,000, and 6,000 Hz, for speech input levels at 65 dB SPL, aligning with recommendations for hearing aid fittings (Baker and Jenstad, 2017; Brennan et al., 2017; Dao et al., 2021). In addition, feedback optimization was enabled for three participants and frequency compression for seven participants. Frequency compression was activated to maximize audibility of calibrated/s/stimuli and verified using on-ear measurements (Scollie et al., 2016).

### 2.2.1 Hearing aid configuration

In studies evaluating hearing aid technology levels, it is often necessary to have the different technology levels represented in different pairs of hearing aids. For the purposes of this study, it was not feasible to provide the participants with three different pairs of hearing aids to fully represent the technology levels, where greater burden would have been placed on the participants to bring along additional hearing aids and swap out the devices during each listening environment evaluation. Instead, we created manual programs which emulated the best capability that could be delivered at each product price point. This was achieved through creating three user activated (manual) programs, removing features and reducing the performance capability of the remaining adaptive features in each consecutive manual program. It is acknowledged that the use of manual programs removes the benefits of an automatic program that can adjust the HI performance based on classification of the situation. Instead, this investigation focused on the subjective benefit of the emulated technology levels when each manual program was user activated and delivered the best performance that would be possible in that device (when running in a fully automatic mode).

The study worn hearing aids included the highest technology level of the Unitron Discover Next hearing instruments, with access to the automatic program and the specifically configured manual programs. The automatic program (termed SoundNav) automatically adjusts the strength of the signal processing features based on an environmental classification (i.e., conversations in quiet, small group, crowd, and noise; no conversation in quiet and noise; and music). For this study, hearing aid configuration included four programs (Table 1): Program 1 (P1) was set to SoundNav; Programs 2 through 4 (P2, P3, and P4) included manual programs that did not include the use of SoundNav. P1 functioned as the base fitting program in which individualized frequency gain adjustments were made; this was held constant across all manual programs. For the automatic program (P1), each signal processing feature's maximum strength varied based on environmental classification.

For all programs, the amount of signal processing adjusted adaptively between a setting of zero and the maximum fitted strength. For noise reduction and speech enhancement, the amount of signal modification was adaptively adjusted based on the signal-to-noise-ratio (SNR) and the fitting strength of the feature. The

TABLE 1 Comparison of signal processing features and settings across programs representing varying technology levels.

| Feature | Program 1 | Program 2 | Program 3 | Program 4 |
|---|---|---|---|---|
| Program access | Automatic (SoundNav) | Manual | Manual | Manual |
| Technology level | Adaptive | Premium | Mid | Basic |
| Sound optimization[a] | Range 1–6 | Strong (6) | Moderate (4) | Weak (2) |
| Speech enhancement | Range 0–3.2 dB | +3.6 dB | +2.8 dB | +2.0 dB |
| Noise reduction | Range: −5.8 to 0 dB | −6.4 dB | −5.2 dB | −4.0 dB |
| Optimization for localization/speech understanding | Pinna effect[b] or fixed wide directional | SpeechPro[c] with fixed wide directional | Fixed wide directional | Spatial awareness |

[a]Incorporates speech enhancement and noise reduction with microphone strategy to maximize signal to noise ratio (Howard, 2014).
[b]Pinna effect is enabled for conversation in quiet or small group, no conversation in quiet, and music; fixed wide directional is enabled for conversation in a crowd or in noise and no conversation in noise.
[c]Includes ability to dynamically locate a target speech signal in one of four quadrants (front, right, left, back) around a listener and to modify directionality, noise cancellation, and speech enhancement, including asymmetrically for speech targets to the side.

microphone mode included a level dependent characteristic such that at average and lower input levels the microphone mode replicated a head related transfer function, while at higher levels the fitted strength determined the microphone mode (such as an adaptive directional beamformer).

The three manual programs under investigation were configured to offer the maximum signal processing of each feature representative of three different technology levels (highest, mid-level, and lowest). The manual program which emulated the highest technology level included the ability to binaurally and asymmetrically adjust several adaptive features (the beamformer, noise canceller, and speech enhancement) based on the location of a speech target in one of four quadrants around the listener (for SpeechPro, the device performance was asymmetrical for speech targets to the side). The other two manual programs which emulated lower price points did not include the ability to modify performance based on a speech target location and did not include any asymmetrical adjustments. The manual program which emulated the lowest technology level included a restricted beamformer setting which replicated an average head related transfer function.

To reduce the likelihood of bias, the automatic program was configured to perform similarly to a mid-level device. Specifically, in the automatic program, SpeechPro was disabled (the microphones were configured as a fixed wide directional beamform) and the adaptive signal processing features (speech enhancement and noise cancellation) were set to a mid-level strength (not the maximum that would be achieved in the highest-level technology product). For all manual programs, the following features were kept at default settings: Wind control (off), AntiShock2 (Moderate), Phase Canceller (Moderate). Feature modification included functionality for speech understanding, localization, and noise reduction.

Programs were preloaded into the hearing aids to limit the number of times the participants had to return for fitting modifications during COVID-19. Participants were instructed to stay in P1 during the acclimatization phase of the study, which also remained the default program throughout the study. P2, P3, and P4 were manually accessible using the multi-function button with program switching functionality (on the top of the hearing aid). Participant instructions for accessing programs P2 through P4 during the trial period included randomization (refer to Phase 2). The use of manual programs made it possible to provide the equivalence of three different hearing aids in the one device by replicating the feature settings that are commercially offered in the chosen technology level. Participants were single blinded to all aspects of hearing aid program feature settings. Participants were instructed to identify the different programs through the number of beeps presented when toggling between the programs (e.g., P2 beeped twice, P4 beeped four times).

## 2.3 Study phases

Following the hearing aid fitting portion of the study, each participant began a two-phase real-world hearing aid trial. Phase 1 consisted of a 2-week acclimatization period allowing participants to become familiar with the new study-worn hearing aid fitting. If participants required additional fine-tuning or adjustments to their study hearing aids, they were instructed to contact the research team prior to beginning the next phase. Phase 2 included a data collection period, spanning a minimum of 2 weeks, and included the use of a proprietary EMA survey application, MobEval3, to survey contextual and perceptual information. This app was installed on loaner tablets (Asus ZenPad 8.0 or Samsung Galaxy Tab A7 Lite- 7″ or A8- 8″) that were provided to participants for the duration of the trial, along with a travel case. The tablets did not require internet access; all data was stored locally on each device. During the hearing aid fitting appointment, participants were given a personalized tutorial of the physical hearing aid features (volume/program switches/charging), tablet features (power and applications), and survey execution within the app. Participants practiced utilizing all features in the laboratory, with a member of the research team until they were comfortable with the technology, prior to starting the trial. Participants also received paper instructions outlining general hearing aid use guidelines and all study procedures; these instructions contained both written and visual representations of the steps involved. Paper instructions were presented to participants to refresh participants on study steps following the acclimatization period.

## 2.4 Data collection

### 2.4.1 Ecological Momentary Assessment

Following the 2 week acclimatization phase, participants were asked to complete EMA surveys using event-based monitoring (Shiffman et al., 2008), in alignment with three pre-identified listening situations over a 14-day period. In this study, participants were instructed to complete surveys when in a social listening situation with at least one communication partner. In addition, they were instructed to complete a minimum of three surveys in each of the following situations, for a total of nine surveys: (1) indoors (at home), (2) indoors (away from home), and (3) outdoors. If a participant chose to collect extra survey data, these data were included in the analyses. Each survey contained a series of short questions and ratings of their listening activity with paired comparisons of hearing aid program preference. Participants were instructed to stay in a listening situation for a minimum of 2 minutes prior to initiating an EMA survey. EMA responses were collected using a variety of question types, including multiple choice, text-based responses, and Likert response scales. A study checklist was provided to each participant to allow them to keep a record of the listening situations they had completed. EMA studies often include prompted survey entries using random or scheduled notifications; however, the research team felt that notifications would not align well to the pre-determined location types, therefore, this study allowed the participants to select the days and times in which they completed the surveys in situations of interest and in the pre-determined location types. Reporting of communication partner type was included as part of the EMA (refer to Section 3.3).

The EMA portion of this study first surveyed participant eligibility according to their in-the-moment involvement in a social situation (with one or more communication partners). In the case where a participant indicated they were not with at least one communication partner, the survey was terminated, and the participant was directed to repeat the survey in an appropriate situation. In the case where the participant indicated they were in an eligible social situation they were prompted to continue the survey.

The EMA survey next collected information to better describe the listening situation the participant was in. Participants were asked to categorize their listening location as either: indoors (at home), indoors (away from home), or outdoors. This was followed by a prompt to include a text-based description of the activity completed in the specified location. Participants were also asked to indicate how many people they were with, according to the following categories: a partner (1), a small group (2–3), or a large group (4 or more); this was followed by a prompt to enter a text-based description of the people/person they were with (provided examples included "my spouse", "my two children"). In addition, participants were asked to indicate where their communication partner(s) was in relation to themselves (e.g., located to the front, to the side, or behind). To subjectively assess the presence and type of background noise, participants were asked if they could hear background sounds during the EMA survey; if they answered "yes," they were then asked to describe the noise as either speech, music, or non-speech.

The next step of the EMA survey was to assess program preference. Depending on the testing condition, participants were asked to toggle to their first evaluation program (P2, P3, or P4), and were then prompted to toggle between the remaining programs to make their evaluations. They were asked to be in the chosen listening situation for at least 2 min and to indicate a preferred program or no preference according to blocks of program pairs (e.g., P4 vs. P2, P2 vs. P3, and P3 vs. P4); these were presented as multiple-choice questions; evaluation order varied between the five testing conditions. All surveys included the same questions; however, the order of preference testing differed; individual program ratings were set to occur in different orders (testing order could have included P3–P4–P2, as one example). Using block randomization, participants were assigned to one of five pre-determined EMA testing orders.

## 2.5 Data analysis plan

Data from the MobEval3 application were stored locally on each tablet and exported upon each participant's completion of Phase 2. Survey data were analyzed using mixed methods with the application of descriptive and statistical analysis to draw quantitative inference and content analyses to describe qualitative data.

### 2.5.1 Mixed methods analyses

#### 2.5.1.1 Text-based content analyses

An content analysis approach was used to guide a systematic categorization scheme for the open text-based responses reported as part of the EMA (Huxley, 2020). Activity-based responses were categorized in alignment with the World Health Organization's International Classification of Functioning, Disability and Health (ICF) using the Activities and Participation categories (World Health Organization, 2004); this provided a description of the types of listening activities across location types, in which the preference data was collected. The ICF categories are separated according to broad coding, first level, and narrowed down to second- and third-level coding. A member of the research team coded each text-based response, verified by a second member of the team. Coding applied the ICF in a systematic manner, including categorizing activities into the nine first level codes. For example, the activity "having supper with my spouse" was categorized as Self-Care (ICF D5), Domestic Life (ICF D6), and as Communication (ICF D3). A second-level item coding method was used, as applicable, for each written entry in the EMA based on participant involvement in a life situation (World Health Organization, 2004). For our example, Self-Care was categorized into Eating (ICF D550) and Domestic Life was categorized into Other Specified Domestic Life such as discussing day's appointments with spouse. A common component of the ICF is the evaluation of capacity and performance; this evaluation was beyond the scope of the current study. Communication-partner-based responses were categorized according to perceived familiarity (immediate family, extended family or friends, acquaintances or groups, and strangers or

tradespeople); one text-based entry could have multiple categories of communication partners.

#### 2.5.1.2 Generalized linear mixed effects regression analyses

Quantitative data analyses were conducted with a generalized linear mixed effects regression model under a Bayesian framework. This Bayesian framework estimates the joint probability distribution of generative model parameters (Leijon et al., 2023). Our model implemented an extension of the Bradley-Terry model to allow for ties in preference ratings (i.e., no preference) to model paired-comparison preference (Critchlow and Flinger, 1991). We included contrast-coded programs (e.g., P3 and P4), location, background noise type, and the interaction between location and background noise type as population-level effects with varying effects for participants. The model was constructed using the Stan programming language (Carpenter et al., 2017) through the cmdstanr package (Gabry and Češnovar, 2021) in R statistical computing software (R Core Team, 2022).

The model estimated a posterior distribution of the probability of preference rating for each combination of participant, location, and background noise type for each Markov chain Monte Carlo (MCMC) iteration (Gallagher et al., 2009). To derive a single estimate of preference ratings for each participant, location, and background noise type, a sum-score was calculated for each MCMC iteration as follows:

$$\text{Sum} - \text{Score}_{iteration} = \sum_{k=1}^{5} \left(p\left(k\right)^{*} k\right)$$

where p(k) is the probability of each preference rating. A sum-score represents the means of the probability distributions for each response choice, i.e., the central tendency of the response distributions.

# 3 Results

## 3.1 Participants

A total of 14 individuals participated in this study. Participants presented with mild to moderately severe symmetrical hearing losses according to better ear 4PTA values ($M = 47$, SD = 7.3). The range in group-level pure-tone audiometric thresholds, as well as group-level mean thresholds per ear, are displayed in Figure 1. Between-ear symmetry ranged from 0 to 15 dB HL, across all participants. Audiometric thresholds were measured using a GSI AudioStar Pro audiometer with ER-3A insert earphones coupled to foam tips; middle ear analyses were completed using a Titan middle ear system as a screen for normal middle ear function.

### 3.1.1 Social interactions

Participants reported daily social interactions (71%) or frequent interactions (29%), as defined by their report of interaction within the last 3 days. Many participants reported living with one person (50%), living alone (14%), or living with two or more people (7%); the remaining participants did not report their living situation (29%).

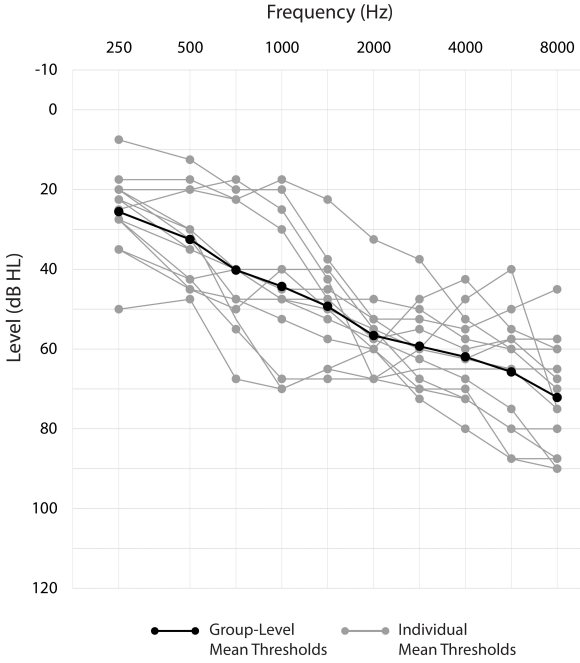


FIGURE 1
Mean group-level and individual audiometric thresholds.

### 3.1.2 Participant experience with technology

Thirteen participants reported owning receiver-in-the-canal (RIC) hearing aids of various makes/models outside of this study (one participant was unable to report this information). All participants were experienced hearing aids users, with at least 1 year of hearing aid experience. Twelve participants reported wearing hearing aids for at least 8 h per day, in their daily life, with the remaining two reporting 6 h or less of hearing aid use.

When asked to report on mobile device ownership and usage, most participants reported owning a tablet ($n = 12$), smartphone ($n = 12$), and/or laptop/desktop ($n = 13$), with variable ratings of smartphone or tablet comfort level [novice ($n = 1$), average ($n = 7$), above average ($n = 5$), and expert ($n = 1$)]. Ten participants reported using these devices every day, in situations both inside and away from their home. When asked how they felt about using new mobile applications (apps), eight reported that they would be comfortable using apps on their own and two indicated that they would need help.

## 3.2 EMA survey compliance

Participants were asked to complete nine surveys each over their 2-week period, for a total of 126 surveys. In fact, participants completed 128 surveys (102% compliance; Table 2). On one occasion a participant initiated a survey and indicated they were in a listening situation without a communication partner, hence the survey self-terminated and is not included in the analysis,

TABLE 2 Participant survey compliance by location.

| Participant | Completed surveys | | |
|---|---|---|---|
| | *n* (% compliance) | | |
| | Indoors at home | Indoors-away from home | Outdoors |
| 1 | 2 (67) | 3 (100) | 3 (100) |
| 2 | 3 (100) | 3 (100) | 3 (100) |
| 3 | 3 (100) | 2 (67) | 3 (100) |
| 4 | 3 (100) | 3 (100) | 3 (100) |
| 5 | 3 (100) | 3 (100) | 3 (100) |
| 6 | 4 (133) | 3 (100) | 5 (167) |
| 7 | 4 (133) | 1 (33) | 2 (67) |
| 8 | 4 (133) | 1 (33) | 5 (167) |
| 9 | 4 (133) | 2 (67) | 2 (67) |
| 10 | 3 (100) | 4 (133) | 3 (100) |
| 11 | 6 (200) | 0 (0) | 0 (0) |
| 12 | 3 (100) | 4 (133) | 2 (67) |
| 13 | 3 (100) | 2 (66) | 1 (33) |
| 14 | 6 (200) | 5 (167) | 6 (200) |

A 100% compliance rate was based on the collection of 3 EMA surveys per location.

Individual participant compliance rates varied from 66 to 188% across all situations. Six participants completed the minimum required location-specific surveys for each location; one participant only completed EMA surveys indoors (at home). Participants had the highest compliance in completing surveys indoors (at home), with only one participant not completing the minimum three surveys; compliance was lowest for indoors (away from home), with six participants not completing the minimum surveys. The group average compliance rate was 121% compliance indoors (at home), 86% compliance indoors (away from home), and 98% compliance in outdoor situations. Participants took an average of 17 days to complete Phase 2 ($SD$ = 9.16). Hearing aid data logging was not used to measure compliance; the Log-it-All feature (i.e., data logging) in the hearing aids is only capable of capturing the cumulative average percentage of time in each environment between fitting appointments and could not have been used to capture details around hearing aid usage per program, per day, or down to the exact time stamps required to evaluate compliance. According to the data collected as part of the EMA survey, the average completion time of the survey was 7:47 min ($SD$ = 4:07); this first included an average of 3:20 min of general questions used to describe the listening situation (i.e., location, communication partner, and type of background noise), completed as part of the block-randomization. Participants first assigned to P2 completed the general questions in an average time of 3:08 min, 3:16 min (P3), and 3:52 min (P4). Time stamps that related to the program switching notification in the survey were used to estimate how long each participant was in each program for. Participants were in P2 for an average of 1:20 min ($SD$ = 0:38), P3 for 1:15 min ($SD$ = 0:38), and P4 for 0:55 min ($SD$ = 0:39).

## 3.3 Location-based activity and participation

As all open-text responses contained communication aspects and at least one communication partner, all data points were coded as a communication activity (ICF: d3). The following Activity and Participation domains applied to the dataset: learning and applying knowledge (ICF: d1); mobility (ICF: d4); self-care (ICF: d5); domestic life (ICF: d6); interpersonal interactions and relationships (ICF: d7); major life areas (ICF: d8); and community, social, and civic life (ICF: d9). Table 3 outlines the frequency of reported activities according to ICF second-level coding and according to participant-reported listening situation; sample statements and communication partners are listed for each category. Communication partners were described using open-ended responses and categorized according to immediate family (68%), extended family/friends (23%), acquaintances/groups (9%), strangers/tradespeople (5%), and pets (2%).

## 3.4 EMA reported listening situations

Data from the 128 completed EMA surveys were analyzed to better describe the listening situations experienced during the project by this group of participants, as outlined in Table 4. EMA surveys were completed in all three locations with 40% of all surveys completed indoors (at home), 28% indoors (away from home), and 32% outdoors. Participants were in a variety of listening situations, with most participants in situations with one listening partner

TABLE 3 Listening activities by location and sample communication partner, according to ICF categorization.

| ICF second-level code (ID) | Paraphrased definition | Sample statement (communication partner/s) | Absolute frequency as reported per location *n* (%) | | | |
|---|---|---|---|---|---|---|
| | | | All locations ($N = 128$) | Indoors at home ($N = 51$) | Indoors-away from home ($N = 36$) | Outdoors ($N = 41$) |
| Communication (d3) | Carrying out conversations | All statements | 128 (100) | 51 (100) | 36 (100) | 41 (100) |
| Community, social, and civic life (d9) | Engaging in organized social life outside the family, including ceremonies, recreation, and leisure (sports, crafts, socializing), and political life. | Movie night gathering of six people, at friend's house discussing movie we've just seen (three couples). | 60 (47) | 9 (18) | 28 (78) | 23 (56) |
| Domestic life (d6) | Engaging in domestic and everyday actions and tasks, including acquisition of goods and household chores. | Shoveling snow in driveway (spouse). | 56 (44) | 36 (71) | 3 (8) | 17 (41) |
| Learning and applying knowledge (d1) | Applying knowledge that is learned, thinking, solving problems, and making decisions. Including watching, listening, and acquiring complex skills. | In a hockey arena watching a game (my spouse, daughter, son-in-law, two great-grandchildren). | 22 (17) | 20 (39) | 2 (6) | 0 (0) |
| Self-care (d5) | Caring for oneself and looking after one's health. Including eating meals. | Eating dinner, with the humming of the fish tank filter-system in the background (partner). | 12 (9) | 4 (8) | 6 (17) | 2 (5) |
| Interpersonal interactions and relationships (d7) | Engaging in basic and complex interactions with people, including formal, informal, and intimate relationships. | [In a] hotel room, speaking with my wife (spouse). | 4 (3) | 2 (4) | 2 (6) | 0 (0) |
| Mobility (d4) | Movement including walking, running, or climbing, and various forms of transportation. | Walking to store from car (spouse). | 4 (3) | 0 (0) | 1 (3) | 3 (8) |
| Major life areas (d8) | Engaging in education, work, and employment. | In an online work meeting on laptop with five people (five work colleagues). | 2 (2) | 1 (2) | 1 (3) | 0 (0) |





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TABLE 4 Situation characteristics per location.

| | *n* (%) | | | |
|---|---|---|---|---|
| Situation characteristics | Indoors at home | Indoors-away from home | Outdoors | Total |
| Total | 51 (40) | 36 (28) | 41 (32) | 128 |
| Group size | | | | |
| A partner (1) | 42 (82) | 16 (44) | 33 (80) | 91 (71) |
| Small group (2–3) | 5 (10) | 8 (22) | 3 (8) | 16 (13) |
| Large group (4 or more) | 4 (8) | 12 (33) | 5 (12) | 21 (16) |
| Type of background noise | | | | |
| Non-speech | 11 (22) | 13 (36) | 37 (90) | 61 (48) |
| Speech | 20 (39) | 11 (30) | 3 (7) | 34 (27) |
| Music | 4 (8) | 1 (3) | 0 (0) | 5 (4) |
| Quiet, no noise | 16 (31) | 11 (30) | 1 (3) | 28 (22) |

(71%), followed by a large group (four or more people; 16%), and least often in situations with a small group (2–3 people; 13%).

Analyses according to type of background noise, including whether the participant classified the noise as non-speech, speech, music, or quiet, and the frequency of the noise (constant vs. intermittent noise), yielded the following EMA results: background noise as constant non-speech (31%), constant speech (22%), or quiet/no noise (21%), with fewer instances of intermittent non-speech (17%), intermittent speech (5%), and fewest situations in constant music (4%). Table 4 displays results according to background noise type, collapsing noise frequency categorization.

## 3.5 Hearing aid technology-level ratings and preferences

Participants' subjective listening preference across the three technology levels were calculated using sum-scores for each combination of program comparison, location, and background noise type (Figure 2). Points represent the median preference rating, error bars depict the 89% highest density credible interval (CI), and asterisks indicate statistically significant preferences (Kruschke, 2014). In most cases, the two higher technology levels (P2 and P3) were preferred over the lowest technology level (P4). In outdoor situations, the highest technology level, P2, was preferred compared to P4 only in speech background noise. P2 was reported as the preferred program over both lower technology levels (P3 and P4) in the indoors when away from home, when the background noise type was speech, which is likely the most challenging situation for listeners to participate in communication. No significant differences were found for preference when in the presence of music. Results from linear mixed effect regression analyses are outlined in Supplementary material.

# 4 Discussion

This study presents findings specific to EMA data collected during real-world, real-time situations and in socially involved listening situations (i.e., including at least one communication partner). Findings suggest that real-world data collection by adults across various socially involved listening situations is a viable way to collect preference ratings, and that some activities may yield higher data collection patterns. Participants were asked to complete surveys while in a situation that involved conversation in one of three pre-defined listening situations: indoors (at home), indoors (away from home), and outdoors.

In alignment with the current literature, the participants' subjective preference ratings were evaluated using repeated measurement using real-time in-the-moment EMA surveying in complex listening situations, allowing for the evaluation of technology using identical measurement processes (Christensen et al., 2024a,b). We also asked our listeners to report on the listening conditions under which the self-reports were made according to classification of real-time (a) location (indoors at home, indoors away from home, and outdoors), (b) background (quiet, non-speech noise, speech noise), and (c) communication partner(s) during data collection. We also asked participants to contribute open-text responses to describe situation-specific activities that they were engaged in while completing the EMA surveys; these were analyzed using content analysis. Previous studies evaluating listener preference for basic vs. premium hearing aid technology level have included the use of back-to-back hearing aid trial periods to evaluate fitting differences within and across hearing aid manufacturers (Cox et al., 2016; Hausladen et al., 2022; Plyler et al., 2021). In comparison, our study incorporated a shortened trial period when evaluating signal processing features differences within one device, using hearing aid programs that exemplified the technology difference of interest.

More recent studies have incorporated smartphone-based EMA systems to inform research designs. For example, EMA methods have been evaluated as part of auditory lifestyle research (Xu et al., 2020; Wu et al., 2018), to compare hearing aid technologies (e.g., traditional vs. advanced noise reduction systems), describing listening experiences as part of daily-life situations (Christensen et al., 2024a,b), and to compare outcomes of different hearing aid technologies using *in-situ* self-report applications (Wu et al., 2020). In addition, EMA methods used to evaluate real-world

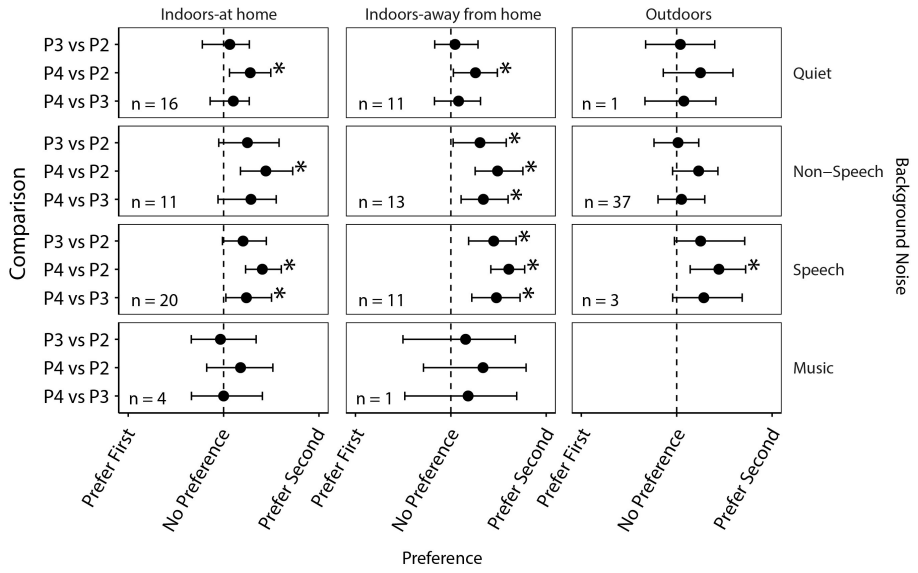


FIGURE 2
Paired comparisons for preference according to location and background noise type. *Indicates significance.

effectiveness of advanced digital noise reduction have evaluated different dimensions of listener experience, including satisfaction, as part of larger lab and real-world test batteries (Wu et al., 2019). The methods reported in this study incorporated a selection of previously reported EMA methods including the assessment of auditory lifestyle through mobile-based, real-time surveying, to facilitate *in-situ* measurement of listener preference for technology levels. Multiple paired comparisons were used to evaluate three levels of hearing aid signal processing features to gain a rich understanding of listener preference in the context of clinically relevant technology level options. The inclusion of real-world, in-the-moment preference ratings via EMA methods provide insight into hearing aid user technology preference, assessed as part of socially involved listening situations. Data collection methods used in this study therefore aimed to reduce participants' recall-bias and potential data collection burden, with the collection of multiple preference ratings built into one real-world hearing aid trial.

## 4.1 EMA compliance by listening situation

A total of 128 EMA surveys with data aligning with each of the pre-defined listening situations were captured. The requirement for participants to have completed EMA surveys with at least one listening partner present may have contributed to the lower frequency of data collected for quiet listening situations, paired with the high occurrence of non-speech categorized background noise. Overall, data collection was lowest for outdoor situations, when participants were experiencing background noise reported as quiet (3%) or speech (7%). Further investigation is needed to explore technology level preferences in outdoor situations and without social distancing restrictions.

High EMA compliance rates were recorded as part of this study, indicating effective completion of in-the-moment EMA surveys accessed through a tablet as part of the participants' daily lives. The highest number of EMA surveys were reported to be completed during participation in activities related to communication within their community, social, and civic life that took place indoors (away from home), or in outdoor situations. The second highest reported ICF category included activities related to domestic life; EMA responses collected during these activities were commonly reported indoors at home when learning or applying knowledge, or when outdoors (often associated with activities within the home's property). The prevalence of home-based findings may be attributed to the data collection timeline occurring during the COVID-19 pandemic, with several provincial lockdowns occurring during data collection and the participants' comfort level and/or ability to participate in social activities away from the home. The least often reported listening situations related to those experienced as part of major life areas, including education, work, and employment. This likely related to the participants' ages, as most were retired, or may have related to participant hesitance to complete the EMA survey during work-based activities. The findings from this study can therefore be generalized to a variety of listening situations, inside and outside of the home, and as experienced by a group of adult Canadian listeners that were socially engaged during COVID-19.

## 4.2 Subjective preference

Participants reported a preference for both premium and mid-level technology levels, when compared to the basic technology level, for indoor listening environments (at home and away

from home), and in environments that included background noise categorized as quiet, non-speech, and speech; this trend in preference was also reported when in outdoor listening environments with background speech noise. Our application of EMA used multiple response formats, including open-text options to allow the listener to describe listening situation-specific activities in greater details. This EMA application has been reported to provide real-time insights into common themes linked to hearing aid use and/or challenges (Vercammen et al., 2023). In our study, commonly reported indoor activities included conversations during meal consumption, when watching TV, and when visiting with family members, whereas when outdoors, commonly reported activities included conversations while relaxing outside or while completing seasonal chores. A preference for the premium-level technology, over the mid- and basic-level technology, was indicated when listeners were located indoors-outside home, when background noise was specific to speech. When participants were located indoors-outside of the home they commonly reported dining in restaurants and participating in other group-based activities, such as sporting events, and educational classes.

Findings from this study suggest that subjective preference ratings for hearing aid technology level were influenced by both the location of the listener, as well as the type of background noise present, with a preference for mid-level and premium technologies, compared to basic technology, across most socially involved listening situations experienced as part of the study. These findings likely relate to differences in the settings and features activated across technology levels (refer to Table 1) that aim to optimize listening in conversation, especially when in the presence of noise. For example, the strength of the sound optimization setting increased from the basic to the premium technology level within this study, which may have contributed variations in reported preference ratings associated with speech understanding, comfort, and/or sound quality listening dimensions. In addition, the premium level technology included an adaptive speech-finding beamformer feature called SpeechPro (dynamic location of target speech signal, including noise cancellation and speech enhancement), which may have contributed to higher perceived listening abilities when in conversations in noise and/or crowds. Plyler et al. (2021), also examined post-trial preference for similar premium vs. basic hearing aid features using recall-based investigator interviews, and reported at the group level these results were not found to be significant. The authors concluded that examination of the laboratory and field trial results revealed that listeners in highly-demanding listening environments performed comparably or better with the premium devices (Plyler et al., 2021). Participants in the current study were engaged in complex and varied environments when completing preference ratings, which included conversation with one or more communication partners and in the presence of speech (27%) or non-speech (48%) background noise as part of the activity. In these contexts, Participants reported preference for the two higher technology levels (P2 and P3) over the lowest technology level (P4); with a greater preference, across locations, for P2 over P4. This study allowed participants to directly compare technologies within the same environment, as part of their daily life.

## 4.3 Limitations

One limitation of survey-based studies is the inability to confirm whether participants completed data collection in the self-reported activity at the logged times (Shiffman et al., 2008). Time stamps of the EMA data suggest that surveys were not completed at scheduled times or at consistent intervals. Participants completed 27% of the surveys in the morning (between 6:00 and 11:59 a.m.), 30% in the afternoon (12:00–4:59 p.m.), and 56% in the evening (4:59 p.m. or later). In addition, compliance rates were recorded to be highest when EMA data was collected in the home and dropped considerably when compared to EMA data collection completed indoors-outside of the home. This may be an indication of the participant's ability to complete, or their comfort around completing, survey-based tasks outside of a more contrived situation, such as their home. Five surveys were initiated with no responses selected throughout; this small number of incomplete surveys may indicate that participants did not feel the survey was too long. It is not possible to know the number of situations that may have been of interest where the participant did not feel comfortable taking the time to complete a survey. To improve participant convenience, future studies could include the use of smaller mobile devices to collect survey data, such as a smartphone, the use of shorter surveys to collect information around situation suitability may also provide more accurate information (e.g., one or two questions that require a quick answer). Future research should consider how we can better capture perceptions in rapidly-changing listening environments as well as provide clear instructions on how to manage *in-situ* surveying in challenging social situations.

Outside of the devices used in this study, one manufacturer's interpretation of what a premium product is comprised of may not be the same as the next. In this study, the listeners reported a preference for high and medium technology levels, when compared to the basic level. This may not be the case across all manufacturers depending on feature composition per technology level. Future research is needed to validate whether these findings generalize across other manufacturers' product lines.

# 5 Conclusions

This study is part of a larger study that aims to pair objective and subjective metrics of hearing aid technology level in socially involved situations. When considering the subjective results, results indicate that adult hearing aid users can reliably complete EMA survey tasks in real-world scenarios related to location, activity classification, and preference; however, further research aimed at optimizing EMA data collection methods is warranted. The findings from this study can be applied to future research and clinical application to inform in-the-moment performance with pre-determined hearing aid program comparisons and/or targeted listening situations. Technology levels including mid to premium features resulted in higher preference ratings when evaluated in socially involved listening situations. Including an assessment of hearing aid users' activity profile, and information related to the presence of communication partners, may help inform technology selection; this type of

assessment information may also inform the use of individualized programs. In the research context of this study, listeners were willing to complete EMA surveys comparing manual programs; this application of EMA methods could translate to clinical practice for evaluation of program preference or other technology level comparisons.

Future research is aimed at exploring the relationship between the objective data captured by the hearing aid classifier in the study-provided hearing aids, with the subjective participant responses obtained during the EMA surveys. This will yield information related to hearing aid classification by technology level which could be used for individualization of device configuration and settings. Furthermore, EMA can be used as a way of determining benefit (or lack thereof) resulting from automatic hearing aid classification, guiding future advancements around the functionality and adjustment of hearing aid technology in different listening environments.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

This study, involving humans, was approved by the Western University Health Sciences Research Ethics Board. The study was conducted in accordance with local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

DG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RO: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. KB: Data curation, Investigation, Resources, Writing – review & editing. JC: Data curation, Formal analysis, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SS: Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing. LC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing.

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## Conflict of interest

LC is an employee of Unitron (Sonova) and supported the supply of hearing instruments and software that were used in this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fauot.2024.1430992/full#supplementary-material

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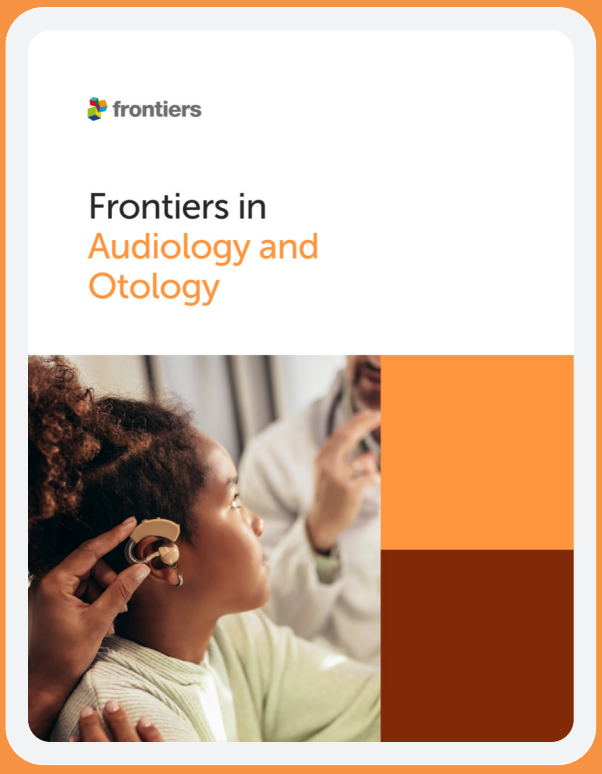


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